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ARTICLE TYPE

Metal-free synthesis of cyano acrylates via cyanuric chloride-mediated three-component reactions involving a cascade consists of Knoevenagel condensation/cyano hydration/esterification

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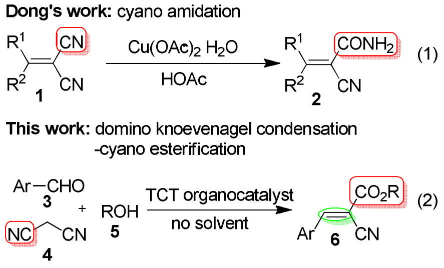
The synthesis of cyano acrylates has been achieved *via* organocatalytic domino Knoevenagel reaction, hydration and esterification under metal-free conditions without using any additional solvent. During the reaction, the *in situ* produced water from the Knoevenagel condensation promotes the hydration of cyano group and initiates the subsequent esterification, which makes up a novel, clean and atom economical route towards the synthesis cyano acrylates.

Achieving multiple chemical transformations in one-pot, one-step operation is a longstanding and central task of modern organic synthesis. Those reactions allowing multiple chemical transformations in one step under one set of reaction conditions are known as domino (also known as cascade or tandem) reactions.[1] Because of their unique advantage of step economics, during the past several decades, the domino reaction has been extensively investigated and exhibited enormous utilities in the synthesis of natural products, biologically functional molecule, fine chemicals as well as material precursors.

On the other hand, organocatalysis which is free of the reliance on metal catalyst is currently one of the most favourable and promising strategies for sustainable organic synthesis owing to its cleanness, atom economics and versatile catalytic models.[2] Under this aspiration, a synthetic concept known as organocatalytic domino reaction which combines the advantages of both organocatalysis and domino reaction is emerging as a powerful tool of in the synthesis of organic proudcts.[3] Cyanuric chloride, also known as 2,4,6-trichloro-1,3,5-triazine (TCT) is a solid organocatalyst of low cost and broad functions.[4] Besides acting as a conventional acid source to catalyze various organic reactions,[5] TCT has displayed more valuable utilities in mediating or promoting a large number of unconventional organic transformations which are hardly possible with common organic or inorganic acid catalysts. For example, TCT has been found as the first organocatalyst to enable the Beckmann rearrangement reactions of ketoximes to provide amides,[6a] the direct conversion of alkyl alcohols to corresponding chlorides,[6b] the carboxylic acid-based Friedel-Crafts acylation,[6c] direct oxidation of alkyl alcohols to carboxylic acids,[6d] formation of formate esters as protection of primary alcohols,[6e] the direct synthesis of isocyanides from formamides,[6f] among others.[7] Despite the availability of all these decent catalytic applications, however, multicomponent domino reactions that allowing fast generation of structurally diverse products using TCT as catalyst or promoter are rarely available.[8]

During our research process in the field of organocatalytic multicomponent domino reactions,[9] we have identified that TCT could mediate the three-component reactions of aldehydes, malonitrile and alcohols to yield cyano acrylates without using additional solvent. While the dehydration-based transformation of cyano group has been known as tough work which frequently relys on harsh acidic or basic conditions for a long period,[10] developing alternative mild and benign catalytic methods of improved sustainability to realize these transformations is therefore an issue of significant concern.[11] For example, Dong and co-worker has recently established a useful copper-catalyzed approach for the selective mono hydration of methylenemalononitriles **1** to provide corresponding cyano amides **2** in HOAc medium (Eq, Scheme1).[12] Considering the urgent necessity in developing sustainable protocol for versatile cyano transformation, we report herein a metal-free organocatalytic version on the three-component synthesis of cyano acrylates **6** starting from aldehydes **3**, malonitrile **4** and alcohols **5** (Eq 2, Scheme 1). To the best of our knowledge, this is the first example on the direct synthesis of cyano acrylates with



Scheme 1 Cyano hydration-based transformation for the synthesis of amides and esters

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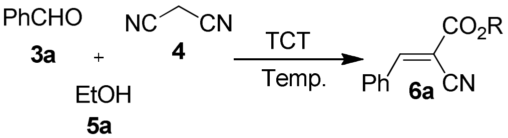
multicomponent reactions involving the domino transformation of Knoevenagel condensation and cyano esterification.

