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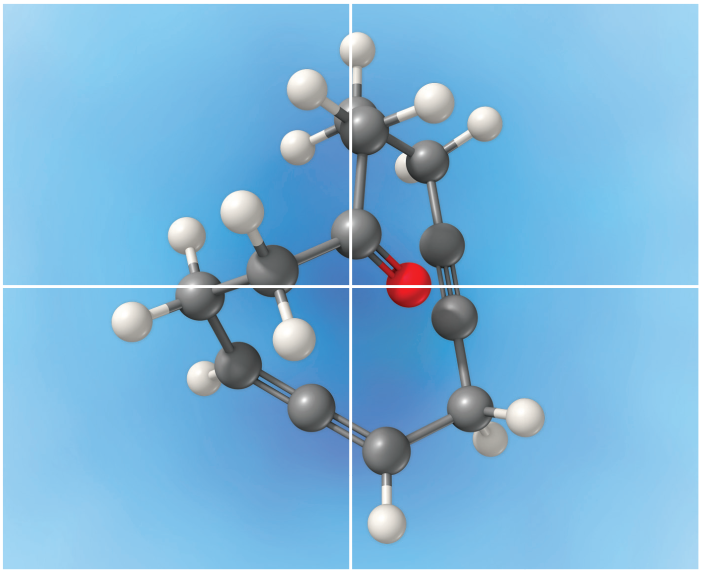

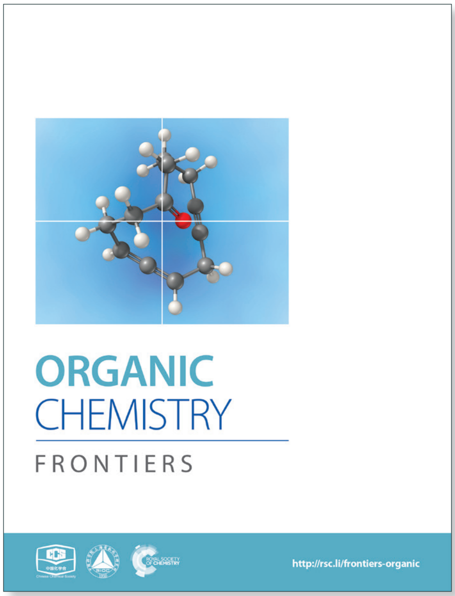

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Functionalized Imidazoliniums from Three-Component Domino Reaction of *N*-Formylmethylcarboxamides with Amines and Isocyanides

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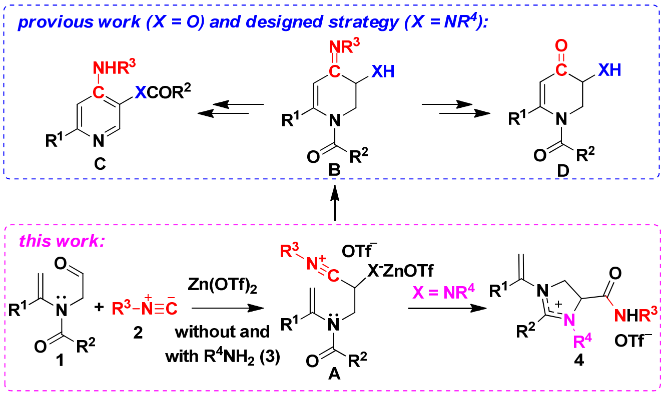
In the presence of $Zn(OTf)_2$, the three-component domino reaction of *N*-formylmethyl-substituted tertiary amides and enamides with amines and isocyanides in acetonitrile at room temperature produced functionalized imidazoliniums in good to excellent yields.

