High Regio- and Stereoselective Synthesis of (*Z*)- or (*E*)-*N*-Acryl Butenedioic Monoimide Derivatives by a Multicomponent Reaction

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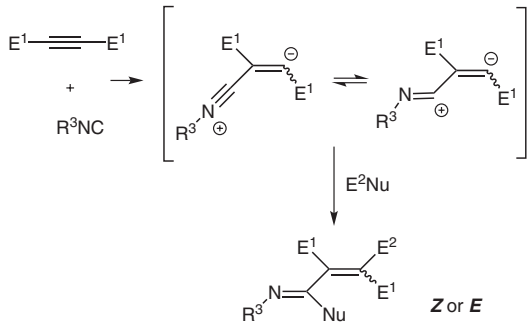
Abstract: An efficient synthesis of (*Z*)- or (*E*)-*N*-acryl butenedioic monoimide derivatives with high regio- and stereoselectivity by the multicomponent reaction of acetylenic esters/ketones, isocyanides, and carboxylic acids is described. The *E*-isomers, obtained in high yields via *E*/*Z* isomerization, are also reported.

Key words: high regio- and stereoselectivity, multicomponent reactions, isocyanides, acetylenic esters/ketones, *N*-acryl butenedioic monoimides

Multicomponent reactions (MCRs) provide a powerful tool towards the one-pot synthesis of diverse and complex compounds due to their superior atom economy; simple experimental procedures, one-pot character, and high bond-forming efficiency.[1] Isocyanide-based MCRs (IMCRs) are more versatile than other MCRs. The great potential of isocyanides for the development of multicomponent reactions lies in their functional group tolerance, diversity of bond-forming processes, and high levels of chemo-, regio-, and stereoselectivity.[2]

Recently, much attention has been paid to the study of IMCRs, especially those involving electron-deficient alkynes.[3] Typically, the adduct from butynedioic acid derivatives and isocyanides could provide a zwitterionic nitrilium intermediate species (Scheme 1),[4] which would be trapped with E-Nu, leading to two isomers.

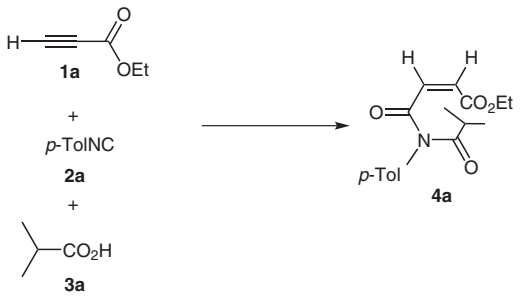


Scheme 1

Although the trapping of the intermediate formed between butynedioic acid derivatives and isocyanides with active hydrogen compound[5] has been described, the chemistry of stereoselectivity of these reactions involving propiolic acid derivatives, has not been investigated yet. On the basis of our studies,[6] we wish to report the multicomponent reaction of propiolic acid derivatives, isocyanides, and carboxylic acids to synthesize (*Z*)- or (*E*)-*N*-acryl butenedioic monoimide derivatives with high regio- and stereoselectivity.

Initially, the reaction of ethyl propiolate (**1a**) with *p*-tolyl isocyanide (**2a**) and isobutyric acid (**3a**) was conducted in MeCN at room temperature for 50 hours, under which conditions a smooth 1:1:1 addition reaction took place (Table 1). However, the desired product (*Z*)-ethyl 7-methyl-4,6-dioxo-5-*p*-tolyloct-2-enoate (**4a**) was isolated only in 44% yield (Table 1, entry 1). Subsequent optimization studies indicated that when the temperature was raised to 50 °C, the yield of product **4a** was greatly increased to 87% (entry 2). Our further investigations proved that DMF and THF did not work well (entries 4, 5).

