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A Novel Three-Component Reaction of Allenoates, Isocyanides, and Carboxylic Acids: Facile Synthesis of Highly Substituted Acryl Imide Derivatives

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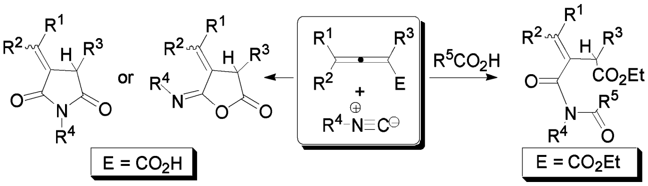

A novel synthesis of highly substituted acryl imide derivatives by the three-component reaction of allenoates, isocyanides, and carboxylic acids was reported, and the intramolecular cyclization reaction of allenoic acids with isocyanides was also described.

Multicomponent reactions provide a powerful tool for the synthesis of diverse and complex compounds because of their atom economy, simple experimental procedures, and high bond forming efficiency.[1] Isocyanide-based multicomponent reactions (IMCRs) play important roles in this realm due to their diversity of bond-forming processes, functional group tolerance, and high levels of chemo-, regio-, and stereoselectivity.[2] Although IMCRs involving electron-deficient acetylenic compounds and active hydrogen compounds have been investigated,[3−5] allene-attended reactions of this kind have not been reported yet.

Considering the great synthetic potentials of allenes which arise from their axial chirality, substituent loading capability,[6] and the higher reactivity of the electron-deficient allenes compared to the corresponding alkynes,[7] we proposed that the adduct between electron-deficient allenes and isocyanides might provide a convenient zwitterionic nitrilium intermediate species which would be trapped with E^+, leading to useful products (Scheme 1). Herein, we wish to report the first three-component reaction of allenoates, isocyanides, and carboxylic acids to synthesize highly substituted acryl imide derivatives.

Initially, the reaction of 4-methylpenta-2,3-dienoate **1a** with *p*-tolyl isocyanide **2a** and benzoic acid **3a** was conducted in CH_2Cl_2 at room temperature for 48 h, which underwent a smooth 1:1:1 addition reaction (Table 1). However, the desired product 3-(benzoyl-*p*-tolylaminocarbonyl)-4-methylpent-3-enoic acid ethyl ester **4a** was isolated only in 43% yield (entry 1, Table 1). Subsequent optimization studies indicated that MeCN was a better solvent, and the yield of product **4a** was greatly increased to 86% at 65 °C (entry 3). Our further investigations proved that DMF, THF, and toluene did not work well (entries 5−8).

With the optimized conditions in hand, we investigated the scope of this reaction. The results indicated that the reaction proceeded smoothly to give the corresponding highly substituted acryl imides **4** in good to excellent yields (Table 2).

As indicated in Table 2, the allenoates could be mono-, di-, or trisubstituents, and the isocyanides or the carboxylic acids could be alkyl or aryl substituted. In addition, it was interesting to observe that when R^1 was different from R^2, the reaction gave the *E*-isomer as the major product in good yield (entries 13 and 14). When R^1 = Ph, R^2 = R^3 = H, the NMR analysis of crude product indicated that the reaction furnished *E*-**4o** as a sole product (entry 14).

Furthermore, when 1-substituted allenoate was employed, the reaction gave the expected product **4m** in 24% yield together with 51% yield of the C═C bond rearranged product **5** (Scheme 2). The formation of compound **5** was probably due to the rearrangement of **4m** under acidic conditions. This was further proved by the fact that when H_2O was employed instead of $PhCO_2H$, the reaction furnished the unrearrangement product **6** as a single product under similar conditions.

