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Direct Three-Component Synthesis of α-Cyano Acrylates Involving Cascade Knoevenagel Reaction and Esterification

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A direct three-component approach has been developed for the synthesis of α-cyano acrylates starting from aldehydes, alcohols and α-cyano acetamide by employing cyanuric chloride as an organocatalyst. A class of structurally diverse α-cyano acrylates have been provided with good to excellent yields via the cascade transformation of Knoevenagel condensation and amide esterification.

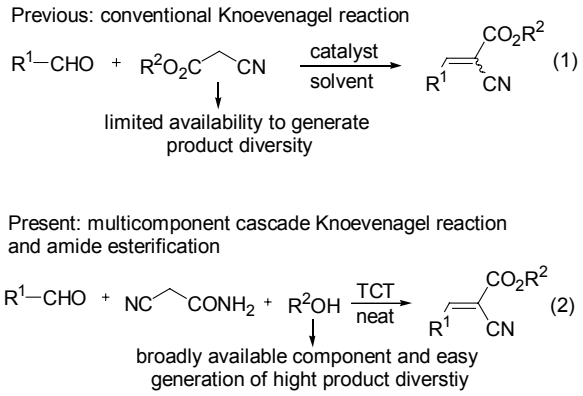
Keywords three-component reaction, acrylates, organocatalysis, Knoevenagel reaction, amide esterification

Introduction

Acrylates are a class of fundamental organic molecules which display invaluable merits as main building blocks in organic synthesis. Owing to their intrinsically versatile reactivity, acrylates have been frequently employed in Michael addition,[1] olefin hydrogenation,[2] C—H bond activation-based cross-coupling,[3] various cycloaddtion reactions[4] as well as Baylis-Hillman reaction.[5] More over, acrylates have been known as a main fragment in many molecules possessing enriched biological activity.[6] As a kind of particularly useful acrylates, the α-cyano acrylates have been reported to possess distinct synthetic application owing to the presence of cyano group.[7]

As a classical approach, the Knoevenagel condensation of cyano methylene substrates with aldehydes has been the dominant option in the preparation of α-cyano acrylates (Eq. 1, Scheme 1).[8] In this method, the synthesis of products containing different ester fragments relies on the employment of different cyano acetates, and the lack of diversity of commercially available reagents is therefore a serious restriction for generating the ester-based product library. Therefore, devising alternative synthetic approach allowing much easier access to acrylates bearing diverse ester substructure is presently an urgent issue. Base on our ongoing efforts in developing diversity-oriented synthetic methods in the form of multicomponent reactions,[9] we report herein the first example on the synthesis of different alkyl acrylates through the three-component reactions of aldehydes, alcohols and cyano acetamide by using cyanuric chloride (2,4,6-trichloro-1,3,5-triazine, TCT)[10] as an organocatalyst without using any additional organic solvent (Eq. 2, Scheme 1). The most noteworthy advantage of this method lies in its expanded ability of generating the ester diversity by simply varying the alcohol component.

Scheme 1 Different routes to α-cyano acrylates



Experimental

A 25 mL round bottom flask was charged with aryl aldehyde **1** (1 mmol), cynano acetamide **2a** (1 mmol), TCT (0.5 mmol) and alcohol **3** (2 mL). The resulting mixture was then heated at 80 ℃ (reflux for low b.p. alcohol) for 12 h at open air atmosphere. After cooling down to room temperature, 5 mL water was added and the suspension was extracted with ethyl acetate (10 mL ×3). The combined organic layer was dried over anhy-

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drous Na_2SO_4 and filtered. The acquired solution was then subjected to reduced pressure to remove the solvent. Purification of the residue with silica gel column chromatography provided pure products with the elution of mixed petroleum ether and ethyl acetate (V(PET)/V(EA) =80∶1).

