Final Report

Synthesis of 2-Oxazolines and Trisubstituted Ureas from Bench-Stable α-Chloroaldoxime *O*-Methanesulfonates

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This project granted by the Thailand Research Fund

Abstract

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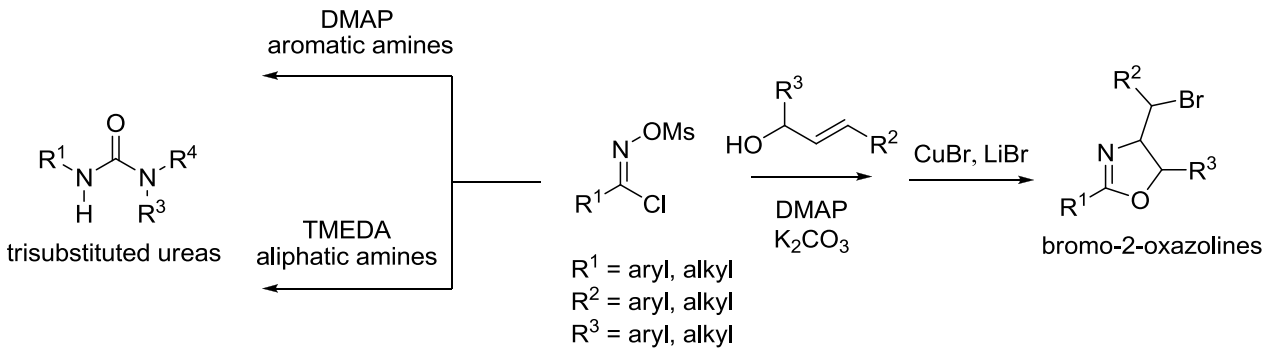
Project Period : 2 years

Abstract:

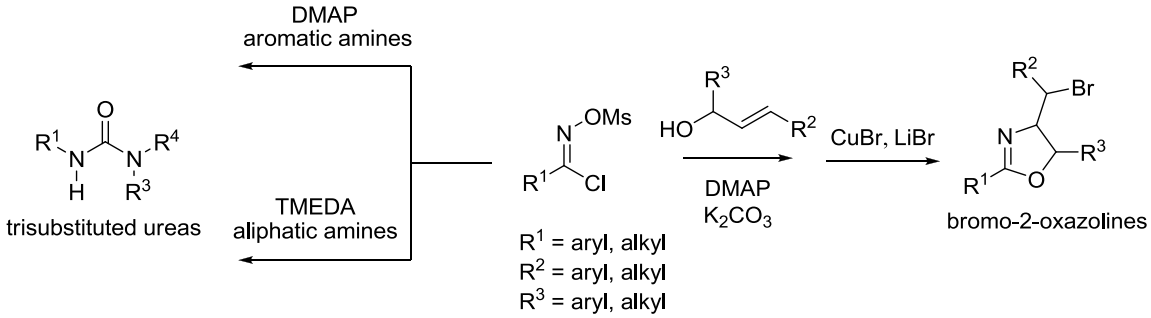


The aim of our research investigation is to explore reactivity of a bench stable α-chloroaldoxime *O*-methanesulfonate in the synthesis of 2-bromooxazoline and trisubstituted urea. Derivatives of 2-bromooxazoline were accomplished via two-step procedures in which the first transformation was nucleophilic substitution with allylic alcohols. The second formation was copper-catalyzed cycloaddition involved addition of bromine radical. On the other hand, trisubstituted ureas were achieved under mind reaction conditions. Two simple protocols were developed to obtain various ureas from both aromatic amines and aliphatic amines.

Keywords : Trisubstituted ueras, oxazolines, copper-catalyzed cyclization, Tiemann rearrangement

Final report content:

1. Abstract

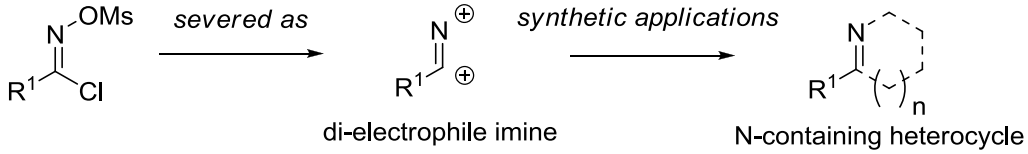


The aim of our research investigation is to explore reactivity of a bench stable α-chloroaldoxime *O*-methanesulfonate in the synthesis of 2-bromooxazoline and trisubstituted urea. Derivatives of 2-bromooxazoline were accomplished via two-step procedures in which the first transformation was nucleophilic substitution with allylic alcohols. The second formation was copper-catalyzed cycloaddition involved addition of bromine radical. On the other hand, trisubstituted ureas were achieved under mind reaction conditions. Two simple protocols were developed to obtain various ureas from both aromatic amines and aliphatic amines.

2. Executive summary

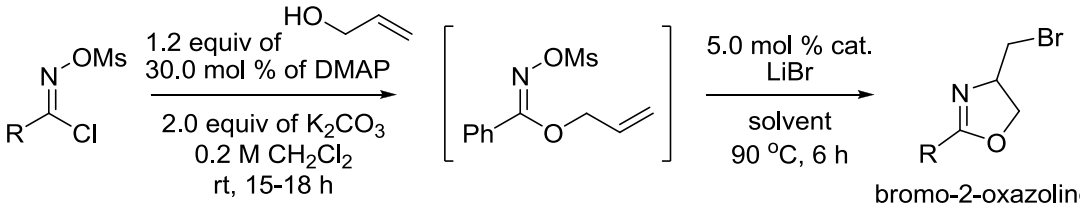
The Chemistry of α-chloroaldoxime *O*-methanesulfonate is fascinated. In addition, this molecule could be stored on the bench without precautious, and prepararation method is straightforward. We have been utilized two chemistries of the α-chloroaldoxime *O*-methanesulfonate. The first is the imine dielectrophile in the heterocycle synthesis (Figure 1).

Figure 1. The imine dielectrophile in heterocycle synthesis



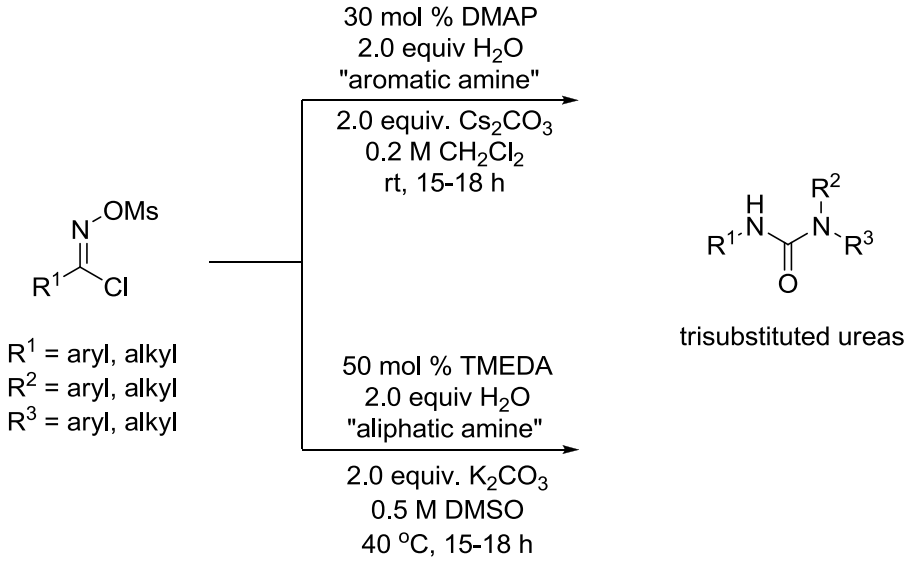
In this chemistry we have been applied this concept to synthesize the bromo-2-oxazoline via two-step procedure. Our methodology consists of two key steps which are an allylic alcohol substitution with the chlorine atom and copper-catalyzed cyclization, triggered by addition of bromine radical (Scheme 1).

Scheme 1. Bromo-2-oxazoline syntheses from α-chloroaldoxime *O*-methanesulfonates



The second chemistry of α-chloroaldoxime *O*-methanesulfonate is the Tiemann rearrangement. We took this chemistry to apply in our synthesis of trisubstituted ureas under mild and straight forward reaction (Scheme 2).

Scheme 2. The synthesis of trisubstituted ureas



The two simple protocols have been established for the secondary aromatic and aliphatic amines. Although reaction mechanism is not clarified, our methodology provides the straight forward synthesis of trisubstituted ureas.

3. Objective

3.1 To accomplished a variety of 2-bromooxazolines via two-step procedure from α-chloroaldoxime O-methanesulfonates and allylic alcohols.

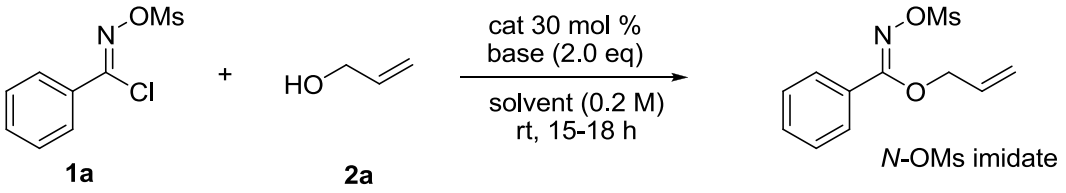
3.2 To achieve various trisubstituted ureas from α-chloroaldoxime O-methanesulfonates and secondary amines.

4. Result and Discussion

4.1 Synthesis of 2-bromooxazolines from a bench-stable α-chloroaldoxime *O*-methanesuldonates and allylic alcohols

Our formation of 2-bromooxazoline was consisted of two consecutive transformations in which the first formation was the nucleophilic substitution to generate allyl *N*-methylsulfonyloxybenzimidate (*N*-OMs imidate) from allylic alcohol, and the second formation was copper-catalyzed bromocyclization to give 2-bromooxaoline. In order to achieve the reaction condition, we began with the first step optimization to obtain *N*-OMs imidate (Table 1)

Table 1. The optimization of N-OMs imidate formation[a]



1a **2a** *N*-OMs imidate

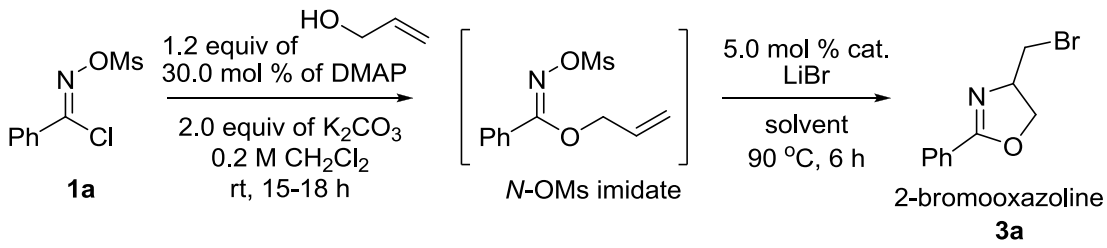
entry	cat.	base	solvent	yield[b]
1	DABCO	NEt_3	CH_2Cl_2	trace
2	DMAP	NEt_3	CH_2Cl_2	28
3	Imidazole	NEt_3	CH_2Cl_2	trace[c]
4	-	NEt_3	CH_2Cl_2	NR[d]
5	DMAP	NEt_3	EtOAc	trace
6	DMAP	K_2CO_3	CH_2Cl_2	94

[a]Reaction conditions: all reaction were carried out with 0.5 mmol of **1a**, 1.2 equiv. of allylic alcohol, 2.0 equiv of base in 2.5 mL of solvent at room temperature for 15-18 hours. [b]Isolated yield. [c]From ^{1}H NMR spectrum of the crude reaction mixture. [d]No reaction.

The reaction of *N*-(methylsulfonyloxy)benzimidoyl chloride (**1a**) and allylic algohol was selected as a model study. We started with the catalysts, DABCO, imidazole and DMAP (Table 1, entry 1-3). The reaction with DMAP as a catalyst gave the best yield, 28%. Note that which out the catalyst, the reaction gave no product (Table 1, entry 4). Then we changed the solvent to higher polarity, EtOAc. Unfortunately we observed only trace amount of the product (Table 1, entry 5). Delightfully, by changing the base to inorganic base, K_2CO_3 the yield of product was greatly improve to 98% yield (Table 1, entry 6). Therefore, our optimal condition was the use of DMAP as catalyst and K_2CO_3 as a base in CH_2Cl_2 at room temperature for 15-18 hours.

In order to make our synthesis become more practical, we designed our method to be two-step procedure. The first step condition was obtained from the Table 1. Then, the crude mixture from the first step was filtered, dried under vacuum and subjected to the optimization reaction of the second step, copper-catalyzed cyclization to achieve 2-bromooxazoline, without any purification.

Table 2. The optimization for the copper-catalyzed cyclization[a]



entry	cat.	Solvent	yield[b]
1	CuBr	CH_3CN	74
2	CuBr	$PhCH_3$	59
3	CuBr	THF	66
4	CuBr	DMF	23
5	$Cu(OAc)_2$	CH_3CN	31
6	$ZnCl_2$	CH_3CN	NR[c]
7	-	CH_3CN	NR[c]
8	CuCl	CH_3CN	25

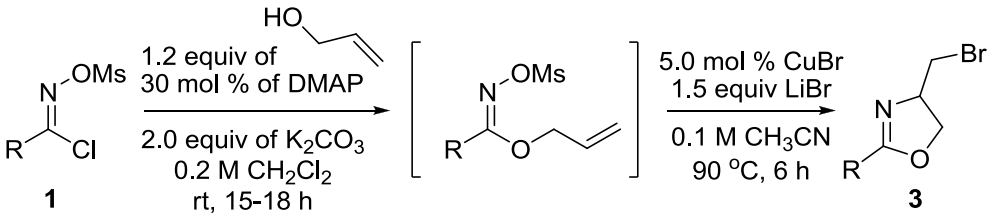
[a]Reaction conditions: all reaction were carried out with the crude mixture of *N*-OMs imidate (derived from 0.5 mmol of 1a) and 1.5 equiv. of LiBr in 5 mL of solvent at 90 °C for 6 hours. [b]Isolated yield. [c]No reaction.

