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One-Pot Tandem Synthesis of Nitriles and Amides from Biomass Platform Compounds

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Abstract

In recent years, research on converting biomass platform compounds into high-value chemicals and pharmaceutical intermediates has garnered huge interest. Nitrile and amide groups are key structures in natural products and biologically active molecules. The direct conversion of biomass platform compounds into nitriles and amides will undoubtedly be an important guide for biomass utilization. In this paper, a facile and efficient triphosgene-assisted one-pot conversion for aldehydes and ketones into nitrile and amides is presented. Triphosgene is a phosgene alternative that contains both ester linkage and chloromethyl units and easily reacts with oximes for the preparation of nitriles and amides. However, due to the hydrolysis of oximes to aldehydes or ketones, the reaction of oximes with triphosgene cannot fully convert the corresponding nitriles and amides. The protocol tandem ensures a smooth

process without the use of organic bases or metal catalysts. Using biomass-derived platform compounds, various functionalized aromatic, aliphatic, and allylic aldehydes and ketones were successfully converted to nitriles and amides in excellent yields. In comparison to step-by-step reactions, this tandem strategy features multi-step reactions in one pot, mild reaction conditions, and fewer by-products.

Keywords
Tandem synthesis; triphosgene; nitriles and amides; biomass platform compounds

1. Introduction

Nitrile and amide groups are key structures of natural products, biologically active molecules, agrochemicals, dyes, or materials science. In the past decade, nitriles have been produced from the conversion of oximes via dehydration [1] and substitution reactions involving cyanogen reagents [2-6]. Furthermore, for the synthesis of amides, carboxylic acid derivatives and amines are traditionally applied via a condensation reaction in harsh conditions [7]. The majority of the synthesis was performed with toxic reagents and cumbersome experimental operations. There has been considerable progress in the generation of nitriles from aldehydes, which has been successfully applied to the wide substrate scope of aldehydes. However, there are few suitable methodologies for the synthesis of both nitriles and amides from aldehydes and ketones, respectively. In comparison to the traditional nucleophilic substitutions using HCN or metal cyanides [8-11], as well as the recent oximation−dehydration strategy [12] with the prepared reagents [13] or additional alkali [14, 15], an environment-friendly alternative was designed using triphosgene. This reagent is inexpensive and can be used without further preparation.

In a recent report [16], the reaction site of oxime was used in the chemical detection of phosgene. Many researchers have reported the synthesis of nitriles or amides from various oximes with phosgene or its substitutes, such as triphosgene and diphosgene. However, most of these applications suffer from toxic phosgene overflow under alkaline conditions (such as adding TEA to the reaction system) and have narrow substrate scope. Phosgene and its substitutes are important industrial feedstocks used in the production of polyurethanes, polycarbonates, pharmaceuticals [17], insecticides, and aniline dyes [18, 19]. Also, phosgene and diphosgene are highly toxic lung irritants even at low conversions. Due to the hazardous effects, they were utilized as chemical warfare agents (CWAs) during World War I and World War II [20]. Triphosgene is a non-volatile alternative to phosgene and is widely used in chemical synthesis. In this paper, triphosgene was utilized as the starting material to achieve the one-pot conversion of aldehydes and ketones to nitriles and amides. The generated HCl plays a good catalytic role in the Beckmann rearrangement reaction.

With the increasing demand for chemicals and fuels derived from fossil resources, the prospects of developing those alternatives from the catalytic transformation of renewable biomass have sparked global concern [21-26]. Among the alternatives to biomass valorization, the production of 5-hydroxymethylfurfural (HMF) from hexoses offers a versatile platform for the synthesis of furan-based chemicals such as furyl diamide, diamidine, diimidate, and diformylfuran [27, 28]. Therefore, aromatic aldehydes and ketones [29-39] such as vanillin veratraldehyde, acetovanillone,