Ethyl 2-cyano-3-phenylacrylate (4a)[9e] White solid. m.p. 62−64 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.26 (s, 1H), 7.99 (d, J=7.2 Hz, 2H), 7.58−7.51 (m, 3H), 4.39 (q, J=7.2 Hz, 2H), 1.40 (t, J=7.2 Hz, 3H).

Ethyl 3-(4-chlorophenyl)-2-cyanoacrylate (4b)[9e] White solid. m.p. 87−88 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.20 (s, 1H), 7.94 (d, J=8.0 Hz, 2H), 7.48 (d, J=8.4 Hz, 2H), 4.39 (q, J=7.2 Hz, 2H), 1.40 (t, J=7.2 Hz, 3H).

Ethyl 3-(4-bromophenyl)-2-cyanoacrylate (4c)[9e] White solid. m.p. 99−101 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.18 (s, 1H), 7.85 (d, J=8.4 Hz, 2H), 7.64 (d, J=8.8 Hz, 2H), 4.39 (q, J=6.8 Hz, 2H), 1.40 (t, J=7.2 Hz, 3H).

Ethyl 2-cyano-3-*p*-tolylacrylate (4d)[9e] White solid. m.p. 82−83 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.21 (s, 1H), 7.90 (d, J=8.4 Hz, 2H), 7.30 (d, J=8.4 Hz, 2H), 4.37 (q, J=7.2 Hz, 2H), 2.43 (s, 3H), 1.39 (t, J=7.2 Hz, 3H).

Ethyl 2-cyano-3-(4-methoxyphenyl)acrylate (4e)[9e] Yellow solid. m.p. 94−95 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.17 (s, 1H), 8.00 (d, J=8.4 Hz, 2H) 6.99 (d, J=8.4 Hz, 2H), 4.36 (q, J=6.8 Hz, 2H), 3.89 (s, 3H), 1.39 (t, J=7.2 Hz, 3H).

Ethyl 2-cyano-3-(3-methoxyphenyl)acrylate (4f)[8a] Yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.21 (s, 1H), 7.59 (s, 1H), 7.51 (d, J=8.0 Hz, 1H), 7.40 (t, J=8.0 Hz, 1H), 7.12−7.09 (m, 1H), 4.38 (q, J=8.0 Hz, 2H), 1.40 (t, J=7.2 Hz, 3H).

Ethyl 3-(2-chlorophenyl)-2-cyanoacrylate (4g)[9e] White solid. m.p. 78−79 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.70 (s, 1H), 8.42 (d, J=7.2 Hz, 1H), 7.52−7.40 (m, 3H), 4.12 (q, J=8.0 Hz, 2H), 1.41 (t, J=6.4 Hz, 3H).

Ethyl 3-(2-bromophenyl)-2-cyanoacrylate (4h)[9e] Pale yellow solid. m.p. 68−70 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.64 (s, 1H), 8.17 (d, J=6.0 Hz, 1H) 7.71 (d, J=9.2 Hz, 1H), 7.47 (t, J=7.6 Hz, 1H), 7.39 (t, J=7.6 Hz, 1H), 4.41 (q, J=7.2 Hz, 2H), 1.42 (t, J=7.2 Hz, 3H).

Ethyl 2-cyano-3-(2,4-dichlorophenyl)acrylate (4i)[11] White solid. m.p. 81−82 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.61 (s, 1H), 8.22 (d, J=8.0 Hz, 1H) 7.53 (d, J=4.0 Hz, 1H), 7.41−7.39 (m, 1H), 4.41 (q, J=6.4 Hz, 2H), 1.41 (t, J=7.2 Hz, 3H).

Ethyl 2-cyano-3-(furan-2-yl)acrylate (4j)[9e] Yellow solid, m.p. 68−69 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.02 (s, 1H), 7.76 (s, 1H), 7.40 (d, J=3.6 Hz, 1H), 6.67 (s, 1H), 4.36 (q, J=7.2 Hz, 2H), 1.38 (t, J=7.2 Hz, 3H).

