Tandem Triphosgene-Assisted Metal-Free One-pot Preparation of Nitriles and Amides from Aldehydes and Ketones

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Abstract:

Here we report a facile and efficient triphosgene-assisted one-pot conversion of aldehydes/ketones into nitriles/amides. The triphosgene, a kind of phosgene alternative, containing both ester linkage and chloromethyl units, easily reacts with oximes for the preparation of nitriles/amides. However, the reaction of oximes with triphosgene can't fully convert corresponding nitriles/amides due to hydrolysis of oximes to aldehydes or ketones. Our protocol tandem proceeds smoothly without the use of organic base and metal catalysts. Diverse functionalized aromatic, aliphatic, and allylic aldehydes/ketones incorporating biomass-derived platform compounds were successfully converted to nitriles and amides in excellent yields. Compared to step-by-step reaction, this tandem strategy is characterized by multi-step reaction in one pot, mild reaction conditions, and fewer by-products.

Introduction

Nitrile and amide groups are all the key structures of natural products, biologically active molecules, agrochemicals, dyes, or materials science. In the past decade, nitriles were obtained from the conversion of oximes via dehydration,[1] as well as substitution reaction involving cyanogen reagents.[2-6] In addition, carboxylic acid derivatives and amines are traditionally applied for the synthesis of amides via a condensation reaction, which needs to happen in harsh conditions.[7] Unfortunately, most synthesis were performed with toxic reagents and cumbersome experimental operation. Though the great progress made in the generation of nitriles from aldehydes and have well applied in the wide substrate scope of aldehydes, there are few suitable methodologies for the synthesis of both nitrile and amide from aldehydes and ketone respectively. Compared with traditional nucleophilic substitutions by using HCN or metal cyanides[8-11] as well as recent popular oximation−dehydration strategy[12] with the prepared reagents[13] or additional alkali[14-15] we designed an environmentally friendly alternative using triphosgene. This reagent is cheap and used without further preparation.

In a recent report,[16] the reaction site of oxime was used in the chemical detection of phosgene. Since then many researchers reported the synthesis of nitriles or amides from various oximes with phosgene or its substitutes (triphosgene and diphosgene). But most of these applications suffer from the effect of toxic phosgene overflow at alkaline conditions (such as adding TEA in the reaction system) and narrow substrate scope. Phosgene and its substitutes are important industrial feedstocks used in the productions of polyurethanes, polycarbonates, pharmaceuticals, insecticides, and aniline dyes.[17-18] On the other hand, phosgene, and diphosgene are highly toxic lung irritation effects even at low conversions, for which have been used as chemical warfare agents (CWAs) during World War I and World War II.[19] As a substitute for phosgene, triphosgene is non-volatile, and widely used in chemical synthesis.

With the increasing demand for fossil resource-derived chemicals and fuels, the viewpoint of developing those alternatives from the catalytic transformation of renewable biomass has received global concern.[20-25] Among the alternatives from biomass valorization, the production of 5-hydroxymethylfurfural (HMF) from hexoses is a versatile platform for the synthesis of furan-based chemicals such as furyl diamide, diamidine, diimidate, and diformylfuran.[26-27] Therefore, oxidative depolymerization of lignin and lignin model compounds can obtain

aromatic aldehydes and ketones[28-38] such as vanillin veratraldehyde, acetovanillone, acetosyringone, and syringaldehyde. To further demonstrate the utility of our protocol, we used our one-pot strategy for the efficacious synthesis of 2,5-dicyanofuran from biomass-derived 2,5- diformylfuran. Besides, we also got fruitful nitriles and amides from lignin-derived monoaldehyde and aromatic ketone. Especially, capsaicin analogs such as nonivamide, capsaicin, and phenylcapsaicin[39] (Figure 1), as typical capsaicinoid compounds, which show prominent anti-inflammatory,[40] and anti-cancer [41] properties, have been widely applied in cancer prevention[42]. Capsaicinoids were usually prepared from vanillin by first reducing vanillin oxime to obtain vanillylamine and then further reacting with acyl chlorides (Schotten–Baumann) to form the final products.[43-46]