Originally, the corporation of benzaldehyde **3a**, malonitrile **4** and EtOH **5a** was run as a model reaction, and the product **6a** was obtained by simply heating the combined substrates in the presence of TCT.[13] With this interesting result initiated by TCT organocatalysis, we then conducted systematic optimization on the reaction conditions. The results from the optimization experiments were shown in Table 1. The main efforts focus on examining the effect of the TCT amount, the temperature as well as the amount of ethanol. First, the reactions in the presence of different amounts of TCT suggested that the yield **6a** increased following the increase of TCT amount from 30 mol % to 70 mol %, and no further increase was observed when 90 mol % of TCT was employed (entries 1-4, Table 1). Subsequently, varying reaction temperatures from rt to 90 °C disclosed that 80 °C was the most appropriate (entries 5-10, Table 1). Later on, altering the amount of ethanol displayed an impact on the efficiency of providing **6a**, and 2 mL EtOH gave the best result (entries 11-12). Finally, other acidic catalysts such as cerium ammonium nitrate (CAN) and *p*-tolsulfonic acid were found incapable of catalyzing this reaction (entries 13-14).

Table 1 Optimizing the reaction addition for the domino synthesis of **6a**[a]

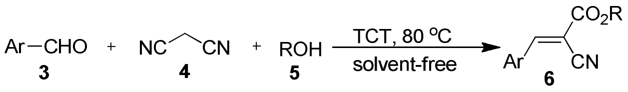


entry	T (°C)	catalyst	EtOH (mL)	Yield (%)[b]
1[c]	70	TCT	2	51
2[d]	70	TCT	2	74
3	70	TCT	2	84
4[e]	70	TCT	2	76
5	rt	TCT	2	51
7	50	TCT	2	57
8	65	TCT	2	60
9	80	TCT	2	86
10	90	TCT	2	72
11	80	TCT	1	65
12	80	TCT	3	84
13	80	*p*-TSA	2	trace
14	80	CAN	2	trace

[a]General conditions: benzaldehyde **3a** (1.0 mmol), malonitrile **4** (1.0 mmol), catalyst (0.7 mmol) and EtOH, stirred at 80 °C for 12 h. [b]Yield of isolated products based on aldehyde. [c]0.3 mmol TCT. [d]0.5 mmol TCT. [e]0.9 mmol TCT.

In light of the optimized reaction conditions, the application scope of this three-component domino reaction has been subsequently investigated. As expected, the organocatalytic protocol was found applicable for synthesizing a variety of different cyano acrylates by simply varying the aldehyde and alcohol components. As showing in Table 2, when EtOH was employed, the aryl aldehydes containing diverse functional groups such as halide, alkyl, alkoxyl, amino and nitro were able to undergo the domino transformation to produce corresponding products with good to excellent yields (**6a**-**6j**, Table 2). In addition, heteroaryl aldehydes, including both electron deficient and enriched ones could also incorporate malonitrile and the EtOH to provide corresponding heteroaryl functionalized cyano acrylates **6k** and **6l** with good yields. More notably, different alkyl alcohols, including linear (**6a-6u**), branched linear (**6v**-**6y**) and cyclic (**6z** and **6aa**) ones, had also been discovered well tolerable to this protocol to provide more diversified cyano acrylate products. Due to the steric hindrance effect to the esterification step, bulky alcohol such as *i*-PrOH was found to provide corresponding products with evidently lower yields (**6v**-**6y**, Table 2). On the other hand, the properties of the substituent in the aldehyde component showed no clear impact on the reaction. Meanwhile, the attempts on employing aliphatic aldehyde to run similar reaction were not successful under the standard catalytic conditions.

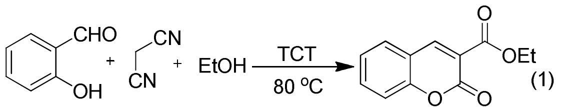
Table 2 Three-component synthesis of different cyano acrylates



Ar	R	product	yield (%)[a]
Ph	Et	**6a**	86
4-ClC_6H_4	Et	**6b**	70
4-BrC_6H_4	Et	**6c**	70
4-MeC_6H_4	Et	**6d**	73
4-$MeOC_6H_4$	Et	**6e**	59
4-$Me_2NC_6H_4$	Et	**6f**	75
2-ClC_6H_4	Et	**6g**	64
2-BrC_6H_4	Et	**6h**	69
2-$NO_2C_6H_4$	Et	**6i**	76
3-$NO_2C_6H_4$	Et	**6j**	74
2-chloropyridin-3-yl	Et	**6k**	79
furyl-2-yl	Et	**6l**	80
Ph	*n*-Pr	**6m**	76
4-ClC_6H_4	*n*-Pr	**6n**	66
4-MeC_6H_4	*n*-Pr	**6o**	64
4-$MeOC_6H_4$	*n*-Pr	**6p**	65
Ph	*n*-Bu	**6q**	65
4-MeC_6H_4	*n*-Bu	**6r**	64
Ph	*n*-pentyl	**6s**	65
4-ClC_6H_4	*n*-pentyl	**6t**	66
4-MeC_6H_4	*n*-pentyl	**6u**	69
Ph	*i*-Pr	**6v**	51
4-ClC_6H_4	*i*-Pr	**6w**	54
4-MeC_6H_4	*i*-Pr	**6x**	53
4-$MeOC_6H_4$	*i*-Pr	**6y**	56
4-MeC_6H_4	cyclohexyl	**6z**	63
4-BrC_6H_4	cyclohexyl	**6aa**	61