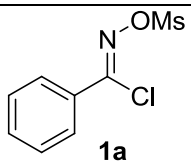
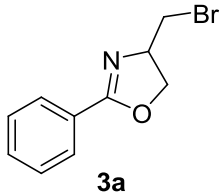
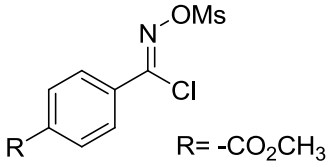
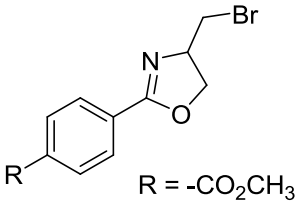
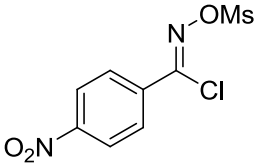
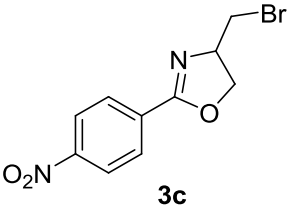
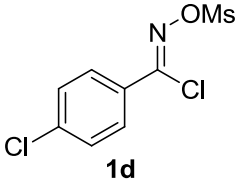
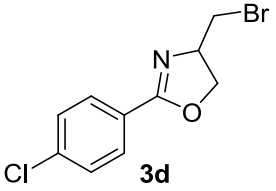
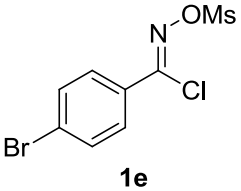
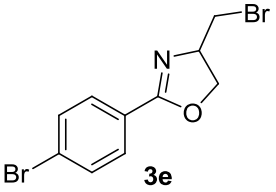
The study from Koganemaru and co-workers in synthesis of oxazolines showed us that bromine radical catalytically was generated from CuBr and LiBr at 80 °C. Subsequently, the bromine radical added to the double bond, followed by cyclization to construct the cyclic molecule. Based on their finding, we conducted the second step optimization by using the CuBr as a catalyst and LiBr as a bromine radical source at 90 °C. This cyclization was applicable with quite wide range of solvents such as non-polar Toluene gave moderate yield. When higher polar solvents were applied for example THF the yield was increased to 66%, and also ACN gave 74% yield (Table 2, entry 1-3). However, the yield of the cyclization was dramatically diminished when DMF (highest polar solvent in our optimization) was applied (Table 2, entry 4). Next we explored catalysts such as $Cu(OAc)_2$, CuCl and $ZnCl_2$. These three catalysts gave the product yield in 31%, 25% and trace amount respectively (Table 2,

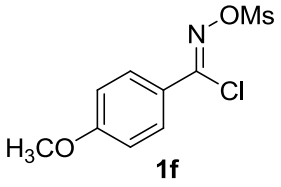
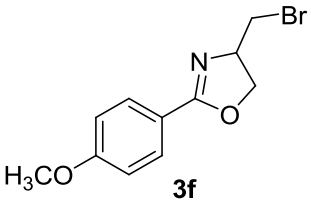
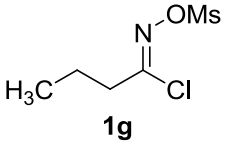
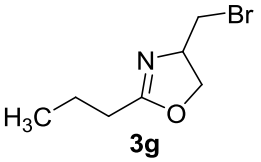
entry 5-7). The result suggested that the reactivity in generation of bromine radical from LiBr was crucial. Therefore, only using catalyst, $ZnCl_2$, for a Lewis acid was not effective in our reaction. Likewise, in the absence of CuBr the product was not generated.

After the optimal condition was obtained, we turned out interest to scope of substrates. A variety of α-chloroaldoxime *O*-methanesuldonates was subjected to our two-step procedure protocol.

Table 3. The synthesis of 2-bromooxazolines from α-chloroaldoxime *O*-methanesuldonates and allylic alohol[a]



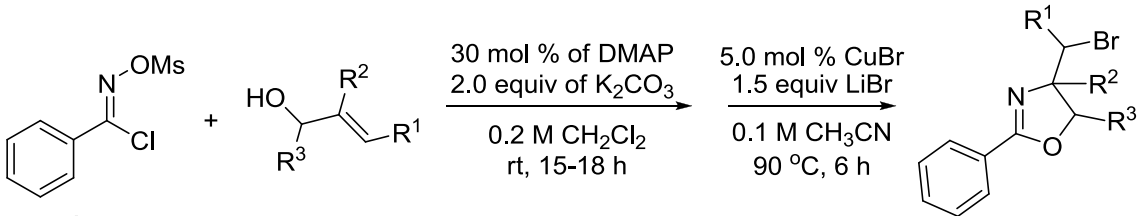
entry	chloroaldoxime	2-bromooxazoline	% yield[b]
1	 **1a**	 **3a**	74
2	 R= -CO_2CH_3 **1b**	 R = -CO_2CH_3 **3b**	86
3	 **1c**	 **3c**	82
4	 **1d**	 **3d**	79
5	 **1e**	 **3e**	72

6	 **1f**	 **3f**	0
7	 **1g**	 **3g**	0

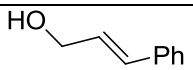
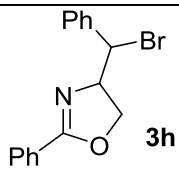
[a]Reaction condition: all reactions were carried out with 0.5 mmol of **1**, 1.2 equiv of allylic alcohol for the first step. Then, the reaction mixture was filtered, concentrated and subjected to second step with the use of 5 mol % CuBr and 1.5 equiv of LiBr. [b]Isolated yield.

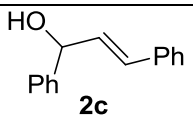
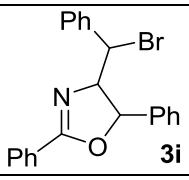
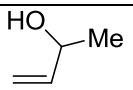
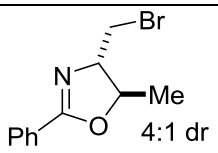
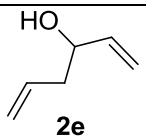
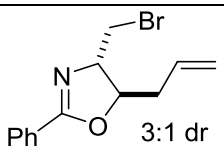
The scope of substrate of our oxazoline synthesis was quite limited. The chloroaldoxime with electron-withdrawing substitutent on aryl ring gave high yield (Table 3, entry 2 and 3). Likewise the chloroaldoximes halogen substituent on aryl ring were also suitable for our two-step procedure of oxazoline synthesis (Table 3, entry 4 and 5). The electronic effect on the aryl ring played a major role in our reaction. The chloroaldoxime with high electron density gave no product (Table 3, entry 6). A ^{1}H NMR of the crude mixture for the first step showed no signal of corresponding imidate. This result suggested that the bottle neck of this substrate was the first step due to low electrophilic of chloroaldoxime, resulted from electron-donating methoxy group. On the other hand, the chloroaldoxime with a simple alkyl substituent showed significantly high signal for the corresponding imidate. Surprisingly, after subjected to the copper-catalyzed cyclization, we did not observe the oxazolines (Table 3, entry 7). Based on this finding, it showed that the imidate derived from alkyl-substituted chloroaldoxime was not applicable for copper-catalyzed bromine radical cycliczation.

Table 4. The synthesis of 2-bromooxazolines from α-chloroaldoxime *O*-methanesuldonate and allylic alcohols[a]



1a + **2** → **3**

entry	allylic alcohols	2-bromooxazolines	%yield[b]
1	 **2b**	 **3h**	trace[c]

2	 **2c**	 **3i**	trace[c]
3	 **2d**	 4:1 dr **3j**	46
4	 **2e**	 3:1 dr **3k**	40

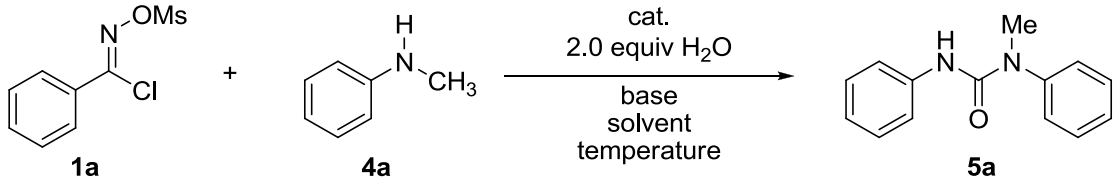
[a]Reaction condition: all reactions were carried out with 0.5 mmol of **1a**, 1.2 equiv of allylic alcohols for the first step. Then, the reaction mixture was filtered, concentrated and subjected to second step with the use of 5 mol % CuBr and 1.5 equiv of LiBr. [b]Isolated yield.

We next turn our attention to a variety of allylic alcohols. The substituents on allylic alcohols greatly impacted on our reaction. The phenyl substitutent on the terminal of double bonds gave trace amount of corresponding oxazolines (Table 4 entry 1 and 2). Based on this result, we assumed that the phenyl substituent sterically inhibited the addition of bromine radical to the double bond, shutting down the intramolecular cyclization. In addition, having phenyl at the carbinol carbon was not suitable in our first step due to its high reactivity of corresponding imidate adduct. However, allylic alcohol with alkyl substituent at carbinol carbon gave the oxazoline in moderate yield with 4:1 diasteromeric ratio (Table 4, entry 3), suggesting that the steric at carbinol carbon was significantly vital to our reaction. Interestingly, when we subjected the hexa-1,5-dien-3-ol, the five-membered ring oxazoline was obstain in moderated yield with 3:1 dr.

4.2 One-pot synthesis of trisubstituted ureas

We initially conducted the reaction by optimizing reaction condition to obtain the highest yield of desired ureas. The reaction of *N*-(methylsulfonyloxy)benzimidoyl chloride (**1a**) and *N*-methylanine (**4a**) was selected as our model study (Table 5).

Table 5. The optimization reaction of *N*-(methylsulfonyloxy)benzimidoyl chloride (**1a**) and *N*-methylanine (**4a**)[a]



1a **4a** **5a**

entry	cat	base	solvent	temp	% yield[b]
1	DMAP	Cs_2CO_3	CH_2Cl_2	rt	86
2	DABCO	Cs_2CO_3	CH_2Cl_2	rt	21
3	Imidazole	Cs_2CO_3	CH_2Cl_2	rt	trace[c]
4	-	Cs_2CO_3	CH_2Cl_2	rt	trace[c]
5	DMAP	K_2CO_3	CH_2Cl_2	rt	60
6	DMAP	K_3PO_4	CH_2Cl_2	rt	43
7	DMAP	NEt_3	CH_2Cl_2	rt	13
8	DMAP	-	CH_2Cl_2	rt	trace[c]
9	DMAP	Cs_2CO_3	THF	rt	47
10	DMAP	Cs_2CO_3	DMSO	rt	20
11	DMAP	Cs_2CO_3	CH_2Cl_2	40 ^{o}C	58

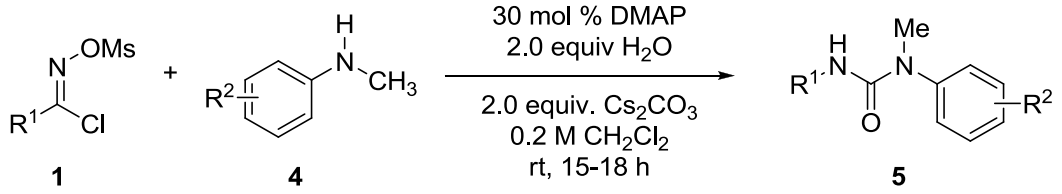
[a]Reaction conditions: all reactions were performed with 0.5 mmol of **1a**, 1.5 equiv. of **2a**, 2.0 equiv. of base and 2.5 mL of solvent, for 15−18 h. [b]Isolated yield. [c]From ^{1}H NMR spectrum of the crude reaction mixture.

The optimization was initially begun with the variety of nucleophilic catalysts, DMAP, DACO and imidazole. DMAP gave the best product yield at 86%. The catalyst was crucial in our catalysis, resulted from trace amount of product in the absence of catalyst (Table 5, entry 1-4). Cs_2CO_3 was a choice of bases in our transformation. We thought the key of selected base might be the solubility. However, when we changed to the soluble base NEt3, the reaction gave to low yield. Note that, base was required in our transformation (Table 5, entry 5-8). Next we aimed for the polarity of the solvent. As our choice of base was inorganic base, we expected that higher polarity would assist the reaction. However, when we changed to DMSO or THF, the yields of product from both bases were low and moderate respectively (Table 5, entry 9 and 10). Our last variation was the temperature. We conducted the reaction

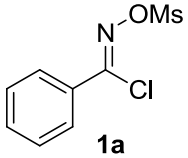
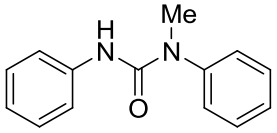
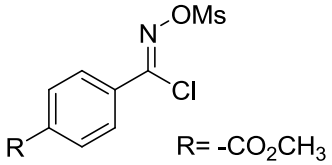
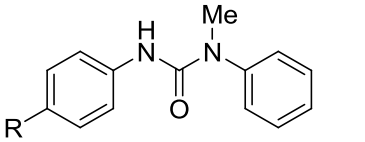
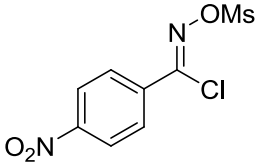
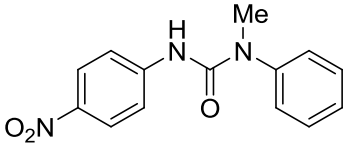
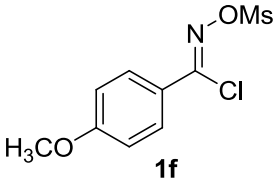
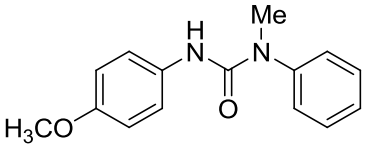
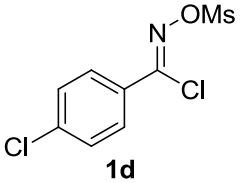
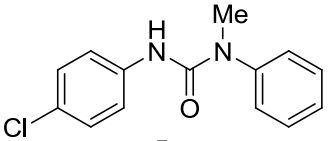
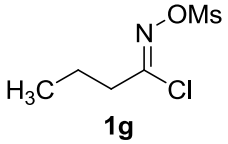
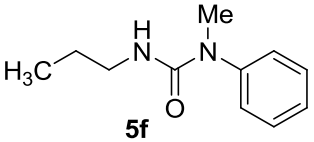
at 40 °C yielding the product in moderate yield, 58%. We also did vary the amount of the DMAP in which the use of 30 mol % of DMAP gave highest yield. Therefore our optimal reaction condition was the use of 30 mol% of DMAP as catalyst and Cs_2CO_3 as a base with 2.0 equivalence of H_2O in CH_2Cl_2 at room temperature for 15-18 hours.