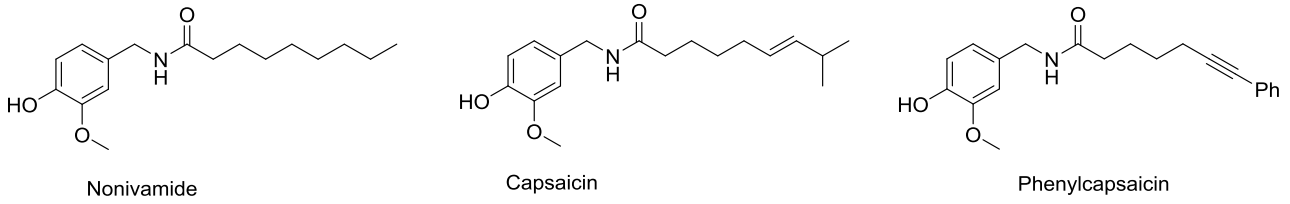


Figure 1. Examples of biologically active capsaicinoids.

Alternatively, the synthesis of capsaicin analogs was to use our approach to prepare the intermediate 4-hydroxy-3-methoxybenzonitrile (P1c-22), which can be easily used to obtain vanillylamine by hydrogenation reduction[47-48], with which reacted with different fatty acid derivatives to form the amide bond and generate the corresponding capsaicinoids,[49-51] as showed in Figure 2.

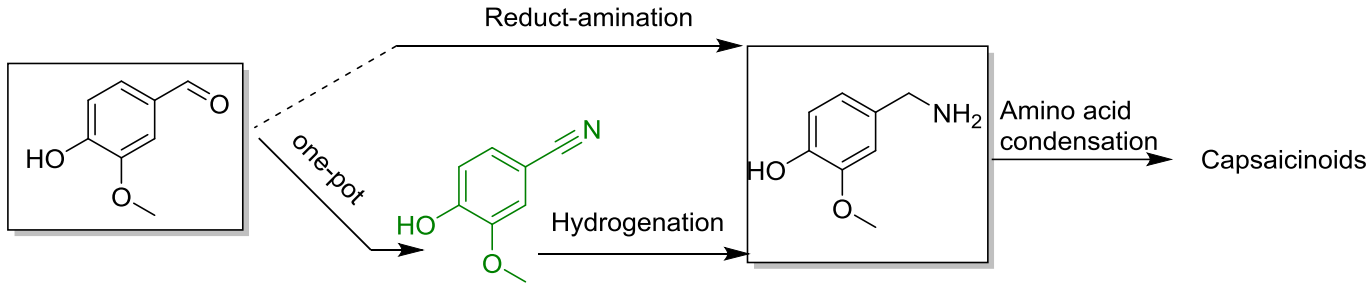
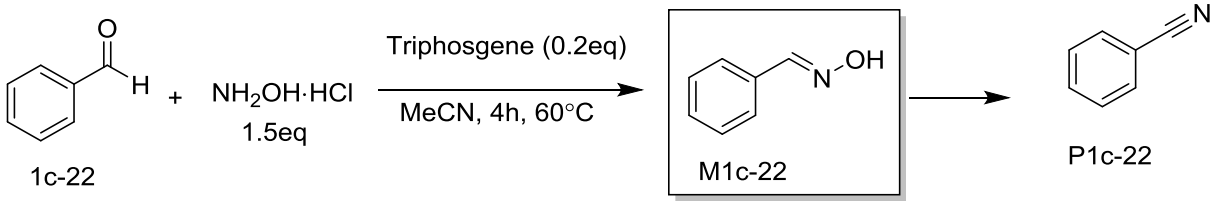


Figure. 2 Methods for preparing capsaicinoids.

Results and discussion

We initially explored the reaction condition of benzaldehyde (1 equiv.) with hydroxylamine hydrochloride (1.5 equiv.) and triphosgene (0.2 equiv.) at 60 °C with acetonitrile as the solvent in the yield of 97% (Table 1). To our delight, the desired product of acetophenone, acetanilide was obtained with a similar method in 81% yield at 80 °C (Table 2). None of the other solvents screened were superior to acetonitrile. We investigated the reaction in the absence of triphosgene, according to benzaldehyde, and the reaction did fully convert but little proceed further after producing the oxime. Besides, acetophenone has a similar pattern but lower conversion. To improve the conversion and selectivity of the aldehydes and ketones in the tandem reaction, we took the approach, which adds hydroxylamine hydrochloride and triphosgene by steps, and we were pleased to observe the desired nitrile and acetanilide product in 99% and 90%, respectively. (refer to ESI† for more details).