2-Substituted imidazolinium salts constitute an interesting and useful class of heterocyclic compounds. Because of resistance to bases, for example, ionic liquid 2-alkyl and 2-aryl imidazolinium salts are used as green media under basic reaction conditions.[1] Functionalized 2-aryl imidazolinium salts have also been found to be able to catalyze Diels-Alder and aza-Diels-Alder reactions.[2] Furthermore, it has been shown that 2-aryl imidazolinium salts derived from chiral diamines act as chiral shift reagents to discriminate a racemic sample of potassium Mosher's carboxylate.[2a,3] Moreover, imidazoliniums provide a simple model of tetrahydrofolate (THF) coenzymes, facilitating the study of group transfer reaction in biosynthesis and metabolism.[4] Among the syntheses of 2-substituted imidazolinium salts reported in literature, *N*-alkylation of 2-substituted imidazolines is a most frequently used method.[3,5] Oxidation of imidazolidines,[1b,2a-b] palladium-catalyzed coupling of imines, CO and acid chlorides[6] have also provided synthetic routes to 2-substituted imidazolinium salts. However, these methods suffer from limitations and drawbacks such as (1) multi-step synthesis of precursors, (2) low selectivity or (3) difficulty in functionalization. Development of efficient and practical methods for the construction of functionalized 2-substituted imidazolinium salts[7] is challenging and highly desirable.

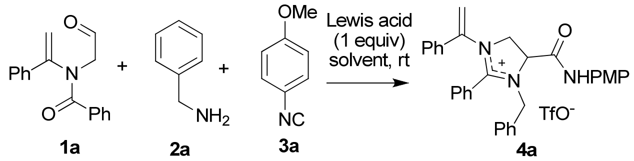
Multicomponent reactions[8] and domino reactions[9] have become very popular strategies in organic synthesis because they provide opportunities of constructing molecules of complexity and diversity from single and generally easy operations. Successful and fruitful multicomponent and domino syntheses rely on, however, the versatility of reactants and designed reaction pathways. Based on their unique and versatile reactivities,[10] for instance, isocyanides have been extensively employed in multicomponent and domino reactions, yielding a wide variety of compounds, including natural products-like and biologically active ones, that are not readily accessible by other methods.[11]

For years, we[12] have been exploring the reactions and synthetic applications of tertiary enamides. Being variants of conventional enamines, tertiary enamides exhibit diminished nucleophilicity due to the effect of *N*-electron-withdrawing group that alleviates the delocalization of nitrogen lone-pair electrons into enaminic carbon.[13] By means of regulating the cross conjugation system of enamide segment, we have demonstrated that tertiary enamides are valuable starting materials in synthesis.[12] Very recently, we discovered that *N*-formylmethyl-substituted tertiary enamides **1** undergo $Zn(OTf)_2$-promoted [5+1] cycloaddition reaction with isocyanides **2** to form six-membered heterocyclic intermediate **B** through **A**. Termination of the reaction cascade by oxidative aromatization and hydrolysis furnished poly-substituted pyridines **C** and 2,3-dihydropyridin-4(1*H*)-ones **D,** respectively (see previous work in Figure 1).[14] As a logical extension, we then became interested in the three-component reaction of tertiary enamides, amines and isocyanides, aiming at the synthesis of amino-substituted pyridine and 2,3-dihydropyridin-4(1*H*)-one derivatives (see designed strategy in Figure 1) that possess interesting biological activities such as blocking the voltage-dependent potassium channel, promoting the release of acetylcholine in the nerve endings, thus can be used for the treatment of Lambert-Eaton myasthenic syndrome (LEMS), reducing the symptoms of downbeat nystagmus (DBN) and improving the cognitive functions during aging[15]. Surprisingly, no targeted products were produced at all from designed three-component reaction. Instead, the reaction afforded unexpectedly imidazolinium salts as the sole products (see this work in Figure 1). We report herein a novel and efficient synthesis of functionalized imidazoliniums by a one-pot three-component domino reaction of *N*-alkenyl- and *N*-alkyl-bearing *N*-formylmethylcarboxamides with isocyanides and aliphatic amines under very mild conditions. The ^{18}O-labeling experiment reveals an intriguing reaction pathway which comprises the formation and fragmentation of a bridged heterocyclic intermediate.



Scheme 1. Reaction pathways of functionalized tertiary enamides with amines and isocyanides.