[a]Yield of isolated products based on aldehyde.

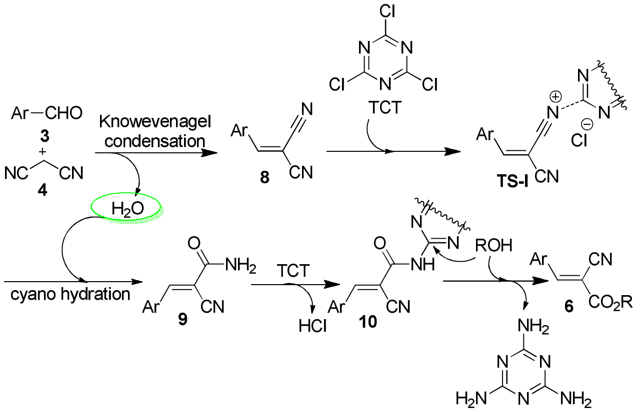
Following the extensive investigation on alcohol-based esterification, we also examined the reactivity of phenols as alternative reaction partners, and conventional substrates of the type such as phenol failed to undergo the expected three-component transformation. However, it was interesting that the salicaldehyde could incorporate malonitrile **4** and EtOH **5a** to yield 2*H*-chroemene **7** (Eq 1). According its structure, the production of **7** involved in the double esterification of the two cyano groups and a further transesterification initiated by the phenol hydroxyl group, which demonstrated the high potential of the present organocatalytic system in not only the synthesis of cyano acrylates, but also in the synthesis of useful heterocyclic products.



(1)

4 5a 7, 64 %

According to the reaction results as well as the known literature on TCT catalysis[6], the mechanism for the present domino reaction is postulated as showing in Scheme 2. Originally, the acidic reaction conditions allow for the Knoevenagel condensation between aryl aldehydes **3** and malonitrile **4** to provide intermediates **8** by releasing water. In the presence of TCT, the water in the reaction system promotes the hydration of a cyano group to give amide intermediates **9** which incorporate TCT to yield intermediates **10** via a formal nucleophilic substitution. Finally, the further nucleophilic substitution of alcohols to **10** led to the production of target products **6**.



Scheme 2 Proposed mechanism for the three-component domino reaction

Conclusions

In conclusion, we have established a novel three-component methodology for the synthesis of cyano acrylates starting from aldehydes, alcohols and malonitrile. The products are generated via the domino transformations of Knoevenagel condensation, cyano hydration and esterification. This method is particularly advantageous for the metal- free reaction conditions requiring no addition solvent and allows for easy and rapid synthesis of cyano acrylates libraries.

Experimental

General procedure for the three-component synthesis of cyano acrylates

To a 25 mL round bottom flask equipped with stirring bar and water condenser were located aldehyde **3** (1.0 mmol), malonitrile **4** (1.0 mmol), TCT (0.7 mmol) and alcohol **5** (2 mL). The resulting mixture was stirred at 80 °C for 12 h (TLC). After completion, the mixture was allowed to cool down to room temperature, and was added with 5 mL water. The resulting mixture was extracted with EtOAc (3×10 mL). The organic layer was combined and dried with anhydrous $MgSO_4$. After filtration, the solvent in the acquired solution was removed under reduced pressure. The residue was subjected to silica gel column chromatography to provide target products using mixed petroleum ether (PE) and ethyl acetate (EA) (V /V PET : EA = 80:1, then 40 : 1) as eluent.

Ethyl 2-cyano-3-phenylacrylate (**6a**).[13] ^1H NMR (400 MHz, $CDCl_3$): δ = 8.26 (s, 1 H), 8.00 (d, *J* = 7.2 Hz, 2 H), 7.59-7.49 (m, 3 H), 4.40 (q, *J* = 7.2 Hz, 2 H), 1.41 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.5, 155.1, 133.4, 131.5, 131.1, 130.1, 115.5, 103.0, 62.8, 14.2.

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