Table 1. Variation of standard condition for the transformation of benzaldehyde to benzonitrile.



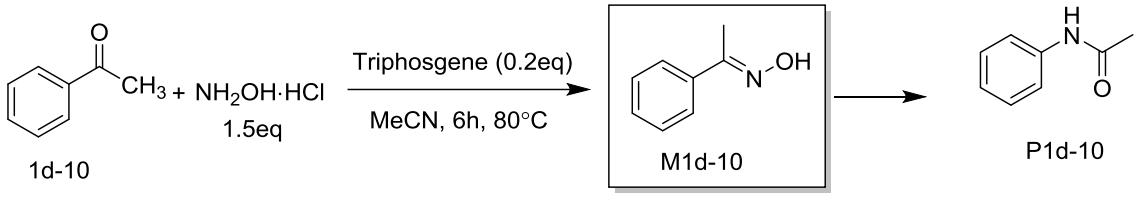
Entry	Change from standard conditions	% Conv.[a]	% yield(M1c)[a]	% yield(P1c)[a]
1	None	97	0	97

2	MeOH instead of MeCN	99	28	39
3	DCE instead of MeCN	0	0	0
4	Toluene instead of MeCN	0	0	0
5	EA instead of MeCN	61	26	35
6	Dioxane instead of MeCN	87	58	29
7	rt (about 30°C)instead of 60°C	10	0	10
9	Without triphosgene	95	48	47
10	After $NH_2OH{\cdot}HCl$ for 1 hour, add triphosgene for another 3 hours.	>99	0	>99

*All reactions were performed on 0.5 mmol scale at 60 °C for 4 h.

[a]Determined by GC with the GC datas of 1c-22, M1c-22 and P1c-22 as reference.

Table 2. Variation of standard condition for the transformation of acetophenone to acetanilide.



Entry	Change from standard conditions	% Conv.[a]	% yield(M1c)[a]	% yield(P1c)[a]
1	None	92	7	81
2	MeOH instead of MeCN	87	84	0
3	DCE instead of MeCN	0	0	0
4	Toluene instead of MeCN	0	0	0
5	EA instead of MeCN	16	14	0
6	Dioxane instead of MeCN	36	36	0
7	rt (about 30°C)instead of 80°C	0	0	0
8	Without triphosgene	56	28	24
9	After $NH_2OH{\cdot}HCl$ for 3 hour, add triphosgene for another 3 hours.	96	4	91

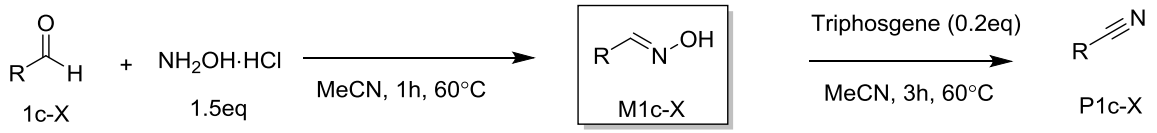
*All reactions were performed on 0.5 mmol scale at 80 °C for 6 h.