Table 1. Reaction of tertiary enamide **1a** with benzylamine **2a** and *p*-methoxyphenyl isocyanide **3a**[a]



entry	Lewis acid	solvent	time	**4a** (%)[b]
1	$Zn(OTf)_2$	CH_3CN	2 h	70
2	$Sc(OTf)_3$	CH_3CN	1.5 h	42
3	$Sm(OTf)_3$	CH_3CN	1.5 h	50
4	$In(OTf)_3$	CH_3CN	2 h	48
5	$Cu(OTf)_2$	CH_3CN	2 h	21
6	$[Cu(CH_3CN)_4]PF_6$	CH_3CN	7 h	-[c]
7	TfOH	CH_3CN	10 min	41
8	$ZnCl_2$	CH_3CN	2 h	52[d]
9	$Zn(OTf)_2$	$CHCl_3$	1 h	64
10	$Zn(OTf)_2$	Toluene	6 h	55
11	$Zn(OTf)_2$	THF	6 h	67
12	$Zn(OTf)_2$	CH_3OH	48 h	50
13[e]	**$Zn(OTf)_2$**	**CH_3CN**	**2 h**	**85**

[a] The ratio between **1a**: **2a**: **3a** was 1 : 1.1 : 1.2. Imine was firstly prepared from the reaction of **1a** and **2a**, and was then treated with **3a**. [b] Isolated yield. [c] $[Cu(PMPNC)_4]PF_6$ complex was obtained in 97% yield. [d] The chloride salt complexed with $ZnCl_2$ was obtained as product. [e] One-pot reaction of **1a** with **2a** and **3a**.

We initiated our study with the examination of the reaction of *N*-formylmethyl-substituted enamide **1a** with benzylamine **2a** and *para*-methoxyphenyl (PMP) isocyanide **3a** (Table 1). Initially, the reaction was conducted by preparation of imine from the reaction of **1a** and **2a** followed by the addition of **3a** in the presence of one equivalent of $Zn(OTf)_2$ under the standard conditions[14] for the reaction of *N*-formylmethyl-substituted enamide **1a** with *para*-methoxyphenyl (PMP) isocyanide **3a**. Out of our expectation, the reaction did not form designed six-membered product. Instead, a five-membered heterocyclic compound, *viz*. imidazolinium triflate **4a** was obtained in 70% yield as the sole product (entry 1, Table 1). The structure of **4a** was elucidated on the basis of spectroscopic date and determined unambiguously by single crystal X-ray diffraction analysis (Figure 1). In order to alter the reaction pathways, other Lewis acids and Brønsted acid were surveyed. As indicated by the results summarized in Table 1, however, formation of products other than **4a** was not observed. The use of $Sc(OTf)_3$, $Sm(OTf)_3$ and $In(OTf)_3$ for example afforded **4a** in the yield ranging from 42% to 50% (entries 2-4, Table 1). The reaction mediated by $Cu(OTf)_2$ gave rise to a very low chemical yield of **4a** (entry 5, Table 1) whereas no three-component reaction took place when $[Cu(CH_3CN)_4]PF_6$ was applied. In the latter case, the reaction resulted in nearly quantitative formation of tetra(*p*-methoxyphenyl isocyanide)copper(I) hexafluorophosphate whose structure was determined by X-ray crystallography (entry 6, Table 1).[16] It was interesting to note that trifluoromethanesulfonic acid (TfOH) was also able to effect the three-component reaction rapidly albeit the yield of product **4a** was only moderate (entry 7, Table 1). Reaction promoted by $ZnCl_2$ proceeded analogously, affording imidazolinium chloride in 52% yield (entry 8, Table 1). Almost equally efficient reaction was observed when acetonitrile was replaced by chloroform (entry 9, Table 1). An elongated reaction time was required for the reaction in toluene, THF and, particularly, in methanol, with product **4a** being isolated in slightly diminished yields (entries 10-12, Table 1)