On the basis of the well-established chemistry of isocyanides,[8] it is reasonable to assume that the nucleophilic addition of isocyanides **2** to allenoates **1** forms the zwitterionic intermediate **7**, which could be trapped with carboxylic acids **3** to produce the imidoyl carboxylate **8**. Subsequently, an acyl group shift from oxygen to nitrogen occurs to produce the final product **4** (Scheme 3).[9]

According to the above three-component reaction, we conceived that allenoic acids, which combine the reactive sites of

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10.1021/jo702382h CCC: $40.75

SCHEME 1

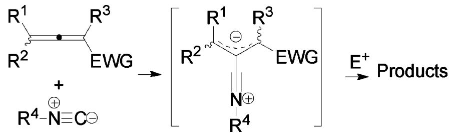
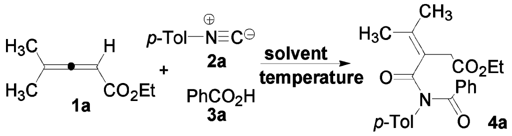


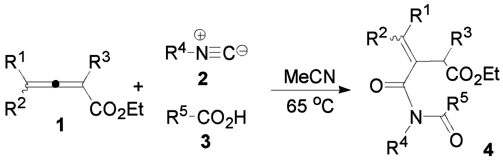
TABLE 1. Effects of Solvent and Temperature on the Three-Component Reaction[a]



entry	solvent	T (°C)	time (h)	**4a**^{b} (%)
1	CH_2Cl_2	rt	48	43
2	MeCN	rt	39	54
3	**MeCN**	**65**	**4.5**	**86**
4	MeCN	85	3	82
5	DMF	65	6	77
6	DMF	85	4	69
7	toluene	85	5	61
8	THF	65	8	67

[a] The reaction was conducted using **1a** (1.0 mmol), **2a** (1.0 mmol), and **3a** (1.0 mmol) in 5 mL of solvent. [b] Isolated yields.

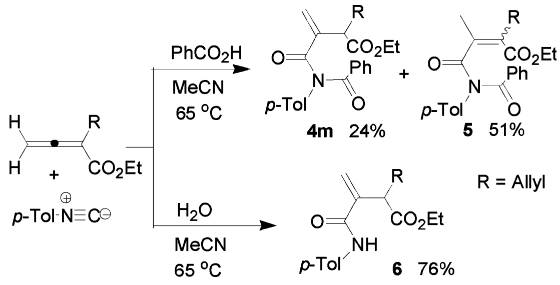
TABLE 2. Three-Component Reaction of Allenoates, Isocyanides, and Carboxylic Acids[a]



entry	1	2	3	yield^{b} (%)	product
1	$R^1 = R^2 =$ Me; $R^3 =$ H (**1a**)	$R^4 =$ *p*-Tol (**2a**)	$R^5 =$ Ph (**3a**)	86	**4a**
2	**1a**	**2a**	$R^5 =$ *i*-Pr (**3b**)	82	**4b**
3	**1a**	$R^4 =$ Bn (**2b**)	**3a**	87	**4c**
4	**1a**	**2b**	**3b**	89	**4d**
5	$R^1 = R^2 = R^3 =$ Me (**1b**)	**2a**	**3a**	79	**4e**
6	**1b**	**2a**	**3b**	83	**4f**
7	**1b**	**2b**	**3a**	86	**4g**
8	**1b**	**2b**	**3b**	84	**4h**
9	$R^1 = R^2 =$ Me; $R^3 =$ allyl (**1c**)	**2a**	**3a**	92	**4i**
10	**1c**	**2a**	**3b**	93	**4j**
11	**1c**	**2b**	**3a**	96	**4k**
12	**1c**	**2b**	**3b**	94	**4l**
13	$R^1 =$ *n*-C_7H_{15}; $R^2 = R^3 =$ H (**1d**)	**2b**	**3a**	89^{c}	**4n** (82:18)^{d}
14	$R^1 =$ Ph;$R^2 =$ $R^3 =$ H (**1e**)	**2a**	**3b**	85^{c}	**4o** (100:0)^{d}

[a] The reactions were conducted using **1** (1.0 mmol), **2** (1.0 mmol), and **3** (1.0 mmol) in 5 mL of MeCN at 65 °C. [b] Isolated yields. [c] Combined yields of *E*,*Z* isomers. [d] *E*/*Z* were estimated by ^{1}H NMR analysis of crude products.