acetosyringone, and syringaldehyde can be obtained by the oxidative depolymerization of lignin and lignin model compounds. To further demonstrate the utility of our protocol, the one-pot strategy was utilized for the efficacious synthesis of 2,5-dicyanofuran from biomass-derived 2,5-diformylfuran. In addition, lignin-derived monoaldehyde and aromatic ketone yielded beneficial nitriles and amides. Capsaicin analogs such as nonivamide, capsaicin, and phenylcapsaicin [40] (see Figure 1), as typical capsaicinoid compounds show prominent anti-inflammatory [41] and anti-cancer [42] properties; these compounds have been widely applied in cancer prevention [43]. Capsaicinoids are usually prepared from vanillin by reducing vanillin oxime to obtain vanillylamine, which further reacts with acyl chlorides (Schotten-Baumann) to form the final products [44-47].

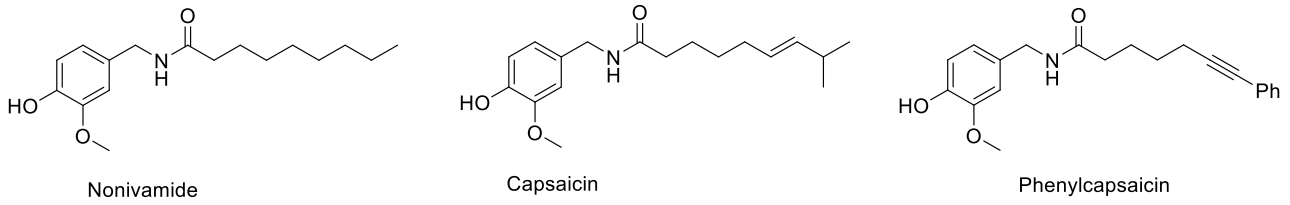


Figure 1 Examples of biologically active capsaicinoids.

Alternatively, to synthesize capsaicin analogs, our method was utilized to prepare the intermediate 4-hydroxy-3-methoxybenzonitrile (P1c-22), which can be easily used to obtain vanillylamine by hydrogenation reduction [48, 49]. As depicted in Figure 2, vanillylamine reacts with different fatty acid derivatives to form the amide bond and generate the corresponding capsaicinoids [50-52].

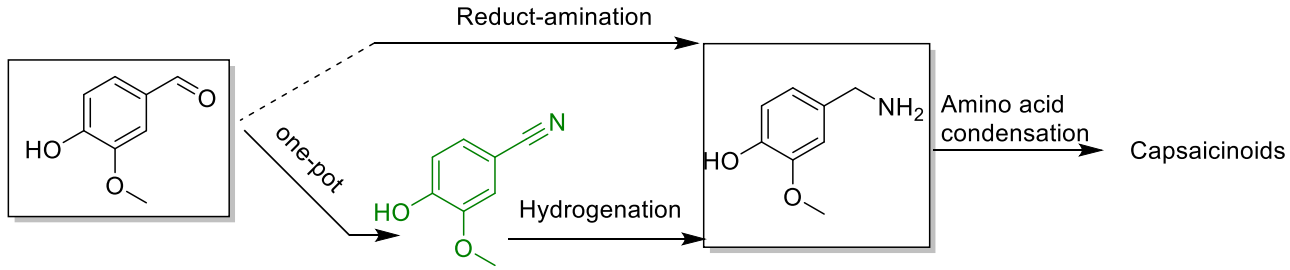
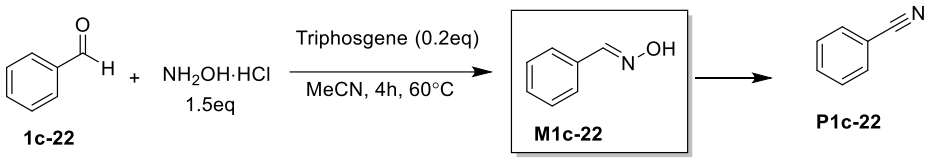


Figure 2 Methods for preparing capsaicinoids.