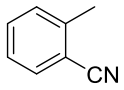
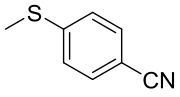
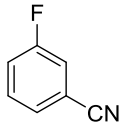
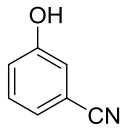
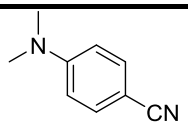
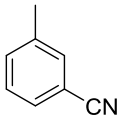
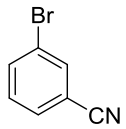
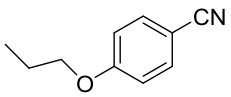
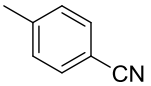
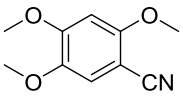
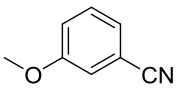
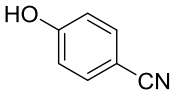
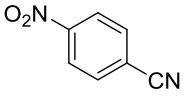
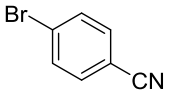
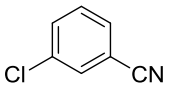
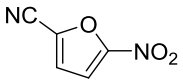
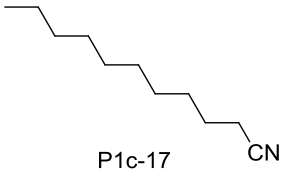
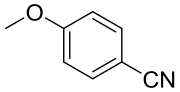
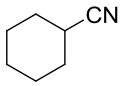
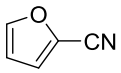
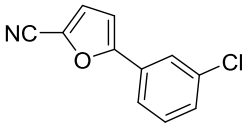
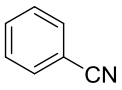
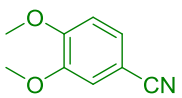
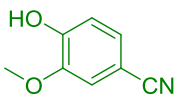
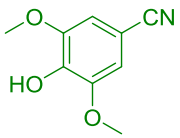
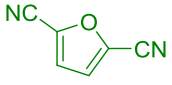
[a]Determined by GC with the GC datas of 1d-10, M1d-10 and P1d-10 as reference.

After optimization of reaction conditions, we further assessed our reaction system for the application in aromatic and aliphatic aldehydes (Table 3). A wide array of aldehyde derivatives with various substituent groups were selectively converted, affording corresponding nitriles in excellent yields. For instance, the tandem conversion of aliphatic aldehydes (1c-17 and 19) gave the corresponding nitrile products in 83–89% yields. Electron-withdrawing groups substituted aromatic aldehydes, such as nitro (1c-13)- and halogen (1c-3,7,14 and 15) substituted benzaldehyde, afforded the corresponding nitrile products with yields above 93%. On the other hand, the yields of nitriles derived from the one-pot transformation of multi-substituent benzaldehyde (1c-10) and electron-donating groups (1c-1,2,4,5,6,8,9,11,12 and 18) substituted substrates were also satisfying. It is worth noting that the effect of steric hindrance did not influence the reactivity. For example, ortho-substituted aldehydes such as (1c-1) gave the corresponding 2-(methyl) benzonitrile (P1c-1) 97%, which obtained the same high yield as m-(methyl) benzonitrile (P1c-6) 99% and p-(methyl) benzonitrile (P1c-9) 98%. Several meta-substituted aldehydes incorporating bromo (1c-7), methoxy (1c-11), hydroxyl (1c-4) substituents were tolerated, delivering the nitrile products in excellent yields of 93–98% with comparable to para-substituted aldehydes. Furthermore, we were pleased to observe the good yield of nitrile product from furfural (1c-20) and its derivatives (1c-16 and 21) above 94% conversion. Herein, our standard protocol was established in the guideline of sustainable development and green chemistry, it is desirable to convert aldehydes from oxidative depolymerization of lignin into corresponding

nitriles under mild conditions, such as vanillin, syringaldehyde, and veratraldehyde, as a result, we got corresponding nitriles in excellent conversion and selectivity. We also examined our standard protocol by subjecting 2,5-diformylfuran (1c-26) to the synthesis of 2,5-dicyanofuran, and obtained the dinitrile product (P1c-26) above 99% conversion and 93% selectivity. It is worth noting that 2,5-dicyanofuran is probably applied in the preparation of biomass-based commercial chemicals such as spices, medicines, and pesticides.[52]

Table 3 Scope of aromatic, heteroaromatic, and aliphatic aldehydes[a]