SCHEME 2



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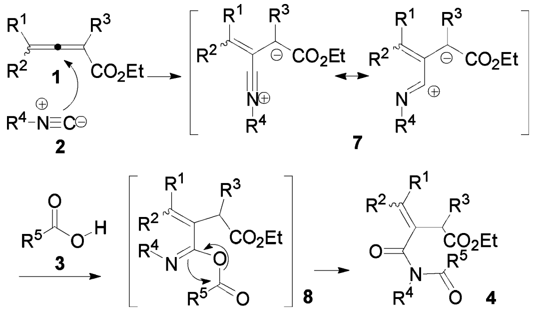
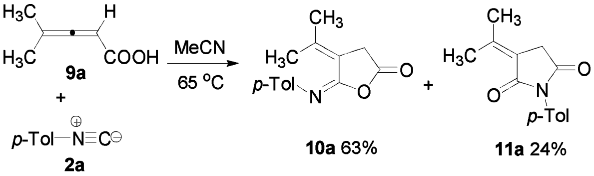
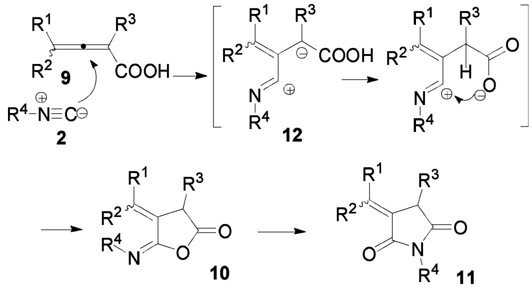


SCHEME 4



SCHEME 5



allene and carboxylic acid into one molecule, could perform the analogous reaction with isocyanides. With such a strategy in mind, we studied the reaction of 4-methylpenta-2,3-dienoic acid **9a** with **2a**. As expected, the reaction afforded 4-isopropylidene-5-*p*-tolyliminodihydrofuran-2-one **10a** in 63% yield and 3-isopropylidene-1-*p*-tolylpyrrolidine-2,5-dione **11a** in 24% yield (Scheme 4).

It could be assumed that the formation mechanism of **10a** and **11a** was similar to that of the above three-component reaction. At first, the zwitterionic intermediate **12** protonates and then conducts an intramolecular nucleophilic attack by carboxylate anion to form 5-iminodihydrofuran-2-one **10**. Pyrrolidine 2,5-dione **11** might be obtained from a process where compound **10** undergoes the shift of acyl group from oxygen to nitrogen in the presence of acid (Scheme 5).[10] Our experiment indicated that heating **10a** in HOAc at 65 °C led to **11a** in 78% yield.

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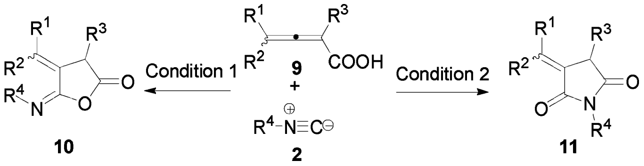
TABLE 3. Reaction of Allenoic Acids with Isocyanides[a]



entry	9	2	yield[b](%)	product
1	$R^1 = R^2 =$ Me; $R^3 =$ H (**9a**)	**2a**	89	**10a**
2	$R^1 = R^2 =$ Me; $R^3 =$ Allyl (**9b**)	**2a**	86	**10b**
3	**9a**	**2a**	95	**11a**
4	**9a**	**2b**	91	**11b**
5	**9b**	**2a**	92	**11c**
6	**9b**	**2b**	94	**11d**
7	$R^1 = n$-C_4H_9; $R^2 = R^3 =$ H (**9c**)	**2a**	90[c]	**11e** (88:12)[d]
8	$R^1 = n$-C_7H_{15}; $R^2 = R^3 =$ H (**9d**)	**2b**	86[c]	**11f** (91:9)[d]
9	$R^1 =$ Ph; $R^2 =$ H; $R^3 =$ Allyl (**9e**)	**2a**	93[c]	**11g** (100:0)[d]
10	$R^1 =$ Ph; $R^2 =$ H; $R^3 =$ Bn (**9f**)	**2b**	88[c]	**11h** (100:0)[d]