2. Results and Discussion

The reaction condition of benzaldehyde (1 equiv.) was initially investigated with hydroxylamine hydrochloride (1.5 equiv.) and triphosgene (0.2 equiv.) at 60 °C with acetonitrile as the solvent, yielding 97% (Table 1). In a similar method, acetanilide, the desired product of acetophenone, was obtained with a yield of 81% at 80 °C (Table 2). None of the other screened solvents were superior to acetonitrile. The reaction was investigated in the absence of triphosgene, according to benzaldehyde, and the reaction did fully convert but did not proceed much further after producing the oxime. Moreover, acetophenone has a similar pattern but lower conversion. To improve the conversion and selectivity of the aldehydes and ketones in the tandem reaction, hydroxylamine hydrochloride and triphosgene were added in steps, and the desired nitrile and acetanilide products were observed with yields of 99% and 90%, respectively. (Refer to ESI† for more details)

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

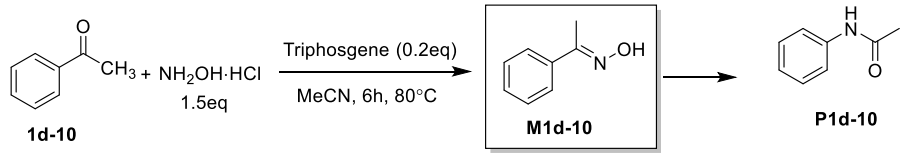


Entry	Change from standard conditions	% Conv.[a]	% yield(M1c)[a]	% yield(P1c)[a]
1	None	97	0	97
2	MeOH instead of MeCN	99	28	39
3	DCE instead of MeCN	0	0	0
4	Toluene instead of MeCN	0	0	0
5	EA instead of MeCN	61	26	35
6	Dioxane instead of MeCN	87	58	29
7	rt (about 30°C) instead of 60°C	10	0	10
9	Without triphosgene	95	48	47
10	After $NH_2OH·HCl$ for 1 h, add triphosgene for another 3 h.	>99	0	>99
11	10 μL HCl (wt 37 %) instead of triphosgene	73	0	73

* Standard conditions: All reactions were performed on 0.5 mmol scale benzaldehyde, 1.5 eq $NH_2OH·HCl$, 0.2 eq triphosgene at 60 °C for 4 h.

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

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



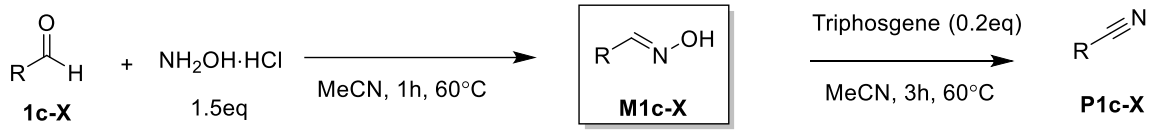
Entry	Change from standard conditions	% Conv.[a]	% yield(M1c)[a]	% yield(P1c)[a]
1	None	92	7	81
2	MeOH instead of MeCN	87	84	0
3	DCE instead of MeCN	0	0	0
4	Toluene instead of MeCN	0	0	0
5	EA instead of MeCN	16	14	0
6	Dioxane instead of MeCN	36	36	0
7	rt (about 30°C) instead of 80°C	0	0	0
8	Without triphosgene	56	28	24
9	After $NH_2OH·HCl$ for 3 h, add triphosgene for another 3 h.	96	4	91
10	10 μL HCl (wt 37 %) instead of triphosgene	68	28	35