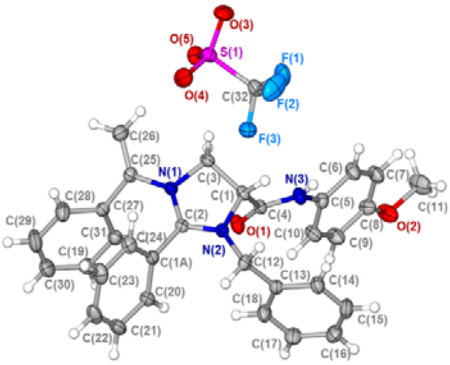
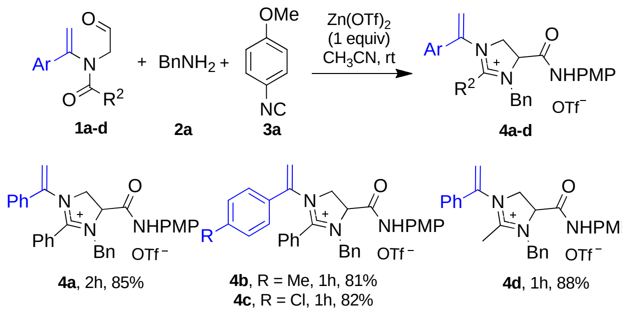


Figure 1. X-ray molecular structure of **4a** (CCDC 1015230)

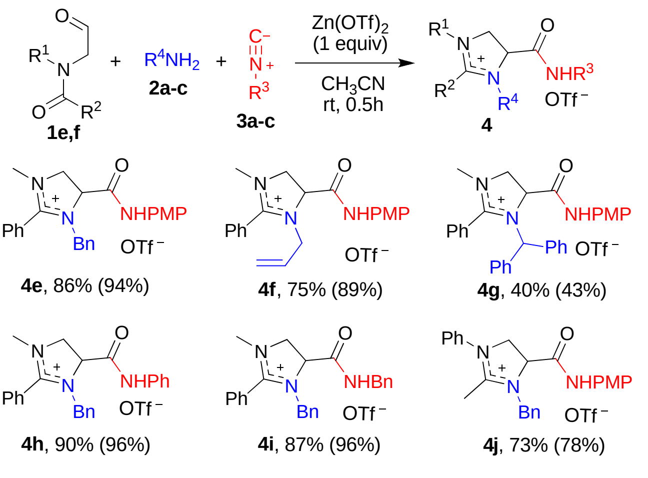
To simplify the operation, a one-pot reaction was executed simply by mixing *N*-formylmethyl-substituted enamide **1a** with para-methoxyphenyl (PMP) isocyanide **2a** and benzylamine **3a** in the presence of one equivalent of $Zn(OTf)_2$ in acetonitrile. Pleasingly, the reaction was found to proceed smoothly at ambient temperature to afford product **4a** in an improved yield (85%) in 2 h (entry 13, Table 1).



Scheme 2. Reaction of tertiary enamides **1a-d** with amine **2a** and isocyanide **3a**

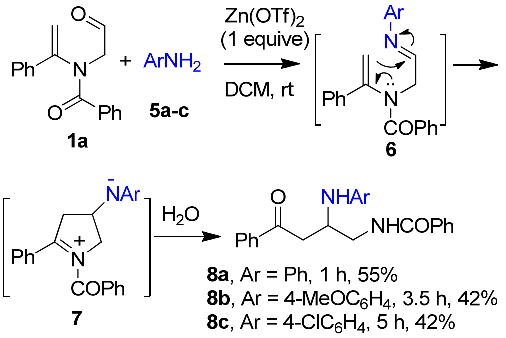
Under optimized one-pot reaction conditions, the scope and limitations of this unprecedented three-component reaction were investigated using other tertiary enamides (Scheme 2). Irrespective of the electronic feature of the substituent on the benzene ring, *N*-aroyl-containing tertiary enamides **1b** (R = 4-MeC_6H_4) and **1c** (4-ClC_6H_4) underwent three-component reaction as efficiently as **1a** to produce 2-aryl-substituted imidazolinium salts **4b** and **4c** in 81% and 82% yield, respectively. In the case of *N*-acetyl-substituted enamide **1d** (Ar = Ph, R^2 = Me), reaction led to the formation of 2-methylated imidazolinium salt **4d** in 88% yield. Higher chemical yield obtained for **4d** is probably due to the lower enaminic reactivity of *N*-acetyl-bearing enamide reactant **1d** than that of *N*-aroyl-substituted analogues **1a-1c**. It appeared that higher enaminic reactivity would cause competitive side reactions such as intramolecular cyclization and ring open reaction (*vide infra*), corroding the yield of imidazolinuim product.