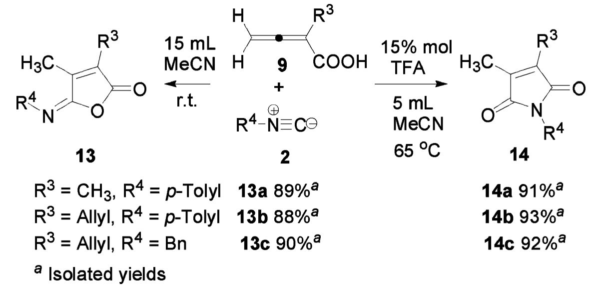
[a] Conditions 1: The reactions were conducted using **9** (1.0 mmol) and **2** (1.0 mmol) in 15 mL of MeCN at room temperature for 27 h. Conditions 2: The reactions were conducted using **9** (1.0 mmol), **2** (1.0 mmol), and **TFA** (0.15 mmol) in 5 mL of MeCN at 65 °C for 4 h. [b] Isolated yields. [c] Combined yields of *E*,*Z* isomers. [d] *E*/*Z* were estimated by ^{1}H NMR analysis of crude products.

To increase the reaction selectivities, optimization studies were undertaken. The experiments demonstrated that performing the reaction at room temperature and increasing the amount of solvent led to a single product **10**, while performing the reaction in the presence of 15% mol of trifluoroacetic acid (TFA) led to **11** with high stereoselectivity (Table 3). *E*-Isomer **11** was obtained predominantly when the R^1 group was much bulkier than the R^2 group.

It is interesting that when 1-substituted allenonic acids were employed, the reactions afforded cyclic imides **13** and **14**, respectively, in which the exocyclic double bonds migrated to the more stable endocyclic position (Scheme 6).

Here, it is important to mention that a large number of cyclic imides such as **10**, **11**, **13**, and **14** have been extensively used in the synthesis of natural and unnatural bioactive heterocyclic compounds[11] and several types of polymers with tailored material characteristics.[12] Hence, it is of value to develop a convenient method for the synthesis of these analogues.

SCHEME 6



In conclusion, we have developed a novel three-component reaction of allenoates, isocyanides, and carboxylic acids, affording an efficient method to synthesize highly substituted acryl imides. In addition, we also found that the reactions of allenoic acids with isocyanides could give two typical cyclic imides, respectively, in good to excellent yields under different conditions. The reactions should be useful due to the wide utilities of these compounds in organic synthesis.

Experimental Section

General Procedure for Synthesis of Highly Substituted Acryl Imides via a Three-Component Reaction of Allenoates, Isocyanides, and Carboxylic Acids. To a stirred solution of allenoate **1** (1.0 mmol) and isocyanide **2** (1.0 mmol) in dry MeCN (2 mL) was added a solution of carboxylic acid **3** (1.0 mmol) in dry MeCN (3 mL). The reaction mixture was then allowed to stir at 65 °C for 5 h. The solvent was removed under reduced pressure, and the residue was separated by silica gel chromatography (petroleum ether−ethyl acetate 7:1 v/v) to afford **4**.

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Supporting Information Available: General experimental details, analytical data for **4**, **6**, **10**, **11**, **13**, and **14**, and ^{1}H and ^{13}C NMR spectra of these compounds. 2D ^{1}H−^{1}H NOESY spectra for **4n**, **4o**, and **11e**−**h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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