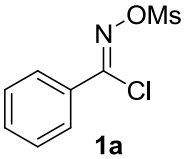
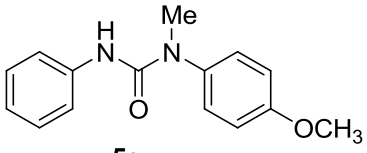
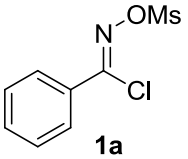
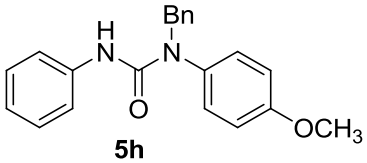
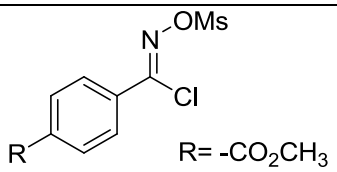
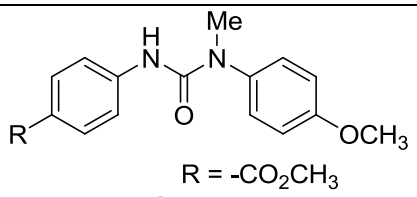
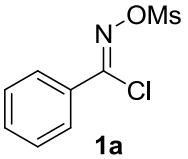
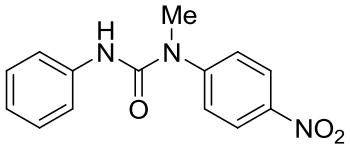
After the optimal condition was achieved, we then explored the scope of substrates for our transformation (Table 6).

Table 6. The formation of ureas from aniline and chloroaldoxime derivatives[a]



1 **4** **5**

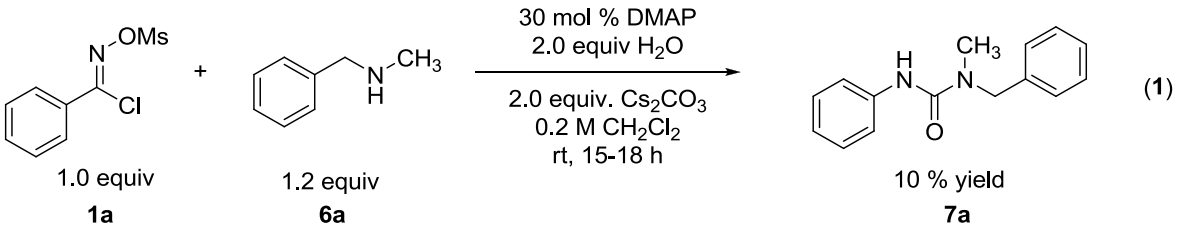
entry	chloroaldoximes	ureas	% yield[b]
1	 **1a**	 **5a**	86
2	 R= -CO_2CH_3 **1b**	 R= -CO_2CH_3 **5b**	95
3	 **1c**	 **5c**	92
4	 **1f**	 **5d**	NR[c]
5	 **1d**	 **5e**	74
6	 **1g**	 **5f**	47

7	 **1a**	 **5g**	72
8	 **1a**	 **5h**	61
9	 **1b**	 **5i**	72
10	 **1a**	 **5j**	NR[c]

[a]Reaction conditions: all reactions were performed with 0.5 mmol of α-chloroaldoxime *O*-methanesulfonates. [b]Isolated yield. [c]No reaction.

The electron density of the aryl substituent of chloroaldoxime played huge role in our catalysis. The chloroaldoximes with electron-withdrawing group substituents on the aryl ring gave high yields (Table 6, entry 2 and 3). On the contrast, the chloroaldoximes with electron-donating group substituent showed no reaction in our reaction (Table 6, entry 4). Interestingly, the α-chloroaldoxime *O*-methanesuldonate with para-chloro substituent on ary ring gave corresponding urea product in high yield, suggesting that the halogen substituted on aryl ring provided favorable electronic effect toward our reaction (Table 6, entry 5). Simple chloroaldoxime with alkyl substituent was also applicable in our transformation yielding moderate yield of urea product (Table 6, entry 6). Next we turned our interest to a variety of anilines. We found that anilines with electron-donating moiety gave high yield of corresponding ureas (Table 6, entry 7-9). Note that, benzyl protecting group of amine was also applicable in our reaction in which it would provide a variety of modification further in synthesis (Table 6, entry 8). On the other hand, the aniline with highly electron-withdrawing group (nitro group) was not aniline of choice in our reaction. It gave no reaction. Therefore, the electronic effect of aniline derivatives was also a crucial in our urea synthesis.

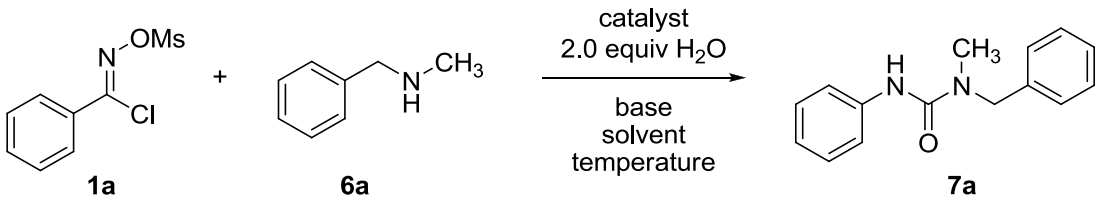
Next we turn our substrate scope to aliphatic amines. Unexpectedly, when *N*-methyl benzylamine was subjected to our standard reaction condition, the reaction gave corresponding urea in low product yield, 10% (reaction **1**).



(**1**)

The result suggested that nucleophilicity of aliphatic amine might be too reactive to our standard reaction condition since the chloroaldoxime was not observed in a ^{1}H-NMR of a crude reaction. In addition, according to a study of Yamamoto and co-workers showed that more equivalence of amines could generate the formation of guanidine structure. Therefore, we switched the used ratio of chloroaldoxime and amine. Satisfactorily, the yield of product urea was improved to 38%. This result gave us a light to improve the product yield. We subsequently further optimize reaction condition for the reaction of chloroaldoxime and aliphatic amine.

Table 7. Optimization of trisubstituted ureas from *N*-methylbenzylamine[a]



entry	cat.	base	solvent	temp.	% yield[b]
1	DMAP	Cs_2CO_3	0.2M CH_2Cl_2	rt	38
2	DMAP	K_2CO_3	0.2M CH_2Cl_2	rt	37
3	DMAP	K_2CO_3	0.5M CH_2Cl_2	rt	41
4	DMAP	K_2CO_3	0.5M THF	rt	40
5	DMAP	K_2CO_3	0.5M DMSO	rt	41
6	DMAP	K_2CO_3	0.5M DMSO	40 ^{o}C	69
7	DMAP	K_2CO_3	0.5M THF	40 ^{o}C	58
8	TMEDA	K_2CO_3	0.5M DMSO	40 ^{o}C	74
9	-	K_2CO_3	0.5M DMSO	40 ^{o}C	65

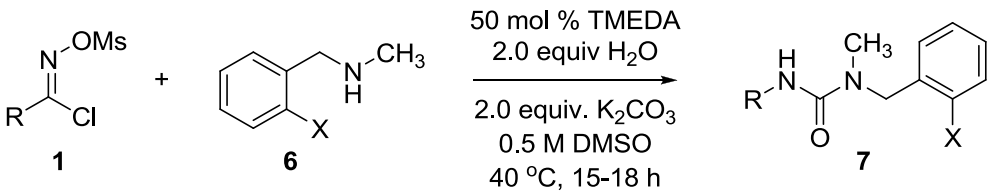
[a]Reaction conditions: all reactions were performed with 0.5 mmol of *N*-methylbenzylamine, 1.2 equiv. of **1a**, 2.0 equiv. of base and 50 mol % of catalyst for 15−18 h . [b]Isolated yield.

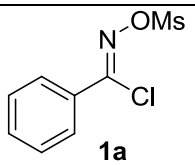
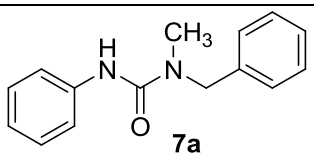
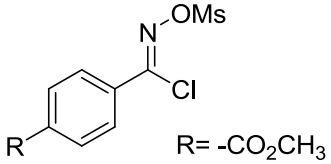
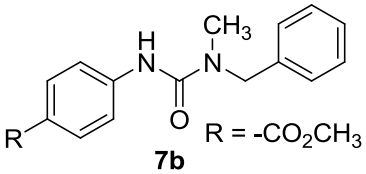
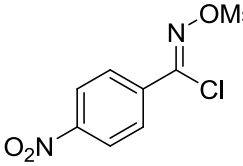
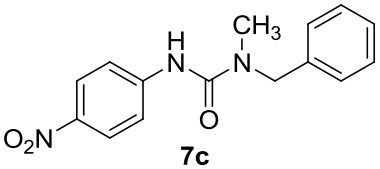
The catalyst loading was investigated in which the use of 50 mol % of catalyst gave the best yield. The use of K_2CO_3 or Cs_2CO_3 as a base, both gave comparable yield. We

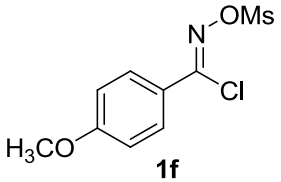
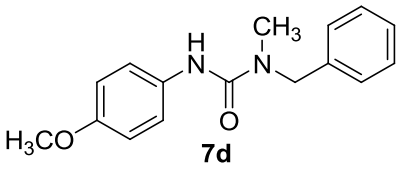
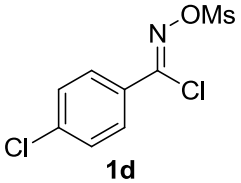
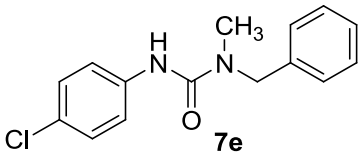
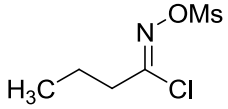
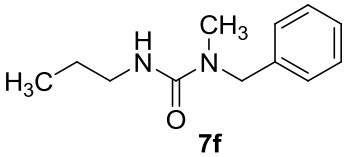
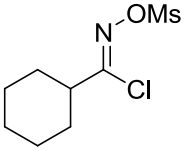
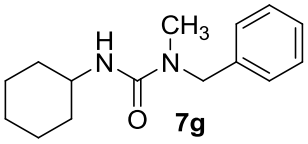
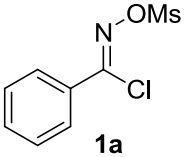
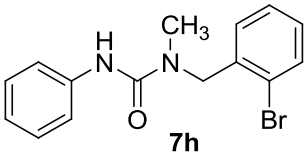
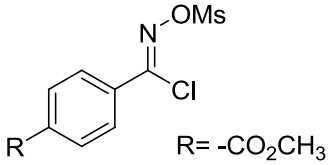
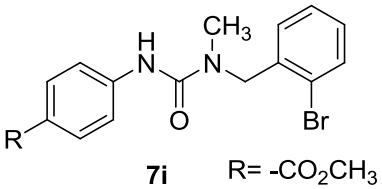
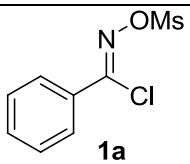
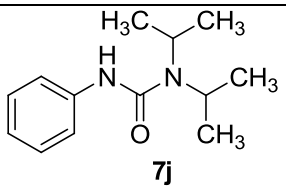
selected K_2CO_3 as our optimal base due to commonness (Table 7, entry 1 and 2). The reaction concentration was increased to 0.5 M resulting yield slightly increased to 41%. Higher polar solvents were had no effect on our reaction. However, we decided to select higher polar solvents because they would allow us to increase temperature of our reaction (Table 7, entry 4 and 5). Changing reaction temperature to 40 ^{o}C, the product yields of both THF and DMSO were increased to 58% and 69% respectively (Table 7, entry 6 and 7). Further increasing temperature did not provide higher product yield. Yamamoto and co-workers have been reported the used of TMEDA as catalyst which catalysed the similar reactions. By changing DMAP to TMEDA, the product yield was slightly increased to 74%. The amount of TMEDA was explored in which the use of 20 mol % and 100 mol % of TMEDA gave 48% and 63% of product yields respectively. Interestingly, the reaction without any catalyst gave slightly good yield, 65% (Table 7, entry 9). This result suggested that the nucleophilic catalyst, DMAP, cased undesired reaction in our urea synthesis from aliphatic amines. In addition, TMEDA provided the optimal condition for our reaction.

In our urea synthesis from aliphatic amines, the use of 50 mol % of TMEDA, 1.2 equivalent of chloroaldoxime and 2.0 equivalent of K_2CO_3 in 0.5 M of DMSO at 40 ^{o}C for 15-18 hours was optimal reaction condition. Therefore, the substrate scope was performed under optimal conditions (Table 8).