Ethyl 2-cyano-3-(4-(dimethylamino)phenyl)acrylate (4k)[9e] Yellow solid. m.p. 124−125 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.06 (s, 1H), 7.93 (d, J=9.2 Hz, 2H), 6.68 (t, J=9.2 Hz, 2H), 4.33 (q, J=7.2 Hz, 2H), 3.10 (s, 6H), 1.37 (t, J=7.6 Hz, 3H).

Ethyl 3-(2-chloropyridin-3-yl)-2-cyanoacrylate (4l)[9e] White solid. m.p. 68−69 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.60 (s, 1H), 8.54 (d, J=6.4 Hz, 2H), 7.42−7.46 (m, 1H), 4.43 (q, J=7.2 Hz, 2H), 1.42 (t, J=7.2 Hz, 3H).

Methyl 2-cyano-3-phenylacrylate (4m)[8h] White solid. m.p. 89−90 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.26 (s, 1H), 7.99 (d, J=7.2 Hz, 2H) 7.55 (d, J=6.8 Hz, 1H), 7.50 (t, J=8.0 Hz, 2H), 3.94 (s, 3H).

Methyl 3-(4-chlorophenyl)-2-cyanoacrylate (4n)[8h] White solid. m.p. 132−133 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.21 (s, 1H), 7.93 (d, J=8.4 Hz, 2H), 7.48 (d, J=8.4 Hz, 2H), 3.94 (s, 3H).

Methyl 2-cyano-3-*p*-tolylacrylate (4o)[12] Pale yellow solid. m.p. 112−113 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.18 (s, 1H), 7.90 (d, J=8.0 Hz, 2H), 7.30 (d, J=7.8 Hz, 2H), 3.93 (s, 3H), 2.43 (s, 3H).

Methyl 2-cyano-3-(4-methoxyphenyl)acrylate (4p)[8h] White solid. m.p. 104−105 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.18 (s, 1H), 8.00 (d, J=8.8 Hz, 2H), 6.99 (d, J=8.4 Hz, 2H), 3.92 (s, 3H), 3.89 (s, 3H).

Propyl 2-cyano-3-*p*-tolylacrylate (4q)[9e] Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.21 (s, 1H), 7.90 (d, J=8.4 Hz, 2H), 7.30 (d, J=8.0 Hz, 2H), 4.27 (t, J=6.4 Hz, 2H), 2.43 (s, 3H), 1.83−1.74 (m, 2H), 1.02 (t, J=7.2 Hz, 3H).

Isopropyl 2-cyano-3-phenylacrylate (4r)[9e] Yellow solid. m.p. 69−70 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.24 (s, 1H), 7.99 (t, J=8.4 Hz, 2H), 7.56−7.49 (m, 3H), 5.24−5.18 (m, 1H), 1.38 (d, J=6.4 Hz, 6H).

Butyl 2-cyano-3-phenylacrylate (4s)[9e] White solid. m.p. 107−109 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.25 (s, 1H), 7.99 (d, J=7.2 Hz, 2H), 7.58−7.49 (m, 3H), 4.33 (t, J=6.4 Hz, 2H), 1.79−1.72 (m, 2H), 1.52−1.43 (m, 2H), 1.00−0.96 (m, 3H).

Pentyl 3-(4-chlorophenyl)-2-cyanoacrylate (4t)[9e] White solid. m.p. 78−79 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.19 (s, 1H), 7.93 (d, J=8.8 Hz, 2H), 7.48 (d, J=8.8 Hz, 3H), 4.32 (t, J=6.8 Hz, 2H), 1.80−1.73 (m, 2H), 1.42−1.36 (m, 4H), 0.93 (t, J=7.2 Hz, 3H).

Cyclohexyl 3-(4-bromophenyl)-2-cyanoacrylate (4u)[9e] Yellow solid. m.p. 144−145 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.16 (s, 1H), 7.85 (d, J=8.4 Hz, 2H), 7.64 (d, J=8.4 Hz, 2H), 5.02−4.96 (m, 1H), 1.93−1.90 (m, 2H), 1.81−1.78 (m, 2H), 1.66−1.54 (m, 3H), 1.48−1.33 (m, 3H).