Table 1 Optimization of Conditions for the Multicomponent Reactions[a]



Entry	Solvent	Temp (°C)	Time (h)	Yield of **4a** (%)[b]
1	MeCN	r.t.	50	44
2	**MeCN**	**50**	**6**	**87**
3	MeCN	70	3	79
4	DMF	50	6	68
5	THF	50	8	54

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

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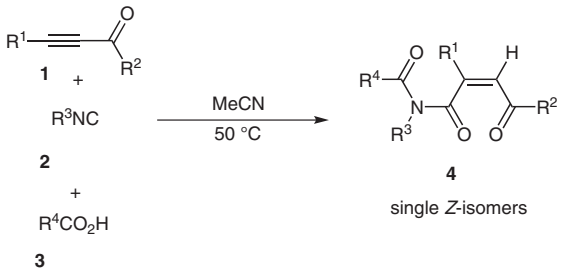
Table 2 Compounds **4** Prepared by the Multicomponent Reaction[a]



Entry	**1** (R^1, R^2)	**2** (R^3)	**3** (R^4)	**4**	Yield (%)[b]
1	**1a** (H, OEt)	**2a** (*p*-tolyl)	**3a** (*i*-Pr)	**4a**	87
2	**1a**	**2b** (Bn)	**3a**	**4b**	92
3	**1a**	**2a**	**3b** (Ph)	**4c**	88
4	**1a**	**2b**	**3b**	**4d**	85
5	**1b** (*n*-Bu, OMe)	**2a**	**3a**	**4e**	80
6	**1b**	**2a**	**3b**	**4f**	76
7	**1c** (Ph, OMe)	**2a**	**3a**	**4g**	65
8	**1c**	**2b**	**3a**	**4h**	61
9	**1d** (H, 4-FC_6H_4)	**2c** (*n*-$C_{11}H_{23}$)	**3c** (4-ClC_6H_4)	**4i**	73
10	**1e** (H, 4-$MeOC_6H_4$)	**2d** (*p*-tolylCH_2)	**3c**	**4j**	77
11	**1f** (H, *p*-tolyl)	**2a**	**3a**	**4k**	75

[a] The reactions were conducted using **1** (1.0 mmol), **2** (1.0 mmol), and **3** (1.0 mmol) in MeCN (5 mL) at 50 °C.
[b] Isolated yields.

With the optimized conditions in hand, we next investigated the reaction of various propiolic acid derivatives, isocyanides, and carboxylic acids under identical conditions.

The results, summarized in Table 2, indicate that when the propiolic acid derivatives were acetylenic esters (Table 2, entries 1–8) and ketones (entries 9–11), the reaction proceeded smoothly to give the products **4** in good yields, and the yields of esters were slightly higher than those of ketones. The results were satisfying in all cases when R^1, R^3, and R^4 were H, alkyl, and aryl groups. The configuration was established by the NOESY spectrum studies (Figure 1). These (*Z*)-*N*-acryl butenedioic monoimides are utilized in Diels–Alder reactions[7] and have been used to synthesize several types of polymers with tailored material characteristics.[8,9]

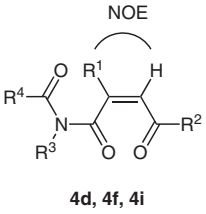


Figure 1 NOE studies in **4**

It is notable that the stereoselectivity of this reaction was excellent and only the *Z*-isomer was observed. The C_2, C_7 stereochemistry was confirmed by X-ray crystallographic analysis of (*Z*)-methyl 3-[benzoyl(*p*-tolyl)carbamoyl]hept-2-enoate (**4f**) (Figure 2).[10]

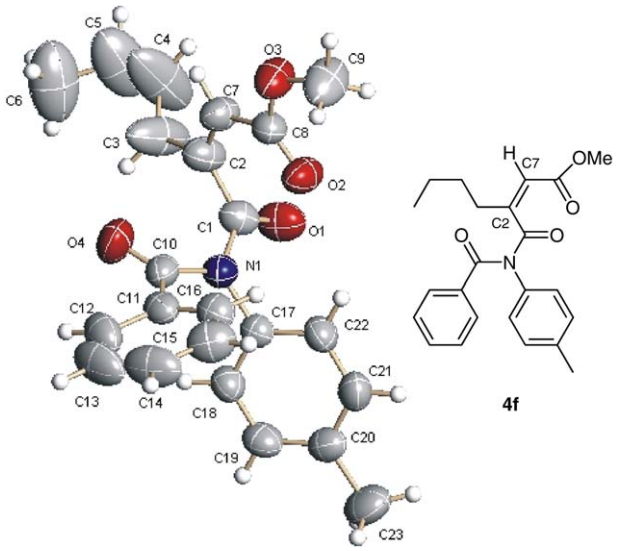
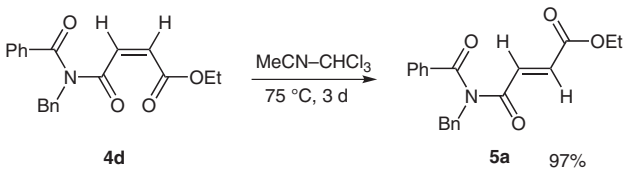