Table 8. The synthesis of ureas from aliphatic amines[a]



entry	chloroaldoxime	urea	% yield[b]
1	 **1a**	 **7a**	74
2	 **1b**	 **7b**	86
3	 **1c**	 **7c**	84

4	 **1f**	 **7d**	76
5	 **1d**	 **7e**	72
6	 **1g**	 **7f**	69
7	 **1h**	 **7g**	44
8	 **1a**	 **7h**	80
9	 **1b**	 **7i**	74
10	 **1a**	 **7j**	25

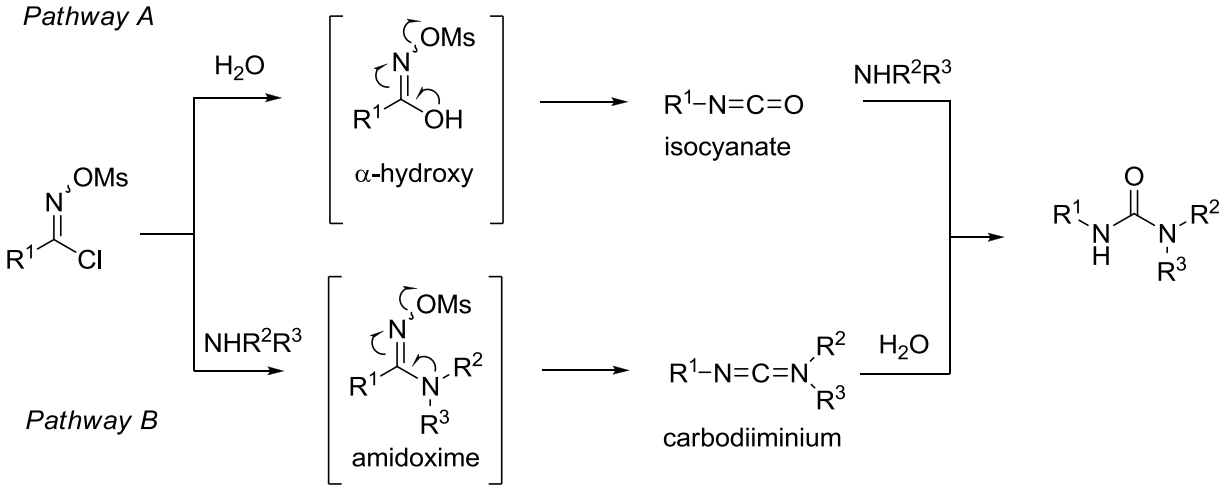
[a]Reaction conditions: all reactions were performed with 0.5 mmol of *N*-methylbenzylamines. [b]Isolated yield.

Unlike aromatic amines, aliphatic amines were applicable in our urea synthesis with a wide range of α-chloroaldoxime *O*-methanesulfonates. In this case, aryl substitutes bearing both electron withdrawing and donating groups gave high yields (Table 8, entries 1-5). Chloroaldoxime with aliphatic substituent also gave high yield (Table 8, entry 6). Similar to Yamamoto's report, we found that the yield diminished when more steric substituent was introduced (Table 8, entry 7). The *N*-methy-2-bromobenzylamine was subjected to our reaction and gave corresponding ureas in good yield (Table 8, entries 8 and 9). The product ureas are good substrate for intramolecular Ullmann type coupling which allows us to apply for six-membered urea ring synthesis. When the more sterically hindered amine (*N,N*-

diisopropylamine) was subjected to the reaction, the product yield was dramatically decreased to 25% (Table 8, entry 10). The result suggested that the steric of the nucleophile impacted to the yield of the ureas.

An attempt to identify reaction mechanism, we were failed to monitor the reaction by ^{1}H NMR technique because the intermediate signals were ambiguously identified from the ^{1}H NMR spectrum of the reaction mixture. Based on studies from Truce, Rajagopalan, Yamamoto, and also our findings, we proposed two highly possible reaction pathways (Scheme 3).

Scheme 3. Possible mechanisms of urea formation



The first pathway was a generation of isocyanate, followed by an addition of secondary amine to give a corresponding urea. The isocyanate was possibly derived from nucleophilic substitution of α-chloroaldoxime *O*-methanesulfonates with water (Scheme 3, Pathway A). The second pathway was involved the generation of carbodiiminium intermediate, derived from the Tiemann rearrangement of amidoxime intermediate. Subsequently, the addition of water to carbodiimium was occurred to obtain a desire urea (Scheme 3, Pathway B). The role of essential DMAP was possibly a nucleophilic catalyst to generate the reactive intermediate in the formation of trisubstituted ureas from secondary aromatic amines.

5. Experimetal

This section is divided to three parts. The first is preparation of the starting materials, α-chloroaldoxime O-methanesulfonates. The second part is the oxazoline synthesis. The last section is the trisubstituted urea synthesis. All of commercially available reagents and reaction solvents were used without any further purification. Solvents for extraction and column chromatography were purified by distillation at their boiling point ranges prior to use.

Thin-layer chromatography (TLC) was performed on silica gel 60 GF_{254} (Merck) and was visualized by fluorescene quenching under UV light. Column chromatography was performed on SilicaFlash® G60 (70-230 Mesh). ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) were recorded on a 300 MHz Bruker FTNMR Ultra Shield spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts are expressed in parts per million (ppm) downfield from TMS (δ 0.00) and coupling constants are reported as Hertz (Hz). Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; m, multiplet. Infrared spectra (IR) were measured on Perkin Elmer Spectrum GX FT-IR system and recorded on wave number (cm^{-1}).

5.1 The preparation of α-chloroaldoxime O-methanesulfonates

***N*-((Methylsulfonyl)oxy)benzimidoyl chloride (1a).** Prepared according to literature procedure.[10a] A dried round bottom flask was charge with 1.0 equiv of benzaldoxime in the mixture of 0.5 M of THF and $CHCl_3$ (1:1 ratio), followed by the portion addition of 1.5 equiv of *N*-chlorosuccinamide (NCS). After the addition was completed, the temperature of reaction was increased to 40 °C. After an hour, the reaction was quenched with water and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was dissolved in EtOAc. The resulting solution was cooled to 0 °C before the slow addition of 2.2 equiv of triethylamine. The reaction mixture was stirred for 10 min. Then, 1.1 equiv of chloromethanesulfonate was added dropwise at 0 °C. After completion of addition, the mixture was allowed to warm to room temperature and stirred for an hour, followed by filtration. The filtrate was washed with water. The organic layer was dried over anhydrous Na_2SO_4, filtrated and concentrated under reduced pressure. The crude mixture was purified by column chromatography (2:1 hexanes:CH_2Cl_2) to afford **1a** as white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.4 Hz, 2H), 7.61—7.56 (m, 1H), 7.51—7.46 (m, 2H), 3.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.1, 132.7, 130.4, 128.8, 128.1, 37.0.

Methyl-4-(chloro(((methylsulfonyl)oxy)imino)methyl) benzoate (1b). Prepared according to the procedure described for **1a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.7 Hz, 2H), 8.01 (d, *J* = 8.7 Hz, 2H), 3.97 (s, 3H), 3.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 148.1, 134.2, 133.7, 129.9, 128.1, 52.6, 37.1.

***N*-((Methylsulfonyl)oxy)-4-nitrobenzimidoyl chloride (1c).** Prepared according to the procedure described for **1a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (d, *J* = 8.7 Hz, 2H),

8.16 (d, *J* = 8.7 Hz, 2H), 3.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.1, 146.8, 136.0, 129.2, 123.9, 37.2

4-Methoxy-*N*-((methylsulfonyl)oxy)benzimidoyl chloride (1f). Prepared according to the procedure described for **1a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.7 Hz, 2H), 6.95 (d, *J* = 8.7 Hz, 2H), 3.88 (s, 3H), 3.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 148.8, 129.9, 122.5, 114.2, 55.6, 36.9.

4-Chloro-*N*-((methylsulfonyl)oxy)benzimidoyl chloride (1d). Prepared according to the procedure described for **1a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.7 Hz, 2H), 7.46 (d, *J* = 8.7 Hz, 2H), 3.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.0, 139.2, 129.3, 129.2, 37.1.

***N*-((Methylsulfonyl)oxy)butyrimidoyl chloride (1g).** Prepared according to the procedure described for **1a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.16 (s, 3H), 2.60 (t, *J* = 7.2 Hz, 2H), 1.69—1.77 (m, 2H), 0.96 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.2, 38.6, 36.7, 19.5, 12.9.

***N*-((Methylsulfonyl)oxy)cyclohexanecarbimidoyl chloride (1h).** Prepared according to the procedure described for **1a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.17 (s, 3H), 2.66—2.59 (m, 1H), 2.03—1.69 (m, 5H), 1.56—1.34 (m, 2H), 1.29—1.19 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.1, 45.7, 30.0, 25.4, 25.3.

5.2 Synthesis of Oxazoline Derivative from α-Chloroaldoxime O-Methanesulfonates

The reaction of *N*-((methylsulfonyl)oxy)benzimidoyl chloride (**1a**) and allyl alcohol is a representative: To a dried 10 mL round bottom flask equipped with a magnetic stirring bar was charged with *N*-((methylsulfonyl)oxy)benzimidoyl chloride (0.5 mmol), *N,N*-dimethylaminopyridine (DMAP) (0.15 mmol), K_2CO_3 (1.0 mmol) and allyl alcohol (0.75 mmol) in CH_2Cl_2 (2.5 mL). The reaction mixture was stirred at room temperature for 15-18 hours. After that, the reaction mixture was filtered though a plug silica, eluted with 1:1 ratio of EtOAc:CH_2Cl_2. The filtrate was concentrated under vacuum to give the crude reaction mixture. To a dried round bottom flask equipped with the crude reaction mixture was added the CuBr (0.025 mmol), LiBr (0.75 mmol) and CAN (2.5 mL). The resulting mixture was sealed, heated at 90 ^{o}C and stirred for 6 hours. After completion of reaction, the reaction mixture was quenched with sat. NH_4Cl and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The crude mixture was purified by column chromatography to afford oxazoline X in 74% yield.

4-(bromomethyl)-2-phenyl-4,5-dihydrooxazole (3a). 74% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95—7.97 (m, 2H), 7.28—7.54 (m, 3H), 4.62—4.67 (m, 1H), 4.51—4.57 (m, 1H), 4.39—4.40

(m, 1H), 3.70 (dd, J = 3.6 and 10.2 Hz, 1H), 3.48 (dd, J = 7.8 and 10.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 131.8, 128.4, 71.7, 67.2, 35.5.

4-(bromomethyl)-2-(4-nitrophenyl)-4,5-dihydrooxazole (3c). 82% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22—8.25 (m, 2H), 8.01—8.10 (m, 2H), 4.66—4.72 (m, 1H), 4.54—4.57 (m, 1H), 4.36—4.41 (m, 1H), 3.66 (dd, J = 3.6 and 10.5 Hz, 1H), 3.48 (dd, J = 6.9 and 10.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7, 149.7, 133.0, 129.5, 123.6, 72.1, 67.37, 35.3.

methyl 4-(4-(bromomethyl)-4,5-dihydrooxazol-2-yl)benzoate (3b). 86% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, J = 8.4 Hz, 2H), 8.02 (d, J = 8.4 Hz, 2H), 4.65—4.71 (m, 1H), 4.54—4.60 (m, 1H), 4.36—4.42 (m, 1H), 3.95 (s, 3H), 3.70 (dd, J = 3.6 and 10.2 Hz, 1H), 3.46 (dd, J = 7.5 and 10.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 164.8, 132.9, 131.2, 129.6, 128.4, 71.9, 67.4, 52.4, 35.3, 29.7.

4-(bromomethyl)-2-(4-chlorophenyl)-4,5-dihydrooxazole (3d). 79% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 4.60—4.67 (m, 1H), 4.49—4.55 (m, 1H), 4.31—4.37 (m, 1H), 3.66 (dd, J = 3.6 and 10.2 Hz, 1 H), 3.42 (dd, J = 7.8 and 10.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.7, 138.0, 129.8, 128.7, 125.7, 71.8, 67.2, 35.5.

4-(bromomethyl)-2-(4-bromophenyl)-4,5-dihydrooxazole (3e). 72% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, J = 8.2 Hz, 2H), 7.56 (d, J = 8.2 Hz, 2H), 4.61—4.70 (m, 1H), 4.51—4.58 (m, 1H), 4.32—4.40 (m, 1H), 3.72 (dd, J = 3.6 and 10.2 Hz, 1 H), 3.45 (dd, J = 7.8 and 10.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.9, 149.8, 132.8, 129.6, 123.6, 72.2, 67.2, 35.2.

4-(bromomethyl)-5-methyl-2-phenyl-4,5-dihydrooxazole (3j). 46% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93—7.96 (m, 2H), 7.27—7.50 (m, 3H), 4.66—4.70 (m, 1H), 4.11—4.14 (m, 1H), 3.69 (dd, J = 3.6 and 10.2 Hz), 3.34 (dd, J = 9.0 and 10.2 Hz), 1.48 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 131.0, 128.8, 128.1, 127.1, 72.8, 64.2, 35.5, 23.2.

5-allyl-4-(bromomethyl)-2-phenyl-4,5-dihydrooxazole (3k). 40% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, J = 7.2 Hz, 2H), 7.40—7.53 (m, 3H), 5.80—5.88 (m, 1H), 5.16—5.24 (m, 2H), 4.62—4.67 (m, 1H), 4.21—4.26 (m, 1H), 3.64 (dd, J = 3.6 and 10.2 Hz), 3.39 (dd, J = 8.4 and 10.2 Hz), 2.50—2.54 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 138.0, 136.1, 131.1, 128.8, 128.1, 127.0, 116.3, 71.2, 69.1, 39.2, 35.6.

5.3 Synthesis of Trisubstituted ureas

5.3.1 General Procedure A: For the Reaction of Aniline Derivatives

The reaction of *N*-((methylsulfonyl)oxy)benzimidoyl chloride (**1a**) and *N*-methylaniline is representative: A dried 10 mL round bottom flask equipped with a magnetic stirring bar was charged with *N*-((methylsulfonyl)oxy)benzimidoyl chloride (**1a**) (0.5 mmol), *N*-methylaniline (0.75 mmol), *N,N*-dimethylaminopyridine (DMAP) (0.15 mmol), water (1.0 mmol) and Cs_2CO_3 (1.0 mmol) in CH_2Cl_2 (2.5 mL). The reaction mixture was stirred at room temperature for 15-20 h. After completion of reaction, the reaction mixture was quenched with sat. NH_4Cl and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The crude mixture was purified by column chromatography (5:1 hexanes:EtOAc) to afford **5a** in 97.29 mg (86% yield).