Cyclohexyl 2-cyano-3-(*p*-tolyl)acrylate (4v)[9e] White solid. m.p. 82−83 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.20 (s, 1H), 7.90 (d, J=8.0 Hz, 2H), 7.30 (d, J=7.6 Hz, 2H), 5.01−4.96 (m, 1H), 2.43 (s, 3H), 1.92−1.90 (m, 2H), 1.81−1.79 (m, 2H), 1.67−1.55 (m, 3H), 1.47−1.33 (m, 3H).

Methyl 2-oxo-2*H*-chromene-3-carboxylate (5a)[13] Pale yellow solid. m.p. 96−97 ℃; ^{1}H NMR (400 MHz, DMSO) δ: 8.58 (s, 1H), 7.68−7.64 (m, 2H), 7.38−7.33

(m, 2H), 3.96 (s, 3H).

Ethyl 2-oxo-2*H*-chromene-3-carboxylate (5b)[13] White solid. m.p. 92—94 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.26 (s, 1H), 7.98 (d, J=7.2 Hz, 2H), 7.56—7.49 (m, 2H), 4.92 (q, J=7.2 Hz, 2H), 1.41 (t, J=6.4 Hz, 3H).

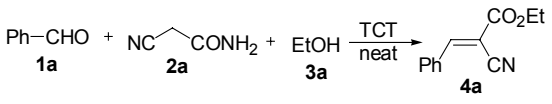
Ethyl 7-methoxy-2-oxo-2*H*-chromene-3-carboxylate (5c)[14] Pale yellow solid. m.p. 120.5—121.1 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.52 (s, 1H), 7.15 (d, J=8.8 Hz, 1H), 6.90 (d, J=8.0 Hz, 1H), 6.82 (s, 1H), 4.40 (q, J=6.8 Hz, 2H), 3.91 (s, 3H), 1.40 (t, J=6.4 Hz, 3H).

Ethyl 6-methyl-2-oxo-2*H*-chromene-3-carboxylate (5d)[15] Pale yellow solid. m.p. 94.4—95.4 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.48 (s, 1H), 7.45 (d, J=8.4 Hz, 1H), 7.40 (s, 1H), 7.24 (d, J=7.2 Hz, 1H), 4.42 (q, J=7.2 Hz, 2H), 2.43 (s, 3H), 1.41 (t, J=6.8 Hz, 3H).

Results and Discussion

At the beginning, the tentative experiment by employing benzaldehyde **1a**, cyano acetanitrile **2a** and ethanol **3a** in the presence of TCT was found to smoothly provide cyano acrylate **4a** with excellent yield (Entry 1, Table 1). Systematic optimization on the reaction conditions was then conducted. However, neither varying the loading of TCT nor varying the reaction temperature was able to improve the result (Entries 2—5). During the attempts of screening catalysts, it was found that $FeCl_3$ and $AlCl_3$ could catalyze the transformation, but provided **4a** with remarkably lower yield (Entries 6—7, Table 1). On the other hand, acidic catalysts such as AcOH, *p*-TSA, TFA, benzoic acid were not able to catalyze this reaction (Entries 8—11, Table 1).

Table 1 Optimization on reaction conditions[a]



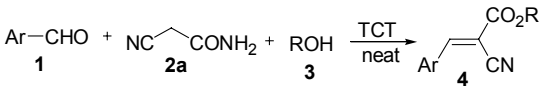
Entry	T/℃	Catalyst/equiv.	Yield[b]/%
1	80	TCT	84
2[c]	80	TCT	62
3[d]	80	TCT	72
4	60	TCT	56
5	90	TCT	64
6	80	$FeCl_3$	62
7	80	$AlCl_3$	60
8	80	AcOH	Trace
9[e]	80	*p*-TSA	nr
10	80	CF_3COOH	nr
11	80	Benzoic acid	nr
12	80	*L*-Proline	nr
13	80	Morpholine	nr

[a] General conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), **3a** (2 mL), catalyst (0.5 mmol), stirred for 12 h. [b] Yield of isolated product. [c] TCT was 0.3 equiv. [d] TCT was 0.7 equiv. [e] nr=no reaction.