Since the carbon-carbon double bond of tertiary enamides did not participated in the cyclization, we then extended substrates from tertiary enamides **1a-d** into *N*-formylmethyl-*N*-methylbenzamide **1e** (R^1 = Me, R^2 = Ph) and *N*-formylmethyl-*N*-phenylacetamide **1f** (R^1 = Ph, R^2 = Me, Scheme 3). In addition to benzylamine **2a** and *para*-methoxyphenyl isocyanide **3a**, aliphatic amines such as allylamine **2b** and (1,1-diphenylmethyl)amine **2c**, and isocyanides such as phenyl isocyanide **3b** and benzyl isocyanide **3c** were employed in the study. To our delight, as depicted in Scheme 3, all substrates tested underwent the same reaction effectively, demostrating the versatility of diversity-orientated three-component domino reaction. When *N*-formylmethyl-*N*-methylbenzamide **1e** was applied as an input, for example, the domino reaction with benzylamine **2a** and *para*-methoxyphenyl isocyanide **3a** gave imidazolinium salt **4e** in 86% yield. Good yield (75%) of *N*-allylated product **4f** was obtained from the reaction with allylamine **2b**. (Diphenylmethyl)amine **2c**, a steric bulky amine, was also accepted as a substrate, albeit the corresponding product **4g** was isolated in a diminished yield. Remarkably, both aromatic isocyanides like **2a** and **2b** and aliphatic one **2c** underwent highly efficient reaction to generate products **4e**, **4h** and **4i**, respectively, in excellent yields. *N*-Formylmethyl-*N*-phenylacetamide **1f** acted similarly as benzamide analog **1e**, and its reaction with **2a** and **3a** yielded 3-benzyl-2-methyl-1-phenylimidazolinium **4j** in 73% yield (Scheme 3). It should be noted that all three-component reactions employing *N*-formylmethylcarboxamides gave improved chemical yields of 2-substituted imidazolinium salts when imines were pre-formed from the interaction of aldehydes and amines (Scheme 3, chemical yields in parentheses). The slightly lower chemical yields obtained from three-component reaction in a one-pot manner than in a step-wise fashion was most likely due to the side reactions between *N*-formylmethylcarboxamides and isocyanides.



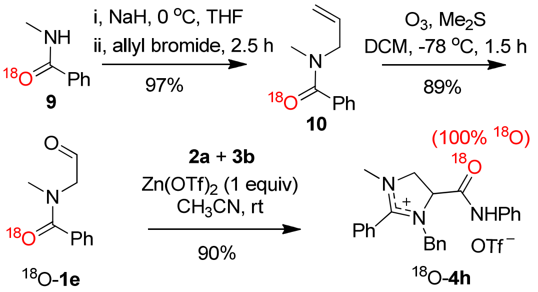
Scheme 3. Three-component domino reaction involving various *N*-formylmethyl-bearing amides, aliphatic amines and isocyanides. Chemical yields in parentheses were obtained from the reactions using pre-formed imines.

It should be pointed out that same three-component domino reaction did not proceed when anilines **5** were utilized instead of aliphatic amines. Under the identical conditions, the reaction of *N*-formylmethyl-substituted enamide **1a**, for example, gave diamine derivatives **8** as the major products in which isocyanides were not involved. It is probably the higher reactivity of aromatic imines **6** generated in situ from the interaction of aldehyde **1** and anilines **5** that is in favor of intramolecular cyclization with enamide moiety to form intermediate **7**. Further hydrolysis of iminium ion **7** led to the ring opening products **8** (Scheme 4).



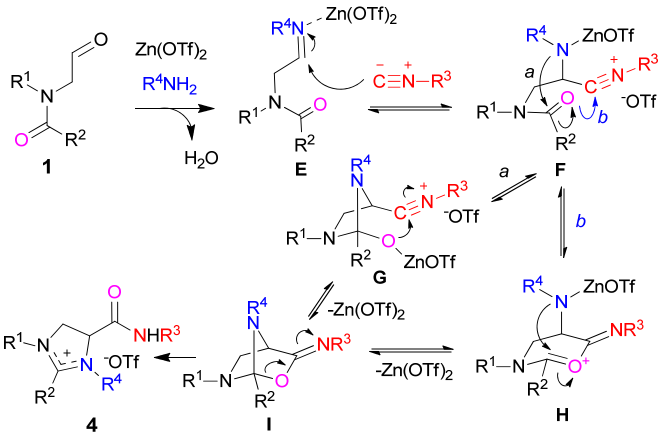
Scheme 4. Reaction of **1a** with anilines **5**