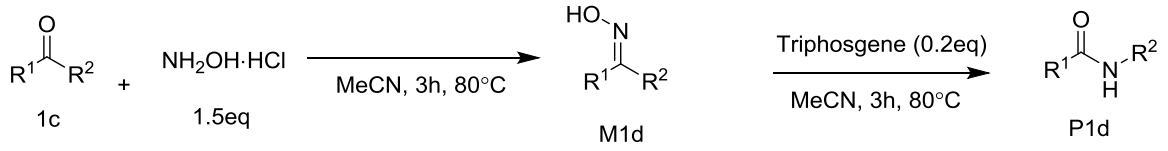


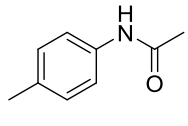
 P1c-1 >99%con. 98%sel.	 P1c-2 >99%con. 98%sel.	 P1c-3 >99%con. 96%sel.	 P1c-4 >99%con. 98%sel.	 P1c-5 >99%con. 95%sel.
 P1c-6 >99%con. 99%sel.	 P1c-7 >99%con. 96%sel.	 P1c-8 >99%con. 98%sel.	 P1c-9 >99%con. 98%sel.	
 P1c-10 >99%con. 96%sel.	 P1c-11 >99%con. 98%sel.	 P1c-12 >99%con. >99%sel.	 P1c-13 >99%con. 98%sel.	 P1c-14 >99%con. 99%sel.
 P1c-15 97%con. 97%sel.	 P1c-16 94%con. 94%sel.	 P1c-17 >99%con. 83%sel.	 P1c-18 >99%con. 97%sel.	
 P1c-19 >99%con. 89%sel.	 P1c-20 >99%con. 87%sel.	 P1c-21 >99%con. 95%sel.	 P1c-22 >99%con. >99%sel.	
 P1c-23 >99%con. >99%sel.	 P1c-24 97%con. >99%sel.	 P1c-25 >99%con. 98%sel.	 P1c-26[b] >99%con. 93%sel.	

Reaction conditions: [a]General procedure A: 0.5 mmol aldehydes, 0.75 mmol $NH_2OH·HCl$, 0.1 mmol triphosgene, 4 mL MeCN, 60 °C, 4 h. [b] General procedure C: 0.5 mmol aldehydes, 0.75 mmol $NH_2OH·HCl$, 0.1 mmol triphosgene, 4 mL MeCN, 60 °C, 4 h. Conversion and Selectivity were determined by GC/^{1}H NMR spectroscopy.

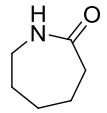
Given the importance and broad application of amide molecules in the textile and pharmaceutical sector, we also examined our standard protocol in the preparation of amide products from various ketones (Table 4). Notably, an array of aliphatic ketones such as (1d-2) and (1d-8) underwent our protocol smoothly giving the corresponding amide products above 85% yields. Phenylacetone with different substituent groups (1d-4, 6) also worked very well. Interestingly, the yields of amide from the transformation of p- methyl substituted and o(p)- methoxy- acetophenone (1d-1, 3 and 7) and naphthophenone were very well, in comparison, the yields of amides obtained from the transformation of o-methyl substituted acetophenone (1d-9) and 3,4-methylenedioxyacetophenone (2) were relatively lower but still satisfactory. Probably owing to the steric hindrance effect, the transformation of para-methyl-substituted acetophenone (1) generated corresponding acetanilide with a higher yield (93%) than ortho-methyl-substituted acetophenone (9) (55%). However, due to the more important electron-induced effect, the conversion of ortho- (7) and para-methoxyl-substituted substrate (3) obtained the target products in a similarly high yield (above 90%). As well as the same reason is true for the lower yield of the conversion of para- chlorine acetophenone (1d-5).

Table 4 Scope of aromatic, heteroaromatic, and aliphatic aldehydes[a]

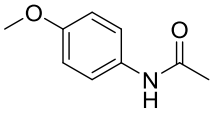



P1d-1

97%con. 93%sel.


P1d-2

>99%con. 85%sel.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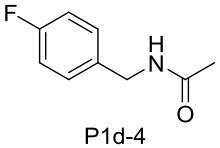
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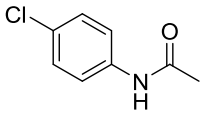
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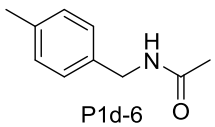
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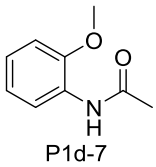
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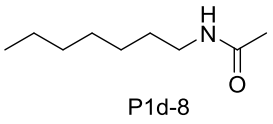
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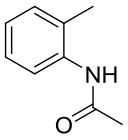
>99%con. 96%sel.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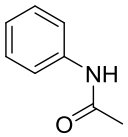
58%con. 94%sel.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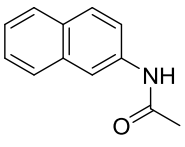
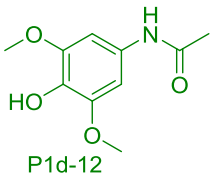
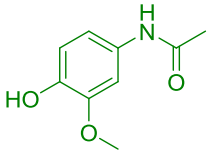
96%con. 95%sel.