Figure 2 X-ray crystal structure of **4f**

Interestingly, when the reaction of (*Z*)-**4d** was carried out in MeCN–$CHCl_3$ at 75 °C for three days, the *trans*-configured product *E*-isomer **5a** was observed in 97% yield (Scheme 2).[11]



Scheme 2

The products of type **5a** containing the (*E*)-butenedioic compounds structural unit is valuable building blocks in organic synthesis and in the preparation of polymer materials.[8,9] Therefore, we proceeded to expand the substrate scope. As shown in Table 3, a number of (*E*)-*N*-acryl butenedioic monoimides **5** were prepared from **4** by isomerization in excellent yields (Table 3).

Table 3 (*E*)-*N*-Acryl Butenedioic Monoimides **5** Prepared by the Isomerization of **4**[a]

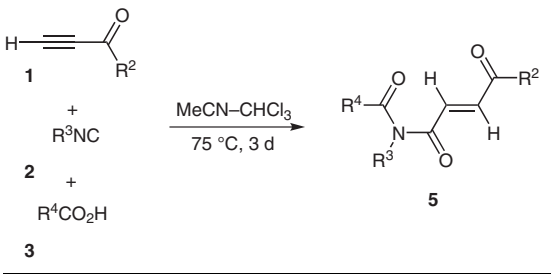
Entry	R^2	R^3	R^4	Yield of **5** (%)[b]
1	OEt	Bn	Ph	**5a**, 97
2	OEt	*p*-tolyl	*i*-Pr	**5b**, 94
3	4-FC_6H_4	*n*-$C_{11}H_{23}$	4-ClC_6H_4	**5c**, 98
4	4-$MeOC_6H_4$	*p*-tolylCH_2	4-ClC_6H_4	**5d**, 95
5	*p*-tolyl	*p*-tolyl	*i*-Pr	**5e**, 93

[a] The reaction was conducted using **4** (0.3 mmol) in MeCN (2 mL) and $CHCl_3$ (0.5 mL) at 75 °C for 3 d.
[b] Isolated yields.

Furthermore, we performed the reaction of acetylenic esters/ketones, isocyanides, and carboxylic acids in MeCN–$CHCl_3$ at 75 °C for three days. As expected, the reaction directly afforded (*E*)-*N*-acryl butenedioic monoimide derivatives **5** in good yields (Table 4).

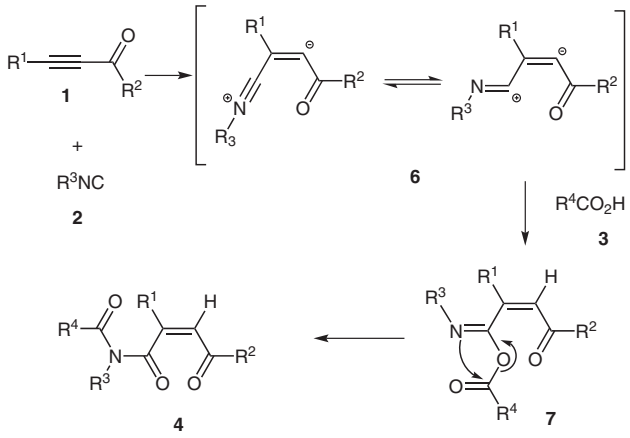
A plausible mechanism of the multicomponent reaction is shown in Scheme 3. On the basis of the well-established chemistry of isocyanides,[12] it is reasonable to assume that the nucleophilic addition of isocyanide **2** to alkyne **1** forms the *Z*-zwitterionic intermediate **6**,[13] which could be trapped with carboxylic acid **3** to produce the imidoyl carboxylate **7**. Subsequently, an acyl group shift from oxygen to nitrogen occurs to produce the final product **4**.[14]