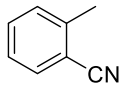
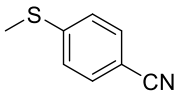
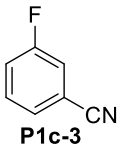
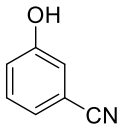
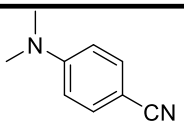
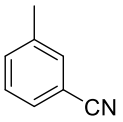
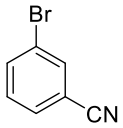
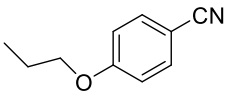
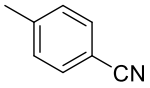
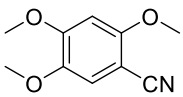
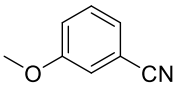
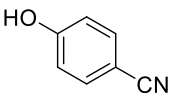
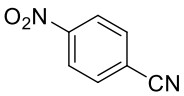
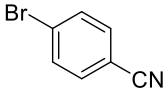
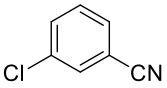
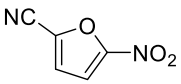
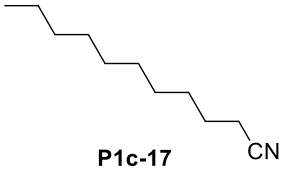
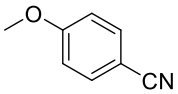
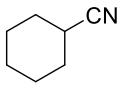
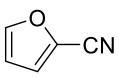
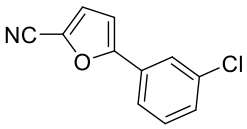
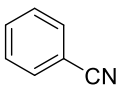
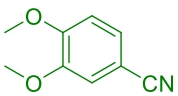
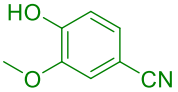
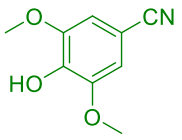
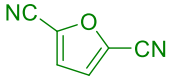
* Standard conditions: All reactions were performed on 0.5 mmol scale acetophenone, 1.5 eq $NH_2OH·HCl$, 0.2 eq triphosgene at 80 °C for 6 h.

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

As shown in Table 3, the reaction system for the application was assessed in aromatic and aliphatic aldehydes after the optimization of the reaction conditions. A wide array of aldehyde derivatives with various substituent groups were converted selectively, yielding 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, to give the corresponding nitrile products with yields exceeding 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 satisfactory. The effect of steric hindrance did not affect the reactivity. For example, ortho-substituted aldehydes such as (1c-1) yielded 97% 2-(methyl) benzonitrile (P1c-1) with the same high yield as 99% m-(methyl) benzonitrile (P1c-6) and 98% p-(methyl) benzonitrile (P1c-9). Several meta-substituted aldehydes incorporating bromo (1c-7), methoxy (1c-11), and hydroxyl (1c-4) substituents were tolerated, delivering the nitrile products in excellent yields of 93-98%, which is comparable to the para-substituted aldehydes. Furthermore, the good yield of nitrile product from furfural (1c-20) and its derivatives (1c-16 and 21) was observed to have a conversion rate of over 94%. Based on sustainable development and green chemistry, our standard protocol was established. Accordingly, 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, corresponding nitriles were obtained with excellent conversion and selectivity. The standard protocol was examined by subjecting 2,5-diformylfuran (1c-26) to the synthesis of 2,5-dicyanofuran and obtaining the dinitrile product (P1c-26) with a conversion of above 99% and selectivity of 93%. It is noteworthy that 2,5-dicyanofuran may be applied in the preparation of biomass-based commercial chemicals such as spices, medicines, and pesticides [53].