L-Proline and morpholine could not catalyze the reaction, either (Entries 12—13, Table 1). The results provided by the entries using different catalysts implied the particular applicability of TCT as the catalyst for this three-component synthesis.

Under the optimized conditions, the scope of this three-component method was investigated by using structurally diverse aryl aldehydes and alcohols. As outlined in Table 2, the present method exhibited excellent tolerance to the stereoselective synthesis of cyano acrylates **4**[16] by subjecting various aryl aldehydes and alcohols. The substituents such as halogen, alkyl, alkoxyl, amino and heteroayl in the aldehyde component as well as alcohols with alkyls of different length, branched alkyls and cyclic alkyl also displayed expected compatibility to this three-component transformation. Aliphatic aldehyde such as propionaldehyde, however, was not tolerated. Most products were provided with good to excellent yields. While the property of the substituted group in the benzaldehyde displayed no evident impact

Table 2 Three-component synthesis of different cyano acrylates



Ar	R	Product	Yield[a]/%
Ph	Et	**4a**	84
4-ClC_6H_4	Et	**4b**	79
4-BrC_6H_4	Et	**4c**	89
4-MeC_6H_4	Et	**4d**	81
4-$MeOC_6H_4$	Et	**4e**	80
3-$MeOC_6H_4$	Et	**4f**	74
2-ClC_6H_4	Et	**4g**	85
2-BrC_6H_4	Et	**4h**	91
2,4-$Cl_2C_6H_4$	Et	**4i**	82
Furyl-2-yl	Et	**4j**	79
4-$Me_2NC_6H_4$	Et	**4k**	81
2-Chloropyridin-3-yl	Et	**4l**	84
Ph	Me	**4m**	89
4-ClC_6H_4	Me	**4nl**	88
4-MeC_6H_4	Me	**4o**	89
4-$MeOC_6H_4$	Me	**4p**	90
Ph	*n*-pro	**4q**	74
Ph	*i*-pro	**4r**	75
Ph	*n*-Bu	**4s**	73
Ph	*n*-pentyl	**4t**	75
4-BrC_6H_4	Cyclohexyl	**4u**	67
4-MeC_6H_4	Cyclohexyl	**4v**	69
Ph	Ph	No[b]	—
Ph	*t*-Bu	No	—

[a] Yield of isolated product based on aldehyde. [b] MeCN was used as solvent and heated at reflux.

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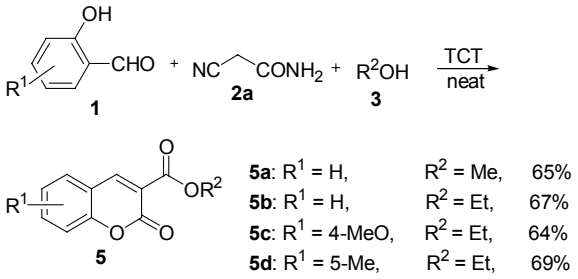
on the reaction results, the heteroaryl-based furyl-2-aldehyde was found to give corresponding product **4j** with relatively inferior yield. On the other hand, the structure of alcohol also affected the formation of related products, a tendency was that the alcohols with bulky hindrance generally led to the production of corresponding alkyl acrylates with slightly lower yield (**4q**—**4v**, Table 2). Bulkyl alcohol such as *t*-BuOH and low nucleophilic phenol were not able to participate in the expect synthesis, which further supports the fact that the nucleophilicity of the *O*-nucleophile is crucial for the reaction.