P1d-11

97%con. 93%sel.


P1d-12

85%con. 94%sel.

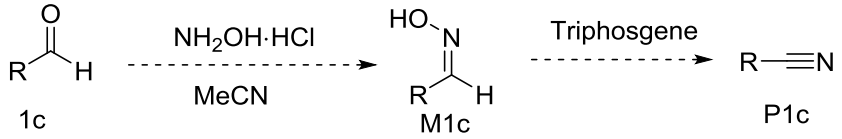

P1d-13

97%con. >93%sel.

[a]Reaction conditions: General procedure B: 0.5 mmol aldehydes, 0.75 mmol $NH_2OH·HCl$, 0.1 mmol triphosgene, 4 mL MeCN, 80 °C, 4 h. Conversion and Selectivity were determined by GC/^{1}H NMR spectroscopy.

A plausible route including two steps for this nitrile one-pot synthesis is illustrated in Scheme 1. Initially, the attack of hydroxylamine hydrochloride to aldehyde gives an intermediate oxime M1c, which then undergoes triphosgene-assisted dehydration to give the desired nitrile product P1c. In this process, there is no doubt about the reaction mechanism of the first step. To investigate the acting property of triphosgene for these oximes, and confirm that the reaction mechanism of the conversion of oxime to nitrile, as described in Scheme 2, 1c-22 was selected as a representative, ^{1}H NMR titration experiments and GC analyses were carried out. ^{1}H NMR spectra recorded after

adding triphosgene to a solution of benzaldehyde oxime in CD_3CN (Figure 3A), which showed that the hydroxyl proton (Hd) signal at 8.9 ppm disappeared and the formyl proton (Hc) signal at 8.3 ppm of benzaldehyde oxime shrunk gradually after the addition of triphosgene, and aldehydic proton signals sharply appeared at 10.1 ppm (Ha), while the proton signal of benzonitrile arose at 7.7 ppm (Hb'). In addition, based on the GC analysis of that final reaction solution, the same result as ^{1}HNMR including benzaldehyde and benzonitrile was obtained and shown in Figure 3B. As for acetophenone oxime, the hydroxyl proton (He) signal at 8.85 ppm disappeared as well as the Ar-H (7.65 ppm) and $-CH_3$ (2.25 ppm) signals were shifted (Hb" to Hb'and Hb; Hd to Hc and He). indicating the conversion of oxime to amide and ketone and shown in Figure 4A. As a result, acetanilide and acetophenone were formed, and the GC data also verified this conclusion (Figure 4B).



Scheme 1. The route of preparation of nitriles (P1c) from aldehydes.