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



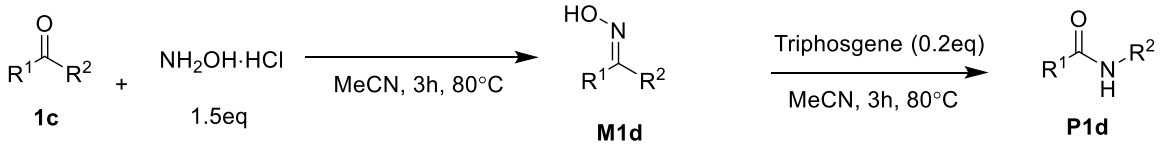
 **P1c-1** >99%con. 98%sel.	 **P1c-2** >99%con. 98%sel.	 **P1c-3** >99%con. 96%sel.	 **P1c-4** >99%con. 98%sel.	 **P1c-5** >99%con. 95%sel.
 **P1c-6** >99%con. 99%sel.	 **P1c-7** >99%con. 96%sel.	 P1c-8 >99%con. 98%sel.	 **P1c-9** >99%con. 98%sel.	
 **P1c-10** >99%con. 96%sel.	 **P1c-11** >99%con. 98%sel.	 **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.	

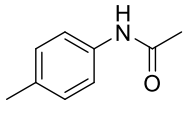
Reaction conditions: [a]General procedure A: 0.5 mmol aldehydes, 0.75 mmol $NH_2OH·HCl$, 0.1 mmol triphosgene, 4 mL MeCN, 60 °C, 4 h. [b] General procedure C: 0.5 mmol aldehydes, 0.75 mmol $NH_2OH·HCl$, 0.1 mmol triphosgene, 4 mL MeCN, 60 °C, 4 h. Conversion and Selectivity were determined by GC/^{1}H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

The standard protocol followed in the preparation of amide products from various ketones (Table 4) was examined, given the relevance and broad application of amide molecules in the textile and

pharmaceutical sectors. An array of aliphatic ketones such as (1d-2) and (1d-8) underwent our protocol smoothly, giving the corresponding amide products with yields of over 85%. Phenylacetone with various substituent groups (1d-4, 6) performed 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 excellent. However, 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. As a consequence of the steric hindrance effect, the transformation of the para-methyl-substituted acetophenone (1) generated corresponding acetanilide with a higher yield (93%) than the ortho-methyl-substituted acetophenone (9) (55%). However, the conversion of ortho-(7) and para-methoxyl-substituted substrate (3) obtained the target products in a similarly high yield (above 90%) due to the more important electron-induced effect. This is the underlying reason for the lower yield of the conversion of para-chlorine acetophenone (1d-5).

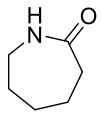
Table 4 Scope of aromatic, heteroaromatic, and aliphatic aldehydes [a].





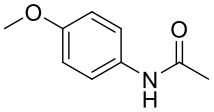
P1d-1

97%con. 93%sel.



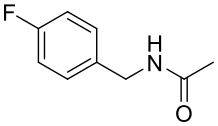
P1d-2

>99%con. 85%sel.



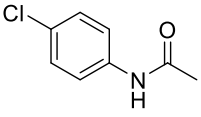
P1d-3

94%con. 93%sel.



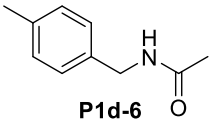
P1d-4

>99%con. 86%sel.



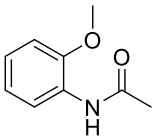
P1d-5

81%con. 61%sel.



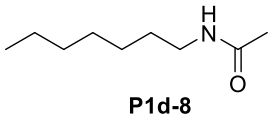
P1d-6

>99%con. 81%sel.



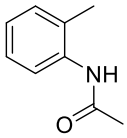
P1d-7

>99%con. 95%sel.



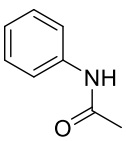
P1d-8

>99%con. 96%sel.



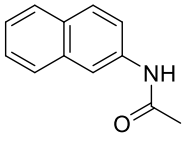
P1d-9

58%con. 94%sel.



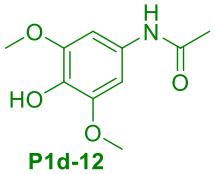
P1d-10

96%con. 95%sel.