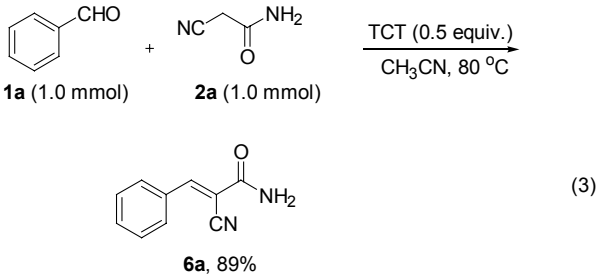
In order to further investigate the utility of the three-component protocol, we subsequently employed salicaldehyde as the aldehyde component to the standard conditions in the presence of alcohols and α-cyano acetamide. Interestingly, the formation of chromenones **5** was achieved via further cascade cyano hydration and intramolecular esterification after the formation of cyano intermediate of type **4** (Scheme 2). Different salicaldehydes and alcohols were also tolerable to this synthesis by providing products **5** with good yields.

Scheme 2 Three-component synthesis of chromenones

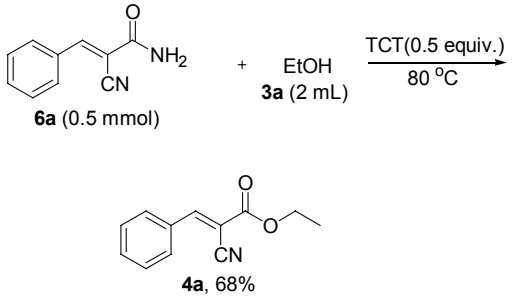


To probe the possible reaction mechanism, related control experiments were designed. Firstly, the reaction of aldehyde **1a** with cyano acetamide **2a** was conducted by using CH_3CN as solvent in the presence of TCT. As expected, without the presence of alcohol, Knoevenagel product **6a** was obtained (Eq. 3). Subsequently, subjecting **6a** with EtOH under the standard TCT catalytic conditions smoothly led to the production of **4a** with fair yield (Eq. 4). The results implied that the Knoevenagel condensation was the initial and key transformation in the three-component cascade reactions.

According to the acquired results, a general reaction mechanism involving the promotion of TCT was proposed and outlined in Scheme 3. The Knoevenagel condensation between aldehyde and cyano acetamides provides olefin intermediate **6**. The incorporation of **6** to TCT can easily take place to provide another intermediate **7**, which facilitates the nucleophilic incorporation of alcohol to yield acrylates **4**. The water provided by the Knoevenagel condensation enables the hydration of the cyano group to allow the second cyclic esterification process in the synthesis of products **5**.

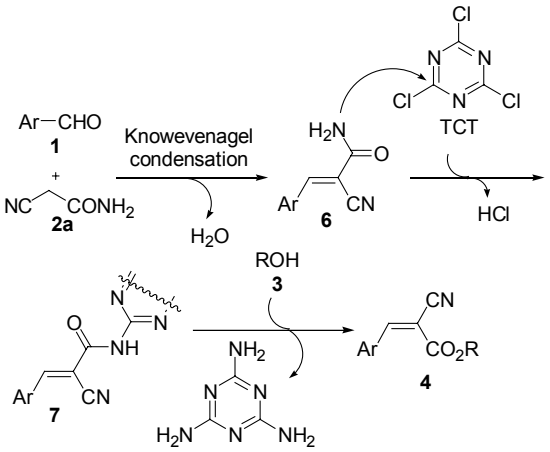


(3)



(4)

Scheme 3 The proposed reaction mechanism



Conclusions

In conclusion, by means of employing TCT as an organocatalyst, we have successfully established a new approach for the three-component synthesis of various alkyl acrylates. Besides the advantage of using simple starting materials, the present method is valuable by allowing easy synthesis of products with significantly broader product diversity than conventional Knoevenagel approach because of the abundant resource of the key alcohol component.

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