1-Methyl-1,3-diphenylurea (5a). Yield 97.29 mg (86%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38—7.36 (m, 2H), 7.34—7.21 (m, 5H), 7.01 (d, *J* = 7.2 Hz, 1H), 6.30 (brs, 1H), 3.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 143.0, 138.9, 130.3, 128.8, 127.8, 127.4, 122.9, 119.3, 37.3.

Methyl-4-(3-methyl-3-phenylureido)benzoate (5b). Prepared according to general procedure A from methyl-4-(chloro(((methylsulfonyl)oxy)imino)methyl)benzoate **(1b)** and *N*-methylaniline. Yield 135.04 mg (95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, J = 8.7 Hz, 2H), 7.45—7.40 (m, 2H), 7.34—7.25 (m, 5H), 6.56 (brs, 1H), 3.78 (s, 3H), 3.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 153.8, 143.4, 142.4, 130.6, 130.4, 128.1, 127.3, 124.0, 117.9, 51.8, 37.4.

1-Methyl-3-(4-nitrophenyl)-1-phenylurea (5c). Prepared according to general procedure A from *N*-((methylsulfonyl)oxy)-4-nitrobenzimidoyl chloride **(1c)** and *N*-methylaniline. Yield 124.78 mg (92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.8 Hz, 2H), 7.55—7.40 (m, 5H), 7.35 (d, *J* = 7.8 Hz, 2H), 6.67 (brs, 1H), 3.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.4, 145.0, 142.4, 142.1, 130.1, 128.5, 127.4, 125.0, 118.0, 37.5.

3-(4-Chlorophenyl)-1-methyl-1-phenylurea (5e). Prepared according to general procedure A from 4-chloro-*N*-((methylsulfonyl)oxy)benzimidoyl chloride **(1d)** and *N*-methylaniline. Yield 96.47 mg (74%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50—7.47 (m, 2H), 7.39—7.29 (m, 3H), 7.23 (d, *J* = 8.7 Hz, 2H), 7.15 (d, *J* = 8.7 Hz, 2H), 6.34 (brs, 1H), 3.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 142.6, 137.6, 130.4, 128.7, 128.0, 127.4, 120.5, 37.3.

1-Methyl-1-phenyl-3-propylurea (5f). Prepared according to general procedure A from *N*-((methylsulfonyl)oxy)butyrimidoyl chloride **(1g)** and *N*-methylaniline. Yield 45.20 mg (47%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45—7.40 (m, 2H), 7.33—7.24 (m, 3H), 4.27 (brs, 1H), 3.27 (s, 3H), 3.14 (q, *J* = 6.9 Hz, 2H), 1.49—1.36 (m, 2H), 0.83 (t, *J* = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 143.5, 130.0, 127.3, 127.2, 42.4, 37.1, 23.3, 11.2.

1-(4-Methoxyphenyl)-1-methyl-3-phenylurea (5g). Prepared according to general procedure A from *N*-((methylsulfonyl)oxy)benzimidoyl chloride (**1a**) and 4-methoxy-*N*-methylaniline. Yield 92.27 mg (72%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28—7.16 (m, 6H), 7.00—6.96 (m, 3H), 6.26 (brs, 1H), 3.85 (s, 3H), 3.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 154.8, 139.0, 135.3, 128.9, 128.8, 122.8, 119.2, 115.5, 55.6, 37.4.

1-Benzyl-1-(4-methoxyphenyl)-3-phenylurea (5h). Prepared according to general procedure A from *N*-((methylsulfonyl)oxy)benzimidoyl chloride (**1a**) and *N*-benzyl-4-methoxyaniline. Yield 101.38 mg (61%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34—7.7.22 (m, 10H), 7.06 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 6.25 (brs, 1H), 4.90 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 154.7, 139.0, 138.4, 133.4, 130.1, 128.8, 128.7, 128.4, 127.3, 122.9, 119.3, 115.3, 55.5, 53.3.

Methyl 4-(3-benzyl-3-(4-methoxyphenyl)ureido)benzoate (5i). Prepared according to general procedure A from methyl-4-(chloro(((methylsulfonyl)oxy)imino)methyl)benzoate **(1b)** and *N*-benzyl-4-methoxyaniline. Yield 140.55 mg (72%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.7 Hz, 2H), 7.40 (d, *J* = 8.7 Hz, 2H), 7.30—7.28 (m, 5H), 7.05 (d, *J* = 9.0 Hz, 2H), 6.91 (d, *J* = 9.0 Hz, 2H), 6.44 (brs, 1H), 4.90 (s, 2H), 3.87 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 159.5, 154.1, 143.3, 137.9, 132.9, 130.7, 130.0, 128.7, 128.4, 127.4, 124.1, 117.9, 115.4, 55.5, 53.4, 51.8.

General Procedure B: For the Reaction of *N*-Benzylamine Derivatives

The reaction of *N*-((methylsulfonyl)oxy)benzimidoyl chloride (**1a**) and *N*-methylbenzylamine is representative: A dried 10 mL round bottom flask equipped with a magnetic stirring bar was charged with *N*-((methylsulfonyl)oxy)benzimidoyl chloride (**1a**) (0.75 mmol), *N*-methylbenzylaniline (0.50 mmol), *N,N,N',N'*-tetramethylethylenediamine (TMEDA) (0.25 mmol), water (1.0 mmol) and K_2CO_3 (1.0 mmol) in DMSO (1.5 mL). The reaction mixture was warmed to 40 ^{o}C and stirred for 15-18 h. After completion of reaction, the reaction mixture was quenched with sat. NH_4Cl and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The crude mixture was purified by column chromatography (5:5:1 hexanes:CH_2Cl_2:EtOAc) to afford **7a** in 88.91 mg (74% yield).

1-Benzyl-1-methyl-3-phenylurea (7a). Yield 88.91 mg (74%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36—7.15 (m, 8H), 7.06—7.02 (m, 2H), 6.64 (brs, 1H), 4.59 (s, 2H), 3.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 139.1, 137.5, 128.9, 128.8, 128.7, 127.6, 127.3, 123.1, 122.3, 120.2, 119.2, 52.3, 34.8.

Methyl 4-(3-benzyl-3-methylureido)benzoate (7b). Prepared according to general procedure B from methyl-4-(chloro(((methylsulfonyl)oxy)imino)methyl)benzoate **(1b)** and *N*-

methylbenzylamine. Yield 128.29 mg (86%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.89 (d, *J* = 8.7 Hz, 2H), 7.44 (d, *J* = 8.7 Hz, 2H), 7.33—7.22 (m, 5H), 7.77 (brs, 1H), 4.54 (s, 2H), 3.84 (s, 3H), 2.98 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0, 155.3, 143.9, 137.1, 130.6, 128.9, 127.6, 127.3, 124.0, 118.7, 52.3, 51.9, 34.8.

1-Benzyl-1-methyl-3-(4-nitrophenyl)urea (7c). Prepared according to general procedure B from *N*-((methylsulfonyl)oxy)-4-nitrobenzimidoyl chloride **(1c)** and *N*-methylbenzylamine. Yield 119.83 mg (84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, J = 9.0 Hz, 2H), 7.54 (d, *J* = 9.0 Hz, 2H), 7.41—7.28 (m, 5H), 6.98 (brs, 1H), 4.61 (s, 2H), 3.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.7, 145.5, 142.4, 136.7, 127.9,127.2, 125.0, 118.5, 52.5, 35.0.

1-Benzyl-3-(4-methoxyphenyl)-1-methylurea (7d). Prepared according to general procedure B from 4-methoxy-*N*-((methylsulfonyl)oxy)benzimidoyl chloride **(1f)** and *N*-methylbenzylamine. Yield 102.73 mg (76%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37—7.24 (m, 7H), 6.82 (d, *J* = 9.0 Hz, 2H), 6.44 (brs, 1H), 4.57 (s, 2H), 3.78 (s, 3H), 2.99 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.3, 155.8, 137.7, 132.2, 128.8, 127.5, 127.3, 127.2, 122.4, 114.0, 55.5, 52.3, 34.7.

1-Benzyl-3-(4-chlorophenyl)-1-methylurea (7e). Prepared according to general procedure B from 4-chloro-*N*-((methylsulfonyl)oxy)benzimidoyl chloride **(1d)** and *N*-methylbenzylamine. Yield 98.91 mg (72%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35—7.28 (m, 7H), 7.24—7.20 (m, 2H), 6.53 (brs, 1H), 4.58 (s, 2H), 3.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 137.8, 137.3, 128.9, 128.7, 128.0, 127.7, 127.3, 121.3, 52.4, 34.8.

1-Benzyl-1-methyl-3-propylurea (7f). Prepared according to general procedure B from *N*-((methylsulfonyl)oxy)butyrimidoyl chloride **(1g)** and *N*-methylbenzylamine. Yield 71.17 mg (69%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33—7.28 (m, 3H), 7.24—7.19 (m, 2H), 4.61 (brs, 1H), 4.46 (s, 2H), 3.16 (q, *J* = 6.9 Hz, 2H), 2.84 (s, 3H), 1.51—1.41 (m, 2H), 0.85 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6, 138.0, 128.6, 127.2, 127.1, 52.1, 42.7, 34.3, 23.5, 11.3.

1-Benzyl-3-cyclohexyl-1-methylurea (7g). Prepared according to general procedure B from *N*-((methylsulfonyl)oxy)cyclohexanecarbimidoyl chloride **(1h)** and *N*-methylbenzylamine. Yield 54.20 mg (44%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35—7.22 (m, 5H), 4.48 (s, 2H), 4.29 (brs, 1H), 3.69—3.64 (m, 1H), 2.86 (s, 3H), 1.94—1.90 (m, 2H), 1.69—1.57 (m, 4H), 1.41—1.26 (m, 2H), 1.18—1.10 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7, 138.1, 128.6, 127.3, 52.2, 49.4, 34.3, 34.1, 33.9, 25.6, 25.0.

1-(2-Bromobenzyl)-1-methyl-3-phenylurea (7h). Prepared according to general procedure B from *N*-((methylsulfonyl)oxy)benzimidoyl chloride (**1a**) and 1-(2-bromophenyl)-*N*-methylmethanamine. Yield 127.68 mg (80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.1

Hz, 1H), 7.40—7.32 (m, 6H), 7.22-7.19 (m, 1H), 7.08—7.05 (m, 1H), 6.38 (brs, 1H), 4.70 (s, 2H), 3.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.7, 138.9, 136.2, 133.1, 129.1, 128.9, 128.0, 123.2, 123.1, 120.0, 52.6, 35.1.

Methyl-4-(3-(2-bromobenzyl)-3-methylureido)benzoate (7i). Prepared according to general procedure B from methyl-4-(chloro(((methylsulfonyl)oxy)imino)methyl)benzoate **(1b)** and 1-(2-bromophenyl)-*N*-methylmethanamine. Yield 139.58 mg (74%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.7 Hz, 2H), 7.54 (d, *J* = 8.1 Hz, 1H), 7.45 (d, *J* = 8.7 Hz, 2H), 7.28—7.20 (m, 2H), 7.15—7.10 (m, 1H), 4.62 (s, 2H), 3.84 (s, 3H), 3.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 155.3, 143.7, 135.9, 133.1, 130.6, 129.1, 128.2, 127.9, 124.1, 123.1, 118.7, 52.6, 52.0, 35.1.

1,1-Diisopropyl-3-phenylurea (7j). Prepared according to general procedure B from *N*-((methylsulfonyl)oxy)benzimidoyl chloride (**1a**) and diisopropylamine. Yield 27.54 mg (25%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40—7.37 (m, 2H), 7.31—7.25 (m, 2H), 7.04—7.00 (m, 1H), 6.25 (brs, 1H), 4.04—3.95 (m, 2H), 1.33 (d, *J* = 6.9 Hz, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.7, 139.3, 128.8, 128.7, 122.7, 119.8, 119.2, 45.8, 21.5.

6. Conclusion

We have accomplished to utilize the α-chloroaldoxime *O*-methanesulfonate in our reactions via two modes, and both of our catalysis designs were carried out under mild and environmental friendly reaction conditions. The first was the di-electrophile intermediate in the generation of oxazolines. Although the α-chloroaldoxime *O*-methanesulfonates with electron-donating group on aryl ring could not undergo our reaction, this methodology allowed us to access a variety of 2-bromooxazolines. The 2-bromooxazoline could be further modified to provide a variety of oxazolines. The second was the Tiemann rearrangement to provide ureas. We have provided two practical protocols in synthesis of trisubstituted ureas from both aliphatic and aromatic secondary amines. Despite of ambiguously proposed mechanisms, the result gave us a clue to further understanding behaviors of α-chloroaldoxime *O*-methanesulfonates. This would give us a light to modify the reaction condition to utilize the mode of α-chloroaldoxime *O*-methanesulfonate reactivities.

7. Appendix

RSC Advances

PAPER

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One-pot synthesis of trisubstituted ureas from α-chloroaldoxime *O*-methanesulfonates and secondary amines†

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Trisubstituted ureas can be synthesized in a one-pot fashion from bench-stable α-chloroaldoxime *O*-methanesulfonates and secondary amines under mild reaction conditions. Two practical protocols have been developed to achieve various urea syntheses from both secondary aromatic amines and aliphatic amines.