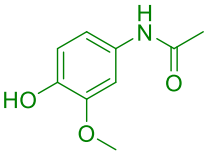
P1d-11

97%con. 93%sel.



P1d-12

85%con. 94%sel.



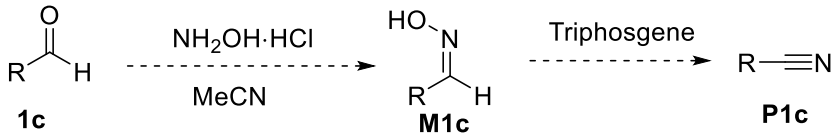
P1d-13

97%con. >93%sel.

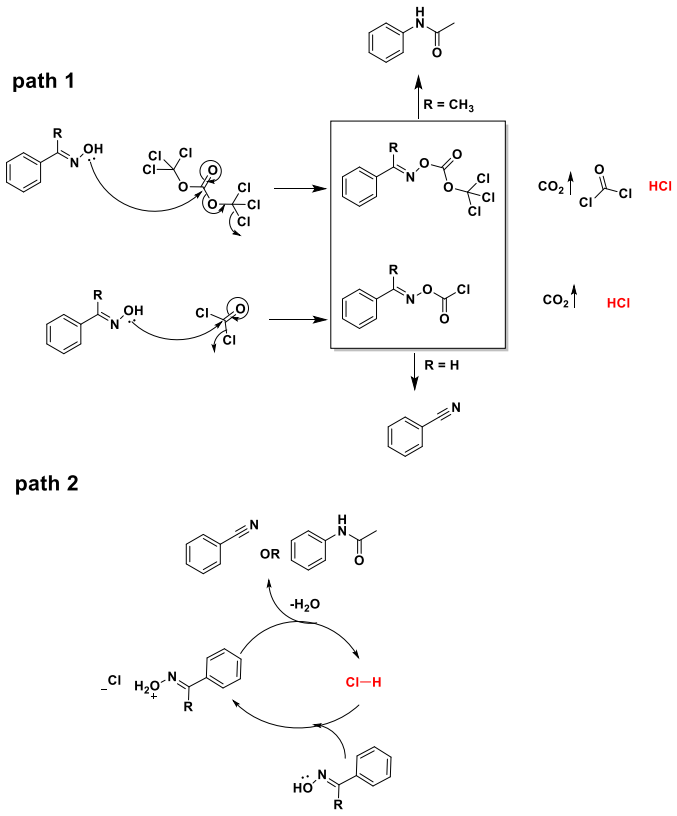
[a] Reaction conditions: General procedure B: 0.5 mmol aldehydes, 0.75 mmol $NH_2OH·HCl$, 0.1 mmol triphosgene, 4 mL MeCN, 80 °C, 4 h. Conversion and Selectivity were determined by GC/^{1}H NMR spectroscopy.

Scheme 1 illustrates a plausible route, including two steps for this nitrile one-pot. Initially, the attack of hydroxylamine hydrochloride on aldehyde gives an intermediate oxime M1c, which then undergoes triphosgene-assisted dehydration to give the desired nitrile product P1c. The reaction mechanism of the first step is clear in this process. To investigate the acting property of triphosgene

for these oximes and confirm the reaction mechanism of the oxime to nitrile conversion, as described in Scheme 2, 1c-22 was selected as a representative; ^{1}H NMR titration experiments and GC analyses were performed. As shown in Figure 3A, the ^{1}H NMR spectra were recorded after adding triphosgene to a solution of benzaldehyde oxime in CD_3CN. The spectra showed that the hydroxyl proton (H_d) signal at 8.9 ppm disappeared and the formyl proton (H_c) signal at 8.3 ppm of benzaldehyde oxime shrank gradually after the addition of triphosgene. The aldehydic proton signals sharply appeared at 10.1 ppm (H_a), while the proton signal of benzonitrile arose at 7.7 ppm ($H_{b'}$). As shown in Figure 3B, based on the GC analysis of that final reaction solution, the same result as ^{1}HNMR, including benzaldehyde and benzonitrile, was obtained. As for acetophenone oxime, the hydroxyl proton (H_e) signal at 8.85 ppm disappeared and the Ar-H (7.65 ppm) and -CH_3 (2.25 ppm) signals were shifted ($H_{b''}$ to $H_{b'}$ and H_b; H_d to H_c and H_e), indicating the conversion of oxime to amide and ketone and shown in Figure 4A. Consequently, acetanilide and acetophenone were formed, and the GC data verified this conclusion (Figure 4B).