The formation of imidazolinium salts **4** from the reaction of *N*-formylmethyl-substituted amides **1** with aliphatic amines **2** and isocyanides **3** implied an intriguing and complex reaction pathway. To shed light on the reaction mechanism, especially the origin of oxygen of amide group in molecule **4**, an ^{18}O-labeling experiment was carried out. Scheme 5 shows the synthesis of ^{18}O-labeled amide ^{18}O-**1e** from *N*-allylation and subsequent ozonization of ^{18}O-labeled *N*-methylbenzamide **9**.[17] Same three-component reaction involving ^{18}O-**1e**, benzylamine **2a** and phenyl isocyanide **3b** afforded almost quantitatively ^{18}O-labeled imidazolinium salt ^{18}O-**4h**. The formation of ^{18}O-**4h** as the sole product, as evidenced by mass spectral data, indicated clearly the complete conversion of ^{18}O-**1e** into ^{18}O-**4h**. It also excluded the possibility of transformation of aldehyde moiety of **1** into the amide functionality of the product and of the involvement of moisture in the reaction.



Scheme 5. Synthesis of ^{18}O-**1e** and its conversion to ^{18}O-**4h**

On the basis of the aforementioned results, a plausible mechanism for the three-component domino reaction was proposed. As depicted in Scheme 6, condensation reaction between aliphatic amines **2** and aldehydes **1** gives imine intermediates **E** with the release of water. Activated by $Zn(OTf)_2$, imines **E** are attacked by isocyanides **3** to afford nitrilium intermediates **F** which undergo intramolecular nucleophilic addition of nitrogen anion to amide group (pathway *a*). Cyclization of the resulting heterocyclic intermediates **G** between alkoxide and nitrilium moieties leads to the formation of 3-imono-2-oxa-6,7-diazabicyclo[2.2.1]heptane intermediates **I**. Alternatively, the nitrilium **F** was first trapped by the amido carbonyl oxygen to give six-membered oxonium intermediate **H** which was further captured by nitrogen anion to form intermediate **I** (pathway *b*). Finally, ring opening reaction via the cleavage of C-O bond assisted by lone-pair electrons of nitrogen furnishes the production of imidazolinium triflates **4**. It is worth addressing that since the nucleophilicity of nitrogen anion is stronger than the enaminic carbon of tertiary enamide (R^1 = CH_2=C(Ar)-), the resulting intermediate **F** tends to undergo addition reaction between nitrogen anion and carbonyl rather than between enamide and nitrilium. In the case of reaction using aromatic amines, on the other hand, intramolecular addition reaction between enamide (R^1 = CH_2=C(Ar)-) and aromatic imine takes place preferentially in comparison to intermolecular addition of isocyanide to aromatic imine within intermediate **E**, thus diverting the reaction pathway to the formation of diamine product **8** (see Scheme 4).



Scheme 6. Mechanism for the three-component domino reaction

Conclusions

In conclusion, we have developed an unprecedented three-component domino reaction of various *N*-formylmethyl-substituted amides with isocyanides and aliphatic amines. The $Zn(OTf)_2$-mediated reaction provides an expedient synthetic route to functionalized imidazoliniums under very mild conditions. An ^{18}O-labeling experiment reveals an intriguing mechanism involving most likely the bridged heterocyclic intermediate.

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Notes and references

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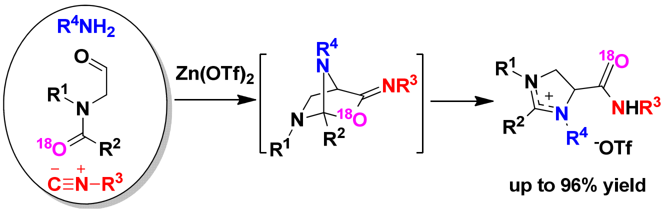

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