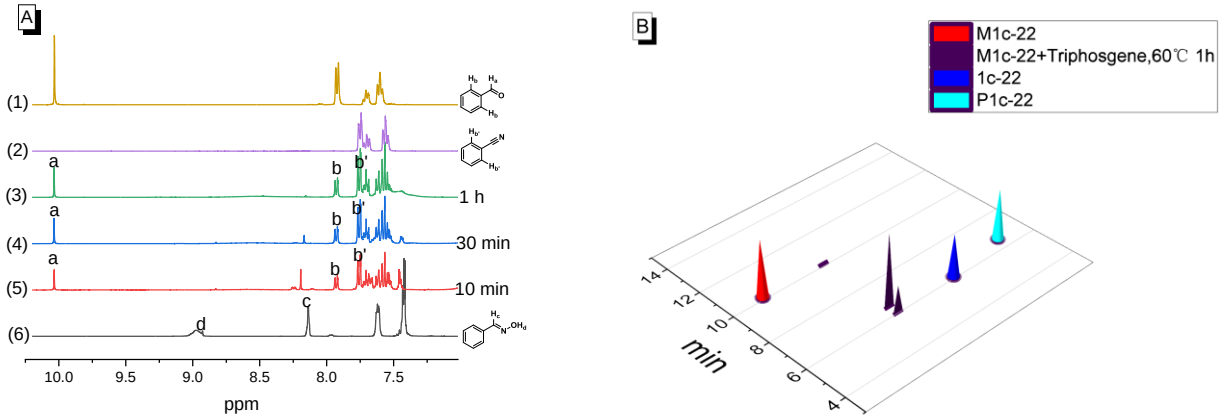


Figure 3. (A) Partial 1H NMR spectra of M1c-22 (0.5 mM) in CD_3CN before (6) and after the addition triphosgene 0.1 equiv in CD_3CN at 60 °C for 10 min (5), 30 min (4), 1 h (3) and reference NMR spectrum of P1c-22 (2) and 1c-22 (1) in CD_3CN. (B) Partial GC spectra of M1c-22 (0.5 mM) with 0.1 equiv triphosgene in CH_3CN at 60 °C for 1h, and reference GC spectrum of 1c-22, M1c-22 and P1c-22 in CH_3CN.

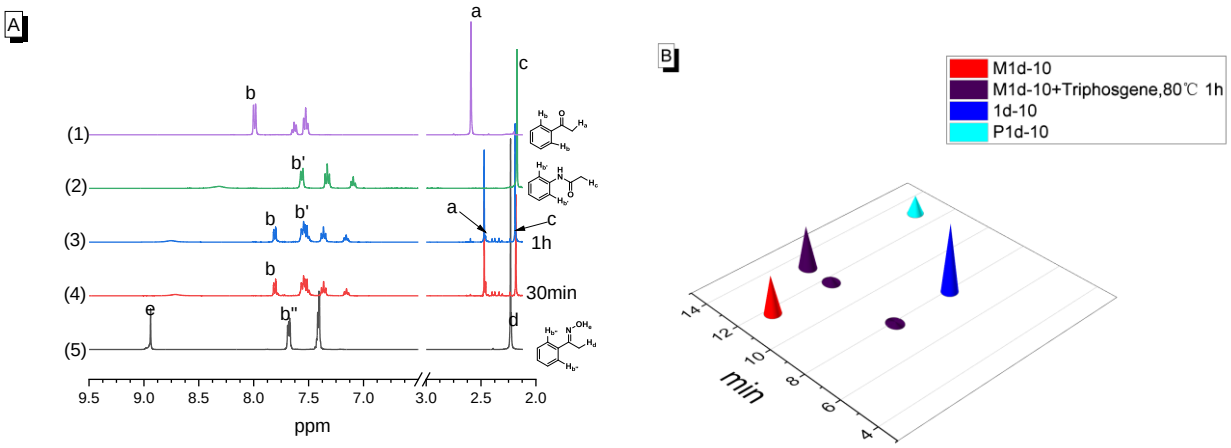
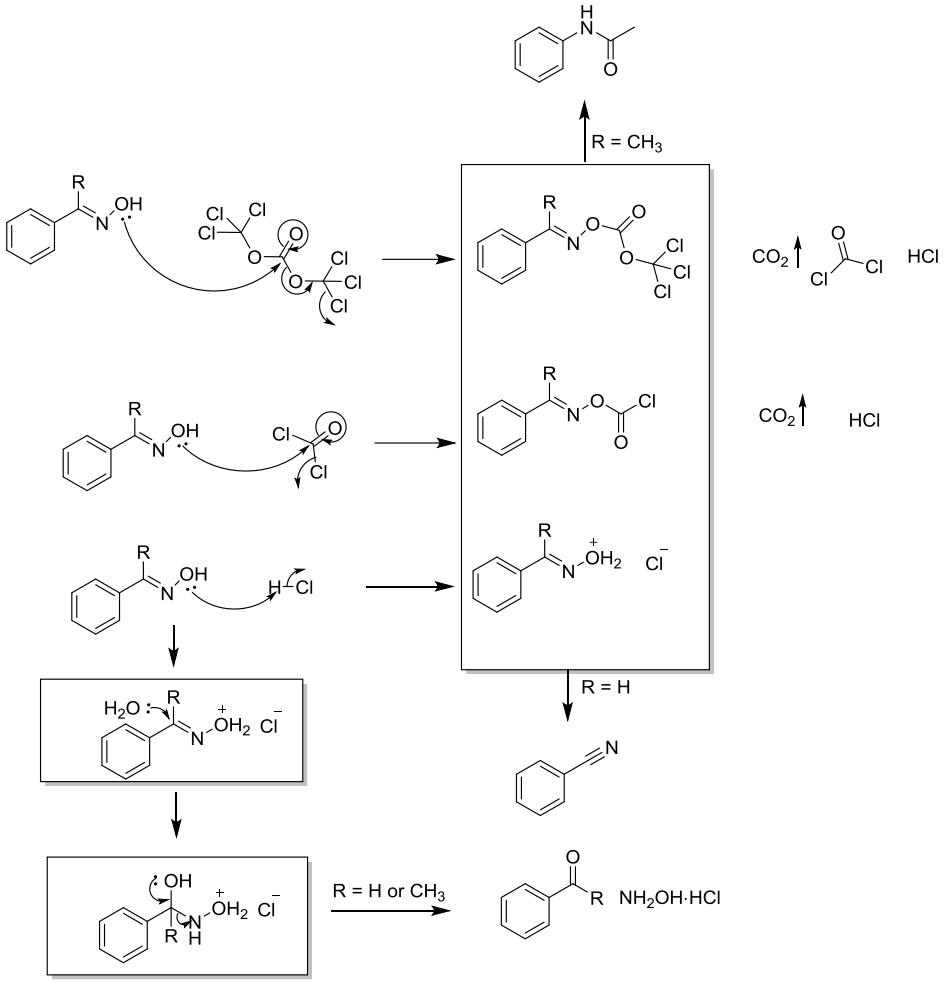