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



Scheme 2 Proposed reaction mechanism of oximes with triphosgene.

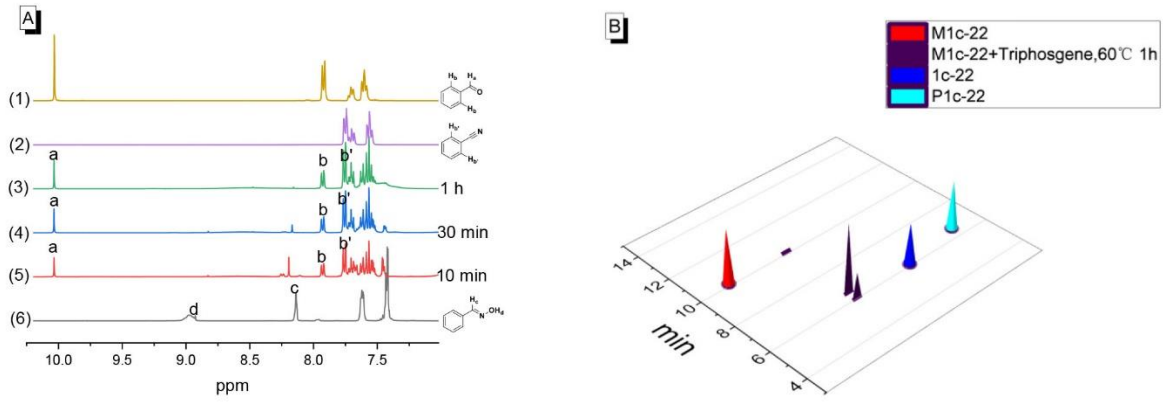


Figure 3 (A) Partial 1H NMR spectra of M1c-22 (0.5 mM) in CD_3CN before (6) and after the addition triphosgene 0.1 equiv in CD_3CN at 60 °C for 10 min (5), 30 min (4), 1 h (3) and reference NMR spectrum of P1c-22 (2) and 1c-22 (1) in CD_3CN. (B) Partial GC spectra of M1c-22 (0.5 mM) with 0.1 equiv triphosgene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