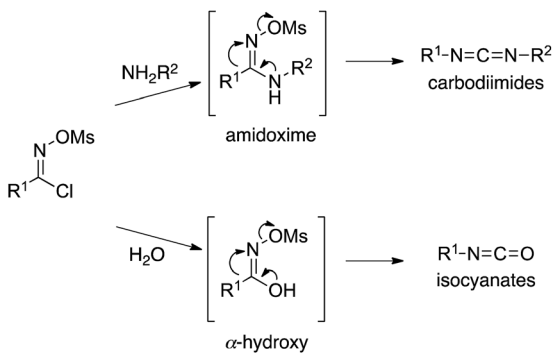
Introduction

Trisubstituted and disubstituted urea moieties comprise one of the most important groups in organic molecules due to their biological activities and importance as components in drug candidates.[1] Furthermore, ureas have been used as organic catalysts[2] and have many applications in material sciences.[3] Typically, urea derivatives have been efficiently synthesized *via* the condensation of amines with the corresponding isocyanates or from the reaction of amines and phosgene.[4] Due to the limited number of commercially available isocyanates and the toxicities of the phosgene, alternative environmentally friendly methodologies to construct the urea core structures have been explored. One of the most attractive methods in symmetrical and asymmetrical urea synthesis was the reaction of carbamic acid derivatives,[5] which are particularly stable under a variety of reaction conditions and inert toward nucleophilic reagents such as, amines. Furthermore, several methodologies have been developed to obtain a variety of isocyanates[6] for asymmetric urea syntheses: the Curtius rearrangement,[7] Hoffmann rearrangement[8] and Lossen rearrangement.[9] However, some of those methodologies required the use of strong bases and metals. Alternatively, we have been inspired by the work of Yamamoto and co-workers in the chemistry of α-chloroaldoxime *O*-methanesulfonates[10] in which this molecule could undergo Tiemann rearrangement[11] to provide versatile carbodiimide intermediates[12] in the presence of primary amines (Scheme 1). Furthermore, this compound was found to be stable and stored at ambient temperature without any precautions. We envisioned that α-chloroaldoxime *O*-methanesulfonates could alternatively generate isocyanates *via* the rearrangement in the presence of water, allowing us to introduce other amines to achieve asymmetrical ureas. Herein, we reported a straightforward approach in the synthesis of trisubstituted ureas from α-chloroaldoxime *O*-methanesulfonates and secondary amines *via* one-pot reaction involving *in situ* generation of the postulated isocyanates under mild reaction conditions.

Results and discussion

Our investigation initially began with the optimization of the reaction conditions. The reaction of α-chloroaldoxime *O*-methanesulfonate **1a** and *N*-methylaniline was selected as a model study (Table 1).

The loading amount of DMAP also was investigated. The 30 mol% of DMAP was vital in our reaction to drive the reaction to completion, and the reaction gave 86% of desired urea. Other common nucleophilic catalysts such as DABCO and imidazole were subjected to the reaction conditions. The reaction with DABCO as the catalyst gave 21% yield (entry 2). On the other



Scheme 1 Rearrangement of α-chloroaldoxime *O*-methanesulfonates.

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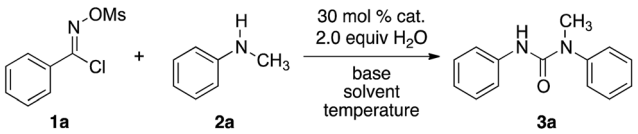
† Electronic supplementary information (ESI) available: This material includes ^{1}H and ^{13}C NMR spectra for all of new compounds. See DOI: 10.1039/c5ra10060g

Table 1 The optimization reaction of α-chloroaldoxime *O*-methanesulfonate (**1a**) and *N*-methylaniline[a]



Entry	Cat.	Bases	Solvent	Temp.	Yield[b]
1	DMAP	Cs_2CO_3	CH_2Cl_2	rt	86
2	DABCO	Cs_2CO_3	CH_2Cl_2	rt	21
3	Imidazole	Cs_2CO_3	CH_2Cl_2	rt	Trace[c]
4	—	Cs_2CO_3	CH_2Cl_2	rt	Trace[c]
5	DMAP	K_2CO_3	CH_2Cl_2	rt	60
6	DMAP	K_3PO_4	CH_2Cl_2	rt	43
7	DMAP	NEt_3	CH_2Cl_2	rt	13
8	DMAP	—	CH_2Cl_2	rt	Trace[c]
9	DMAP	Cs_2CO_3	THF	rt	47
10	DMAP	Cs_2CO_3	DMSO	rt	20
11	DMAP	Cs_2CO_3	CH_2Cl_2	40 °C	58

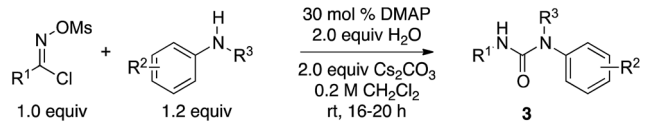
[a] Reaction conditions: all reactions were performed with 0.5 mmol of **1a**, 1.5 equiv. of **2a**, 2.0 equiv. of base and 2.5 mL of solvent, for 15–18 h. [b] Isolated yield. [c] From ^{1}H NMR spectrum of the crude reaction mixture.

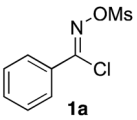
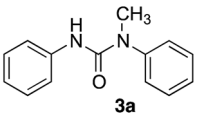
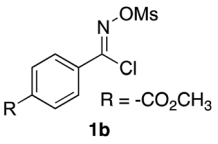
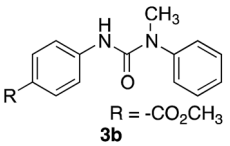
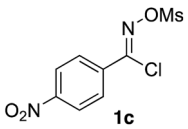
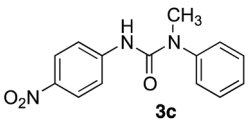
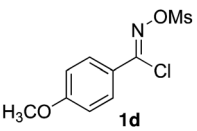
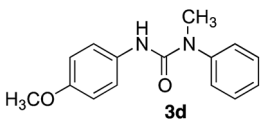
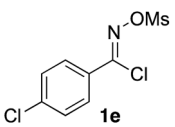
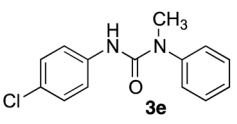
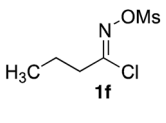
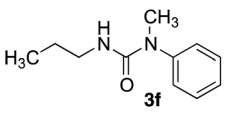
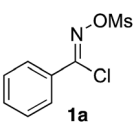
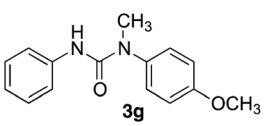
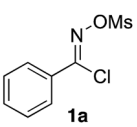
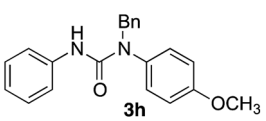
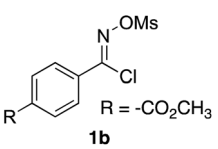
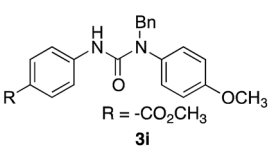
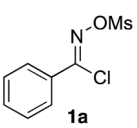
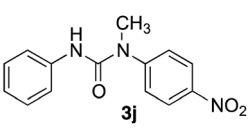
hand, imidazole gave only trace amount of urea product (entry 3). The control experiment with no catalyst was also performed. As we expected, with no catalyst the reaction gave trace amount of urea (entry 4). The reaction was carried out with a variety of bases. In this transformation Cs_2CO_3 gave the highest product yield (entries 1, 5 and 6). We initially believed that the solubility of the inorganic base in organic solvent played an important role in the reaction. But with amine base, the reaction also gave urea in low yield (entry 7). Note that, the presence of base was crucial in our reaction, the reaction without base gave trace amount of desired urea (entry 8). We then turned our attention to the effect of solvent polarity (entries 9 and 10). THF and DMSO were subjected to the optimization. Both gave lower product yields, especially DMSO, despite that **1a** was completely consumed. The result suggested that undesired side-reaction was pronounced in high polar solvent. Elevation of reaction temperature also triggered undesired reaction pathways, reaching 58% yield from 100% conversion of the reactant (entry 11).

After having established optimal reaction conditions, we next explored the scope of substrates in our urea formations. Unsubstituted aryl α-chloroaldoxime *O*-methanesulfonates gave good yield of urea with *N*-methyl anilines (entry 1). The aryl groups bearing electron-withdrawing substituents gave high yields (entries 2 and 3). In contrast, the aryl group bearing electron-donating substituent showed no reactivity in our urea transformation (entry 4). Based on these results we believed that the electrophilicity of chloroaldoxime motif played an important role in our reaction (Table 2).

However, *para*-chloro phenyl group of α-chloroaldoxime *O*-methanesulfonate gave the corresponding urea product in good yield (entry 5), suggesting that the electronic effect of halogen

Table 2 The formation of ureas from α-chloroaldoxime *O*-methanesulfonates and aniline derivatives[a]

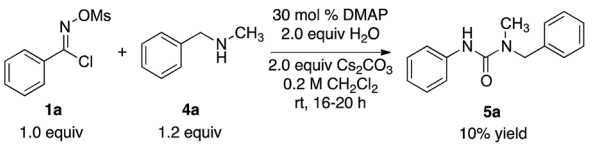


Entry	Chloroaldoximes	Ureas	Yield[b]
1	 **1a**	 **3a**	86
2	 **1b**	 **3b**	95
3	 **1c**	 **3c**	92
4	 **1d**	 **3d**	NR[c]
5	 **1e**	 **3e**	74
6	 **1f**	 **3f**	47
7	 **1a**	 **3g**	72
8	 **1a**	 **3h**	61
9	 **1b**	 **3i**	72
10	 **1a**	 **3j**	NR[c]

[a] Reaction conditions: all reactions were performed with 0.5 mmol of α-chloroaldoxime *O*-methanesulfonates. [b] Isolated yield. [c] No reaction.

substituents was favourable in our reaction. Simple alkyl substituent of α-chloroaldoxime *O*-methanesulfonate was also applicable in our urea transformation with moderate yield (entry 6). While aniline group bearing electron-donating moiety gave good yield too (entry 7). *N*-Benzyl aniline groups (entries 8 and 9) were applicable in our ureas formation with good yields. In addition, *N*-methyl *para*-nitro aniline group gave no desired product (entry 10). This result suggested that the nucleophilicity of nitrogen atom of aniline was also crucial in our reaction.

In order to expand our substrate scopes, we next turned our attention to saturated alkyl secondary amines by investigating a reaction of **1a** and *N*-methylbenzylamine with our optimal conditions (1).

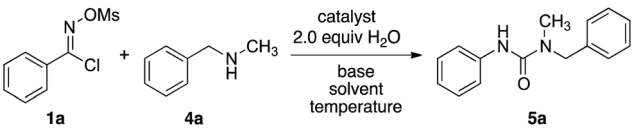


(1)

Surprisingly, the reaction gave the desired urea in very low yield albeit the amine being more nucleophilic than that of aniline derivatives. Moreover, ^{1}H NMR spectrum of the crude reaction mixture showed that **1a** was completely consumed. The result suggested that the higher nucleophilicity of amines might result in undesired reaction pathways and give unidentified side-products. According to the study of Yamamoto and co-workers, one of the possible ways was the formation of guanidine structures when more equivalence of amines was applied.[10b] We subsequently switched the ratio of the starting materials in which the amine was now used as a limiting reagent. As expected the product yield increased to 38%. The result gave us a clue that the reaction with saturated alkyl secondary amines can potentially be improved. Therefore, we further optimized reaction conditions by using the α-chloroaldoxime *O*-methanesulfonate **1a** and *N*-methylbenzylamine as a reaction model (Table 3).

Catalyst loading was increased to 50 mol% in order to give the highest yield and achieve reaction completion. Using K_2CO_3 or Cs_2CO_3 as base, both reactions gave a comparable yield (entries 1 and 2). We therefore selected more common base as our optimal base which was K_2CO_3. By changing the concentration of reaction the yield slightly increased to 41% (entry 3). Higher polar solvents had no affect in the reaction (entries 4 and 5). However, the solvent with higher polarity would allow us to increase the temperature of the reaction. Switching solvent to DMSO or THF and increasing the temperature to 40 °C, the product yield satisfyingly increased to 69% and 58% respectively (entries 6 and 7). Note that, further increase in temperature did not afford greater product yield. Yamamoto and co-workers previously found that TMEDA may have acted as a nucleophilic catalyst and base.[10a] Based on their finding, we subsequently subjected TMEDA as a catalyst (50 mol%) in our reaction. Satisfyingly, the yield of urea was elevated to 74% (entry 8). The amount of TMEDA was also crucial in which the yield of urea was dropped to 48% yield when 20 mol% was employed. The product yield was slightly decreased to 63% yield when 1.0 equivalent was used in reaction. Interestingly, without any nucleophilic catalyst, the reaction also proceeded in good yield (entry 9). This result suggested that DMAP caused undesired reaction pathways in our urea synthesis from saturated amines. Although we could not clarify the role of TMEDA in our reaction, it provided an optimal condition for our urea synthesis based on the result with 50 mol% TMEDA.

Table 3 The optimization reaction of α-chloroaldoxime *O*-methanesulfonate (**1a**) and *N*-methylbenzylamine[a]



Entry	Cat.	Bases	Solvent	Temp.	Yield[b]
1	DMAP	Cs_2CO_3	0.2 M CH_2Cl_2	rt	38
2	DMAP	K_2CO_3	0.2 M CH_2Cl_2	rt	37
3	DMAP	K_2CO_3	0.5 M CH_2Cl_2	rt	41
4	DMAP	K_2CO_3	0.5 M THF	rt	40
5	DMAP	K_2CO_3	0.5 M DMSO	rt	41
6	DMAP	K_2CO_3	0.5 M DMSO	40 °C	69
7	DMAP	K_2CO_3	0.5 M THF	40 °C	58
8	TMEDA	K_2CO_3	0.5 M DMSO	40 °C	74
9	—	K_2CO_3	0.5 M DMSO	40 °C	65

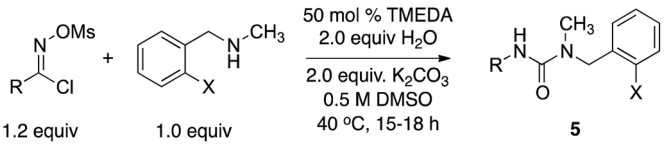
[a] Reaction conditions: all reactions were performed with 0.5 mmol of *N*-methylbenzylamine, 1.2 equiv. of **1a**, 2.0 equiv. of base and 50 mol% of catalyst for 15–18 h. [b] Isolated yield.