Figure 4. (A) Partial ^{1}H NMR spectra of M1d-10 (0.5 mM) in CD_3CN before (6) and after the addition triphosgene 0.1 equiv in CD_3CN at 80 °C for 10 min (5), 30 min (4), 1 h (3) and reference NMR spectrum of P1d-10 (2) and 1d-10 (1) in CD_3CN. (B) Partial GC spectra of M1d-10 (0.5 mM) with 0.1 equiv triphosgene in CH_3CN at 80 °C for 1h, and reference GC spectrum of 1d-10, M1d-10 and P1d-10 in CH_3CN.

Therefore, the reaction mechanism of the conversion of aldoxime to nitrile or amide should be described as follows: the hydroxyl of oxime attacks triphosgene and forms O-((trichloromethoxy)carbonyl) oxime as intermediate as well as phosgene and HCl as byproducts, which reacts nucleophilically with phosgene or HCl and undergoes the same path to form O-chlorocarbonyl oxime or amino oxonium. Soon, the deprotonation of the carbonyl oxime and amino oxonium convert to the final nitrile. Besides, the transformation of aldoxime into amide undergoes Beckman Rearrangement. However, Part of the oxime raw material will be hydrolyzed to aldehyde and ketone result in the lower selectivity and yield, shown in Scheme 2.



Scheme 2. Proposed reaction mechanism of oximes with triphosgene.

Conclusions

Utilizing the tandem reaction of aldehydes and ketones with hydroxylamine hydrochloride in the presence of triphosgene to construct nitriles and amides, respectively, we successfully have applied the practical protocol in the wide scope of substrates with diverse functional groups even including biomass-derived aldehydes and ketones in excellent conversions and yields. Among them, the nitrile prepared from vanillin can be used as a precursor for the synthesis of capsaicin. As a comparison, the conversion of oximes exhibits slightly inferior when directly reacting with triphosgene. More importantly, a plausible mechanism was proposed that the reaction undergoes deprotonation or rearrangement process and the one-pot reaction from aldehydes as precursors was found to be more applicable than the conversion of oximes to nitriles.

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Author contributions J. G. L. and L. L. M supervised and designed the research. X.Z.W wrote the original manuscript. J. G. L reviewed and corrected the manuscript. All authors discussed the results and assisted during manuscript preparation.

Competing interests The authors declare no competing financial interests.

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