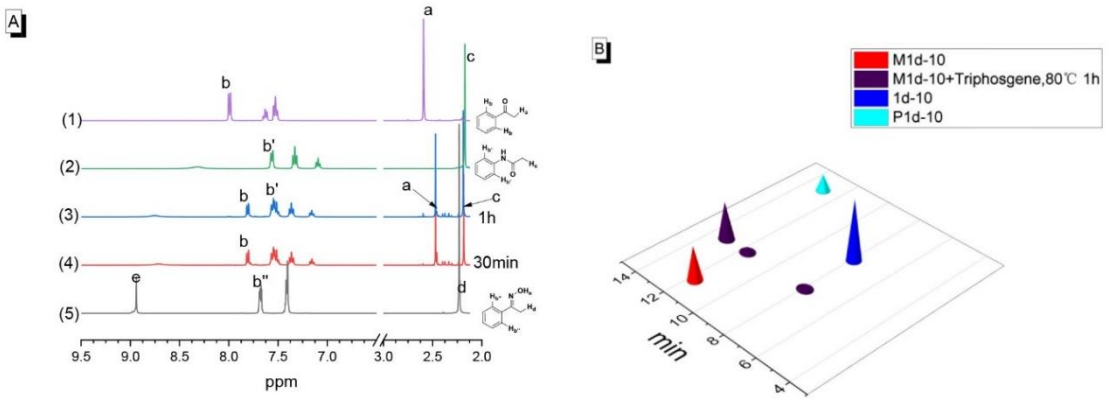


Figure 4 (A) Partial ^1H NMR spectra of M1d-10 (0.5 mM) in CD_3CN before (6) and after the addition triphosgene 0.1 equiv in CD_3CN at 80 °C for 10 min (5), 30 min (4), 1 h (3) and reference NMR spectrum of P1d-10 (2) and 1d-10 (1) in CD_3CN. (B) Partial GC spectra of M1d-10 (0.5 mM) with 0.1 equiv triphosgene in CH_3CN at 80 °C for 1 h, 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: Along **path 1**, the hydroxyl of oxime attacks triphosgene forming O-((trichloromethoxy)carbonyl) oxime as intermediate, as well as phosgene and HCl, which reacts nucleophilically with phosgene or HCl and follows the same path to form O-chlorocarbonyl oxime or amino oxonium. Soon, the deprotonation of the carbonyl oxime and amino oxonium converts to the final nitrile. Along **path 2**, HCl functioned as a catalyst to facilitate Beckman Rearrangement, which was consistent with the reported acid catalysis in general. The experiments verified the catalytic effect of HCl (Table 1, Entry11; Table 2, Entry10). Besides, the transformation of aldoxime into amide also undergoes Beckman Rearrangement by using triphosgene and HCl, as shown in Scheme 2.

3. Conclusions

The practical protocol was successfully applied to a wide scope of substrates with diverse functional groups, including biomass-derived aldehydes and ketones with excellent conversions and yields by utilizing the tandem reaction of aldehydes and ketones with hydroxylamine hydrochloride in the presence of triphosgene to construct nitriles and amides, respectively. Among them, the nitrile prepared from vanillin can be used as a precursor for the synthesis of capsaicin. The conversion of oximes is slightly inferior when directly reacting with triphosgene. Furthermore, a plausible mechanism was proposed that the reaction undergoes deprotonation or rearrangement, 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.

Additional Materials

The following additional materials are uploaded at the page of this paper.

1. Figure S1: ^{1}H NMR (400 MHz, $CDCl_3$) after the reaction of 1c-1.
2. Figure S2: GC (1c-1 retention time: 8.345 min) after the reaction of 1c-1.
3. Figure S3: ^{1}H NMR (400 MHz, $CDCl_3$) after the reaction of 1c-2.
4. Figure S4: GC (1c-2 retention time: 13.926 min) after the reaction of 1c-2.
5. Figure S5: ^{1}H NMR (400 MHz, $CDCl_3$) after the reaction of 1c-3.
6. Figure S6: GC (1c-3 retention time: 5.833 min) after the reaction of 1c-3.
7. Figure S7: ^{1}H NMR (400 MHz, $CDCl_3$) after the reaction of 1c-4.
8. Figure S8: GC (1c-4 retention time: 11.966 min) after the reaction of 1c-4.
9. Figure S9: ^{1}H NMR (400 MHz, $CDCl_3$) after the reaction of 1c-5.
10. Figure S10: GC (1c-5 retention time: 15.51 min) after the reaction of 1c-5.
11. Figure S11: ^{1}H NMR (400 MHz, $CDCl_3$) after the reaction of 1c-6.
12. Figure S12: GC (1c-6 retention time: 8.2 min) after the reaction of 1c-6.
13. Figure S13: ^{1}H NMR (400 MHz, $CDCl_3$) after the reaction of 1c-7.
14. Figure S14: GC (1c-7 retention time: 10.894 min) after the reaction of 1c-7.
15. Figure S15: ^{1}H NMR (400 MHz, $CDCl_3$) after the reaction of 1c-8.

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