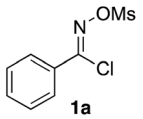
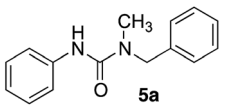
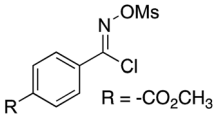
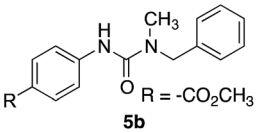
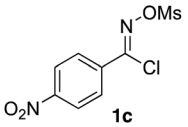
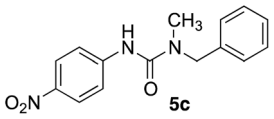
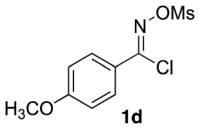
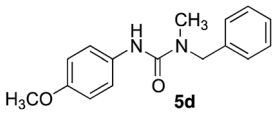
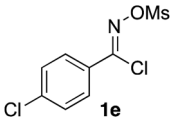
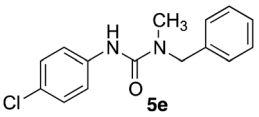
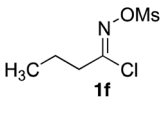
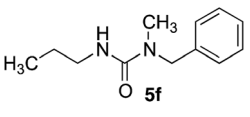
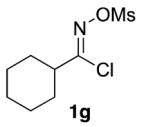
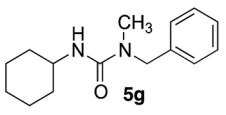
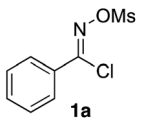
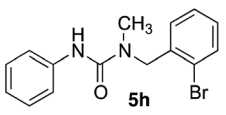
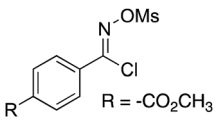
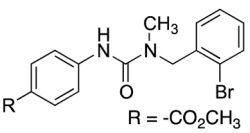
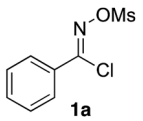
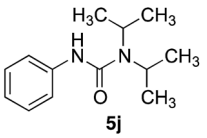
Using the optimized reaction conditions, we then explored the feasibility of the reactions of α-chloroaldoxime *O*-methanesulfonates and saturated secondary amines (Table 4).

With aliphatic amines, a wide range of α-chloroaldoxime *O*-methanesulfonates was applicable. Aryl substitutes bearing both electron withdrawing and donating groups gave high yields (entries 1–5). Aliphatic pendent also gave high yield (entry 6). Similar to Yamamoto's report, we found that the yield diminished when more steric substituent was introduced (entry 7).[10b] In order to provide an alternative method for synthesizing six-membered ring cyclic ureas, we subjected *N*-methyl-2-bromobenzylamine to our reaction, which gave corresponding ureas, good substrate for intramolecular Ullmann type coupling,[13] in high yields (entries 8 and 9). When the more sterically hindered amine (*N*,*N*-diisopropylamine) was subjected to the reaction, the product yield was dramatically decreased to 25% (entry 10). The result suggested that the steric of the nucleophile was also detrimental the yield of the ureas.

We next turned our attention to the possible mechanism in our urea transformation. An attempt to monitor the reaction by ^{1}H NMR technique was failed because the intermediate signals were ambiguously identified from the ^{1}H NMR spectrum of the reaction mixture. However, a study by Truce and Naik showed that the α-chloroaldoxime *O*-methanesulfonates did not react with gaseous ammonia at room temperature but it did react with ammonium hydroxide in acetone. This study suggested that the nucleophilicity of amines affected the substitution

Table 4 The formation of ureas from α-chloroaldoxime *O*-methanesulfonates and *N*-methylbenzylamines[a]



Entry	Chloroaldoximes	Ureas	Yield[b]
1	 1a	 5a	74
2	 1b	 5b	86
3	 1c	 5c	84
4	 1d	 5d	76
5	 1e	 5e	72
6	 1f	 5f	69
7	 1g	 5g	44
8	 1a	 5h	80
9	 1b	 5i	74
10	 1a	 5j	25

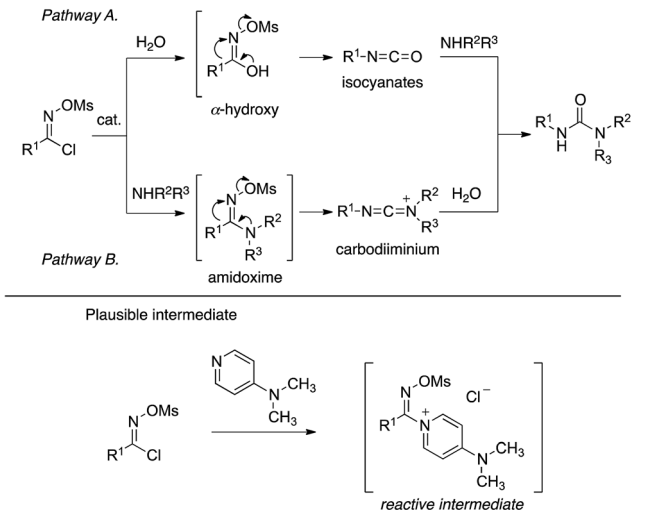
[a] Reaction conditions: all reactions were performed with 0.5 mmol of *N*-methylbenzylamines. [b] Isolated yield.

reaction.[14] Rajagopalan and Talaty also showed that pyrrolidine could undergo substitution reaction with α-chloroaldoxime *O*-methanesulfonate to give amidoxime intermediate.[15] Based on these studies, including Yamamoto's finding[10a] and our results, we proposed two highly possible pathways. Firstly, α-hydroxy intermediate was generated from nucleophilic substitution of α-chloroaldoxime *O*-methanesulfonate with water, which could undergo a rearrangement to give isocyanate intermediate *in situ*, followed by the addition of corresponding secondary amine to give urea (Scheme 2, pathway A). On the other hand, we could not rule out the possibility of nucleophilic amines substituting α-chloroaldoxime *O*-methanesulfonate to generate amidoxime intermediate, followed by the Tiemann rearrangement to give carbodiiminium. Subsequently, carbodiiminium reacted with water to give a desire urea (Scheme 2, pathway B). The role of essential DMAP was possibly a nucleophilic catalyst to generate the reactive intermediate in the formation of trisubstituted ureas from secondary aromatic amines (Scheme 2, plausible intermediate).

Experimental

General procedure

Commercially available reagents and reaction solvents were used without further purification. Solvents for extraction and column chromatography were distilled at their boiling point ranges prior to use. Thin-layer chromatography (TLC) was performed on silica gel 60 GF_{254} (Merck) and was visualized by fluorescence quenching under UV light. Column chromatography was performed on SilicaFlash®G60 (70–230 mesh). ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) were recorded on a 300 MHz Bruker FTNMR Ultra Shield spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts are expressed in parts per million (ppm) downfield from TMS (δ 0.00) and coupling constants are reported as Hertz (Hz). Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; m, multiplet. Infrared spectra (IR) were



Scheme 2 Possible reaction mechanisms.

measured on Perkin Elmer Spectrum GX FT-IR system and recorded on wave number (cm^{-1}).

General procedure for synthesis of α-chloroaldoxime *O*-methanesulfonates

***N*-((Methylsulfonyl)oxy)benzimidoyl chloride (1a).** Prepared according to literature procedure.[10a] A dried round bottom flask was charge with 1.0 equiv. of benzaldoxime in the mixture of 0.5 M of THF and $CHCl_3$ (1 : 1 ratio), followed by the portion addition of 1.5 equiv. of *N*-chlorosuccinimide (NCS). After the addition was completed, the temperature of reaction was increased to 40 °C. After an hour, the reaction was quenched with water and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was dissolved in EtOAc. The resulting solution was cooled to 0 °C before the slow addition of 2.2 equiv. of triethylamine. The reaction mixture was stirred for 10 min. Then, 1.1 equiv. of chloromethanesulfonate was added dropwise at 0 °C. After completion of addition, the mixture was allowed to warm to room temperature and stirred for an hour, followed by filtration. The filtrate was washed with water. The organic layer was dried over anhydrous Na_2SO_4, filtrated and concentrated under reduced pressure. The crude mixture was purified by column chromatography (2 : 1 hexanes : CH_2Cl_2) to afford **1a** as white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, J = 8.4 Hz, 2H), 7.61–7.56 (m, 1H), 7.51–7.46 (m, 2H), 3.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.1, 132.7, 130.4, 128.8, 128.1, 37.0. Other data was identical to the literature values.[10a]

Methyl-4-(chloro(((methylsulfonyl)oxy)imino)methyl)benzoate (1b). Prepared according to the procedure described for **1a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, J = 8.7 Hz, 2H), 8.01 (d, J = 8.7 Hz, 2H), 3.97 (s, 3H), 3.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 148.1, 134.2, 133.7, 129.9, 128.1, 52.6, 37.1. Other data was identical to the literature values.[16]

***N*-((Methylsulfonyl)oxy)-4-nitrobenzimidoyl chloride (1c).** Prepared according to the procedure described for **1a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (d, J = 8.7 Hz, 2H), 8.16 (d, J = 8.7 Hz, 2H), 3.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.1, 146.8, 136.0, 129.2, 123.9, 37.2. Other data was identical to the literature values.[17]

4-Methoxy-*N*-((methylsulfonyl)oxy)benzimidoyl chloride (1d). Prepared according to the procedure described for **1a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, J = 8.7 Hz, 2H), 6.95 (d, J = 8.7 Hz, 2H), 3.88 (s, 3H), 3.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 148.8, 129.9, 122.5, 114.2, 55.6, 36.9; IR (thin film) ν 3422, 1607, 1510, 1372, 1261, 1148, 820, 522 cm^{-1}; HRMS (ESI†) $[M + Na]^+$ calcd for $C_9H_{10}ClNO_4S$ 285.9917, found 285.9917.

4-Chloro-*N*-((methylsulfonyl)oxy)benzimidoyl chloride (1e). Prepared according to the procedure described for **1a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, J = 8.7 Hz, 2H), 7.46 (d, J = 8.7 Hz, 2H), 3.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.0, 139.2, 129.3, 129.2, 37.1. Other data was identical to the literature values.[18]

***N*-((Methylsulfonyl)oxy)butyrimidoyl chloride (1f).** Prepared according to the procedure described for **1a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.16 (s, 3H), 2.60 (t, J = 7.2 Hz, 2H), 1.69–1.77 (m, 2H), 0.96 (t, J = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.2, 38.6, 36.7, 19.5, 12.9. Other data was identical to the literature values.[10a]

***N*-((Methylsulfonyl)oxy)cyclohexanecarbimidoyl chloride (1g).** Prepared according to the procedure described for **1a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.17 (s, 3H), 2.66–2.59 (m, 1H), 2.03–1.69 (m, 5H), 1.56–1.34 (m, 2H), 1.29–1.19 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.1, 45.7, 30.0, 25.4, 25.3. Other data was identical to the literature values.[10a]

Synthesis of trisubstituted ureas

General procedure for one-pot synthesis of trisubstituted ureas from α-chloroaldoxime *O*-methanesulfonates and secondary amines

General procedure A: for the reaction of aniline derivatives. The reaction of *N*-((methylsulfonyl)oxy)benzimidoyl chloride (**1a**) and *N*-methylaniline is representative: a dried 10 mL round bottom flask equipped with a magnetic stirring bar was charged with *N*-((methylsulfonyl)oxy)benzimidoyl chloride (**1a**) (0.5 mmol), *N*-methylaniline (0.75 mmol), *N*,*N*-dimethylaminopyridine (DMAP) (0.15 mmol), water (1.0 mmol) and Cs_2CO_3 (1.0 mmol) in CH_2Cl_2 (2.5 mL). The reaction mixture was stirred at room temperature for 15–20 h. After completion of reaction, the reaction mixture was quenched with sat. NH_4Cl and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The crude mixture was purified by column chromatography (5 : 1 hexanes : EtOAc) to afford **3a** in 97.29 mg (86% yield).

*1-Methyl-1,3-diphenylurea (**3a**).* Yield 97.29 mg (86%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.36 (m, 2H), 7.34–7.21 (m, 5H), 7.01 (d, J = 7.2 Hz, 1H), 6.30 (brs, 1H), 3.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 143.0, 138.9, 130.3, 128.8, 127.8, 127.4, 122.9, 119.3, 37.3. Other data was identical to the literature values.[19]

*Methyl-4-(3-methyl-3-phenylureido)benzoate (**3b**).* Prepared according to general procedure A from methyl-4-(chloro(((methylsulfonyl)oxy)imino)methyl)benzoate (**1b**) and *N*-methylaniline. Yield 135.04 mg (95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, J = 8.7 Hz, 2H), 7.45–7.40 (m, 2H), 7.34–7.25 (m, 5H), 6.56 (brs, 1H), 3.78 (s, 3H), 3.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 153.8, 143.4, 142.4, 130.6, 130.4, 128.1, 127.3, 124.0, 117.9, 51.8, 37.4; IR (thin film) ν 3332, 2962, 2950, 1713, 1677, 1594, 1519, 1456, 1247, 1175, 1111, 767, 698 cm^{-1}; HRMS (ESI†) $[M + H]^+$ calcd for $C_{16}H_{16}N_2O_3$ 285.1239, found 285.1241.

*1-Methyl-3-(4-nitrophenyl)-1-phenylurea (**3c**).* Prepared according to general procedure A from *N*-((methylsulfonyl)oxy)-4-nitrobenzimidoyl chloride (**1c**) and *N*-methylaniline. Yield 124.78 mg (92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, J = 7.8 Hz, 2H), 7.55–7.40 (m, 5H), 7.35 (d, J = 7.8 Hz, 2H), 6.67 (brs, 1H), 3.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.4, 145.0, 142.4, 142.1, 130.1, 128.5, 127.4, 125.0, 118.0, 37.5. Other data was identical to the literature values.[20]

*3-(4-Chlorophenyl)-1-methyl-1-phenylurea (**3e**).* Prepared according to general procedure A from 4-chloro-*N*-((methylsulfonyl)oxy)benzimidoyl chloride (**1e**) and *N*-methylaniline.

Yield 96.47 mg (74%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50–7.47 (m, 2H), 7.39–7.29 (m, 3H), 7.23 (d, J = 8.7 Hz, 2H), 7.15 (d, J = 8.7 Hz, 2H), 6.34 (brs, 1H), 3.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 142.6, 137.6, 130.4, 128.7, 128.0, 127.4, 120.5, 37.3. Other data was identical to the literature values.[21]

*1-Methyl-1-phenyl-3-propylurea (**3f**).* Prepared according to general procedure A from *N*-((methylsulfonyl)oxy)butyrimidoyl chloride (**1f**) and *N*-methylaniline. Yield 45.20 mg (47%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.40 (m, 2H), 7.33–7.24 (m, 3H), 4.27 (brs, 1H), 3.27 (s, 3H), 3.14 (q, J = 6.9 Hz, 2H), 1.49–1.36 (m, 2H), 0.83 (t, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 143.5, 130.0, 127.3, 127.2, 42.4, 37.1, 23.3, 11.2; IR (thin film) ν 3354, 2962, 1655, 1569, 1495, 1339, 760, 700 cm^{-1}; HRMS (ESI†) $[M + Na]^+$ calcd for $C_{11}H_{16}N_2O$ 215.1160, found 215.1160.

*1-(4-Methoxyphenyl)-1-methyl-3-phenylurea (**3g**).* Prepared according to general procedure A from *N*-((methylsulfonyl)oxy)-benzimidoyl chloride (**1a**) and 4-methoxy-*N*-methylaniline. Yield 92.27 mg (72%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28–7.16 (m, 6H), 7.00–6.96 (m, 3H), 6.26 (brs, 1H), 3.85 (s, 3H), 3.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 154.8, 139.0, 135.3, 128.9, 128.8, 122.8, 119.2, 115.5, 55.6, 37.4. Other data was identical to the literature values.[21]

*1-Benzyl-1-(4-methoxyphenyl)-3-phenylurea (**3h**).* Prepared according to general procedure A from *N*-((methylsulfonyl)oxy)-benzimidoyl chloride (**1a**) and *N*-benzyl-4-methoxyaniline. Yield 101.38 mg (61%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.7.22 (m, 10H), 7.06 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 6.25 (brs, 1H), 4.90 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 154.7, 139.0, 138.4, 133.4, 130.1, 128.8, 128.7, 128.4, 127.3, 122.9, 119.3, 115.3, 55.5, 53.3; IR (thin film) ν 2928, 2420, 1672, 1511, 1441, 1248, 752, 693, 556 cm^{-1}; HRMS (ESI†) $[M + H]^+$ calcd for $C_{21}H_{20}N_2O_2$ 333.1603, found 333.1602.

*Methyl 4-(3-benzyl-3-(4-methoxyphenyl)ureido)benzoate (**3i**).* Prepared according to general procedure A from methyl-4-(chloro(((methylsulfonyl)oxy)imino)methyl)benzoate (**1b**) and *N*-benzyl-4-methoxyaniline. Yield 140.55 mg (72%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, J = 8.7 Hz, 2H), 7.40 (d, J = 8.7 Hz, 2H), 7.30–7.28 (m, 5H), 7.05 (d, J = 9.0 Hz, 2H), 6.91 (d, J = 9.0 Hz, 2H), 6.44 (brs, 1H), 4.90 (s, 2H), 3.87 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 159.5, 154.1, 143.3, 137.9, 132.9, 130.7, 130.0, 128.7, 128.4, 127.4, 124.1, 117.9, 115.4, 55.5, 53.4, 51.8; IR (thin film) ν 3346, 2950, 1713, 1674, 1511, 1279, 1247, 1175, 769, 699, 561 cm^{-1}; HRMS (ESI†) $[M + H]^+$ calcd for $C_{23}H_{22}N_2O_4$ 391.1658, found 391.1654.

General procedure B: for the reaction of N-benzylamine derivatives. The reaction of *N*-((methylsulfonyl)oxy)benzimidoyl chloride (**1a**) and *N*-methylbenzylamine is representative: a dried 10 mL round bottom flask equipped with a magnetic stirring bar was charged with *N*-((methylsulfonyl)oxy)benzimidoyl chloride (**1a**) (0.75 mmol), *N*-methylbenzylaniline (0.50 mmol), *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) (0.25 mmol), water (1.0 mmol) and K_2CO_3 (1.0 mmol) in DMSO (1.5 mL). The reaction mixture was warmed to 40 °C and stirred for 15–18 h. After completion of reaction, the reaction mixture was quenched with sat. NH_4Cl and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The crude mixture was purified by column chromatography (5 : 5 : 1 hexanes : CH_2Cl_2 : EtOAc) to afford **5a** in 88.91 mg (74% yield).

*1-Benzyl-1-methyl-3-phenylurea (**5a**).* Yield 88.91 mg (74%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.15 (m, 8H), 7.06–7.02 (m, 2H), 6.64 (brs, 1H), 4.59 (s, 2H), 3.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 139.1, 137.5, 128.9, 128.8, 128.7, 127.6, 127.3, 123.1, 122.3, 120.2, 119.2, 52.3, 34.8. Other data was identical to the literature values.[22]

*Methyl 4-(3-benzyl-3-methylureido)benzoate (**5b**).* Prepared according to general procedure B from methyl-4-(chloro(((methylsulfonyl)oxy)imino)methyl)benzoate (**1b**) and *N*-methylbenzylamine. Yield 128.29 mg (86%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.89 (d, J = 8.7 Hz, 2H), 7.44 (d, J = 8.7 Hz, 2H), 7.33–7.22 (m, 5H), 7.77 (brs, 1H), 4.54 (s, 2H), 3.84 (s, 3H), 2.98 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0, 155.3, 143.9, 137.1, 130.6, 128.9, 127.6, 127.3, 124.0, 118.7, 52.3, 51.9, 34.8; IR (thin film) ν 3334, 2950, 1716, 1650, 1525, 1411, 1280, 1247, 1175, 1111, 770, 700; HRMS (ESI†) $[M + H]^+$ calcd for $C_{17}H_{18}N_2O_3$ 299.1395, found 299.1391.

*1-Benzyl-1-methyl-3-(4-nitrophenyl)urea (**5c**).* Prepared according to general procedure B from *N*-((methylsulfonyl)oxy)-4-nitrobenzimidoyl chloride (**1c**) and *N*-methylbenzylamine. Yield 119.83 mg (84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, J = 9.0 Hz, 2H), 7.54 (d, J = 9.0 Hz, 2H), 7.41–7.28 (m, 5H), 6.98 (brs, 1H), 4.61 (s, 2H), 3.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.7, 145.5, 142.4, 136.7, 127.9, 127.2, 125.0, 118.5, 52.5, 35.0. Other data was identical to the literature values.[23]

*1-Benzyl-3-(4-methoxyphenyl)-1-methylurea (**5d**).* Prepared according to general procedure B from 4-methoxy-*N*-((methylsulfonyl)oxy)benzimidoyl chloride (**1d**) and *N*-methylbenzylamine. Yield 102.73 mg (76%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.24 (m, 7H), 6.82 (d, J = 9.0 Hz, 2H), 6.44 (brs, 1H), 4.57 (s, 2H), 3.78 (s, 3H), 2.99 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.3, 155.8, 137.7, 132.2, 128.8, 127.5, 127.3, 127.2, 122.4, 114.0, 55.5, 52.3, 34.7; IR (thin film) ν 3330, 2934, 1651, 1538, 1413, 1379, 1296, 1238, 1034, 826, 753, 700, 568, 523; HRMS (ESI†) $[M + Na]^+$ calcd for $C_{16}H_{18}N_2O_2$ 293.1266, found 293.1266.

*1-Benzyl-3-(4-chlorophenyl)-1-methylurea (**5e**).* Prepared according to general procedure B from 4-chloro-*N*-((methylsulfonyl)oxy)benzimidoyl chloride (**1e**) and *N*-methylbenzylamine. Yield 98.91 mg (72%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.28 (m, 7H), 7.24–7.20 (m, 2H), 6.53 (brs, 1H), 4.58 (s, 2H), 3.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 137.8, 137.3, 128.9, 128.7, 128.0, 127.7, 127.3, 121.3, 52.4, 34.8. Other data was identical to the literature values.[10]

*1-Benzyl-1-methyl-3-propylurea (**5f**).* Prepared according to general procedure B from *N*-((methylsulfonyl)oxy)butyrimidoyl chloride (**1f**) and *N*-methylbenzylamine. Yield 71.17 mg (69%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.28 (m, 3H), 7.24–7.19 (m, 2H), 4.61 (brs, 1H), 4.46 (s, 2H), 3.16 (q, J = 6.9 Hz, 2H), 2.84 (s, 3H), 1.51–1.41 (m, 2H), 0.85 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6, 138.0, 128.6, 127.2, 127.1, 52.1, 42.7,

34.3, 23.5, 11.3; IR (thin film) ν 3331, 2930, 1644, 1532, 1440, 1380, 1310, 1244, 1025, 751, 634 cm^{-1}; HRMS (ESI†) $[M + H]^+$ calcd for $C_{12}H_{18}N_2O$ 207.1497, found 207.1586.

*1-Benzyl-3-cyclohexyl-1-methylurea (**5g**).* Prepared according to general procedure B from *N*-((methylsulfonyl)oxy)cyclohexanecarbimidoyl chloride (**1g**) and *N*-methylbenzylamine. Yield 54.20 mg (44%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.22 (m, 5H), 4.48 (s, 2H), 4.29 (brs, 1H), 3.69–3.64 (m, 1H), 2.86 (s, 3H), 1.94–1.90 (m, 2H), 1.69–1.57 (m, 4H), 1.41–1.26 (m, 2H), 1.18–1.10 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7, 138.1, 128.6, 127.3, 52.2, 49.4, 34.3, 34.1, 33.9, 25.6, 25.0. Other data was identical to the literature values.[23]

*1-(2-Bromobenzyl)-1-methyl-3-phenylurea (**5h**).* Prepared according to general procedure B from *N*-((methylsulfonyl)oxy)-benzimidoyl chloride (**1a**) and 1-(2-bromophenyl)-*N*-methylmethanamine. Yield 127.68 mg (80%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, $J = 8.1$ Hz, 1H), 7.40–7.32 (m, 6H), 7.22-7.19 (m, 1H), 7.08–7.05 (m, 1H), 6.38 (brs, 1H), 4.70 (s, 2H), 3.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.7, 138.9, 136.2, 133.1, 129.1, 128.9, 128.0, 123.2, 123.1, 120.0, 52.6, 35.1; IR (thin film) ν 3331, 2930, 1644, 1532, 1440, 1244, 1025, 751, 693 cm^{-1}; HRMS (ESI†) $[M + Na]^+$ calcd for $C_{15}H_{15}BrN_2O$ 341.0265, found 341.0265.

*Methyl-4-(3-(2-bromobenzyl)-3-methylureido)benzoate (**5i**).* Prepared according to general procedure B from methyl-4-(chloro(((methylsulfonyl)oxy)imino)methyl)benzoate (**1b**) and 1-(2-bromophenyl)-*N*-methylmethanamine. Yield 139.58 mg (74%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, $J = 8.7$ Hz, 2H), 7.54 (d, $J = 8.1$ Hz, 1H), 7.45 (d, $J = 8.7$ Hz, 2H), 7.28–7.20 (m, 2H), 7.15–7.10 (m, 1H), 4.62 (s, 2H), 3.84 (s, 3H), 3.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 155.3, 143.7, 135.9, 133.1, 130.6, 129.1, 128.2, 127.9, 124.1, 123.1, 118.7, 52.6, 52.0, 35.1; IR (thin film) ν 3335, 2950, 1716, 1652, 1594, 1526, 1411, 1281, 1249, 1176, 1112, 1026, 751 cm^{-1}; HRMS (ESI†) $[M + H]^+$ calcd for $C_{17}H_{17}BrN_2O_3$ 377.0501, found 377.0498.

*1,1-Diisopropyl-3-phenylurea (**5j**).* Prepared according to general procedure B from *N*-((methylsulfonyl)oxy)benzimidoyl chloride (**1a**) and diisopropylamine. Yield 27.54 mg (25%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.37 (m, 2H), 7.31–7.25 (m, 2H), 7.04–7.00 (m, 1H), 6.25 (brs, 1H), 4.04–3.95 (m, 2H), 1.33 (d, $J = 6.9$ Hz, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.7, 139.3, 128.8, 128.7, 122.7, 119.8, 119.2, 45.8, 21.5. Other data was identical to the literature values.[24]

Conclusions

Mild and practical synthesis of trisubstituted ureas *via* one-pot reaction of the bench-stable α-chloroaldoxime *O*-methanesulfonates and secondary amines was accomplished. Two categories of secondary amines were carried out using two protocols, both of which were mild and operated under simple reaction conditions. The substrate scope was general for saturated secondary amines. For secondary aromatic amines, the electrophilicity of α-chloroaldoxime *O*-methanesulfonates and the nucleophilicity of amines played important role. Although we could not determine the mechanism of the urea transformation, this methodology enriched the chemistry of α-chloroaldoxime *O*-methanesulfonates. Further applications of reaction and a study of reaction mechanism are ongoing.

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8. Output (Acknowledge the Thailand Research Fund)

8.1 International Journal Publication

- “One-Pot synthesis of trisubstituted ureas from α-chloro *O*-methanesulfonates and secondary amines” *RSC Adv.* **2015**, *5*, 5857-58594.

8.2 Application

- Since our research is the basic research and mainly focus on knowledge of synthetic methodologies, our finding in synthesis of oxazolines will be subjected to a subject course (324-434) of heterocyclic chemistry for undergraduate students in department of chemistry. Likewise, the synthesis of ureas will be subjected to the subject course (324-731) of amide bond formation.

8.3 Others e.g. national journal publication, proceeding, international conference, book chapter, patent

- The 10th International Conference on Cutting-Edge Organic Chemistry in Asia (ICCEOCA-10) for poster session.