Table 4 Compounds **5** Prepared by the Multicomponent Reaction[a]



Entry	R^2	R^3	R^4	Yield of **5** (%)[b]
1	**1a** (OEt)	**2b** (Bn)	**3b** (Ph)	**5a**, 81
2	**1d** (4-FC_6H_4)	**2c** (*n*-$C_{11}H_{23}$)	**3c** (4-ClC_6H_4)	**5c**, 71
3	**1d**	**2c**	**3a** (*i*-Pr)	**5f**, 70
4	**1f** (*p*-tolyl)	**2b**	**3a**	**5g**, 68
5	**1e** (4-$MeOC_6H_4$)	**2b**	**3d** (*i*-C_5H_{11})	**5h**, 74
6	**1f**	**2d** (*p*-tolylCH_2)	**3a**	**5i**, 69

[a] The reaction was carried out using **1** (1.0 mmol), **2** (1.0 mmol), and **3** (1.0 mmol) in MeCN (4 mL) and $CHCl_3$ (1 mL) at 75 °C for 3 d.
[b] Isolated yields.



Scheme 3

In conclusion, we have demonstrated the multicomponent reaction of acetylenic esters/ketones, isocyanides and carboxylic acids as a direct, efficient and operationally convenient approach to (*Z*)- or (*E*)-*N*-acryl butenedioic monoimide derivatives with high regio- and stereoselectivity. The reactions could be useful due to their atom-economical manner, control of stereoselectivity, and potential synthetic utilities in organic synthesis.

All reactions were performed under N_2. Anhyd solvents were distilled prior to use: THF and toluene were distilled from sodium–benzophenone; MeCN was distilled from P_2O_5. Petroleum ether (PE) refers to the fraction with boiling point in the range of 60–90 °C. All ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ with TMS as the internal standard. Chemical shifts are expressed in ppm and *J* values are given in Hz. Melting points are uncorrected.

Multicomponent Reaction of Acetylenic Esters/Ketones, Isocyanides, and Carboxylic Acids Leading to 4a–k; General Procedure

Alkyne **1** (1.0 mmol), isocyanide **2** (1.0 mmol), and carboxylic acid **3** (1.0 mmol) were mixed in anhyd MeCN (5 mL). The mixture was then allowed to stir at 50 °C for 6–17 h. The solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography (PE–EtOAc, 8:1 to 4:1) to afford **4** (Table 2).

(*Z*)-Ethyl 4-Oxo-4-(*N*-*p*-tolylisobutyramido)but-2-enoate (4a)

Mp 79–81 °C.

IR (KBr): 2979, 1719, 1701, 1632, 1388, 1210, 1170 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.25 (m, 4 H), 6.75 (d, *J* = 11.8 Hz, 1 H), 5.84 (d, *J* = 11.8 Hz, 1 H), 4.20 (q, *J* = 7.1 Hz, 2 H), 2.81–2.69 (m, 1 H), 2.40 (s, 3 H), 1.28 (t, *J* = 7.1 Hz, 3 H), 1.07 (d, *J* = 6.7 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.6, 169.3, 165.2, 139.7, 139.1, 134.8, 130.3, 128.4, 119.0, 60.7, 34.1, 21.2, 19.0, 14.1.

MS: *m*/*z* (%) = 303 (M^+, 5), 99 (100), 107 (100).

Anal. Calcd for $C_{17}H_{21}NO_4$ (303.15): C, 67.31; H, 6.98; N, 4.62. Found: C, 67.35; H, 6.89; N, 4.69.

4b

Oil.

IR (neat): 3033, 2979, 1720, 1690, 1386, 1155 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.33 (t, *J* = 7.3 Hz, 2 H), 7.26 (t, *J* = 7.3 Hz, 1 H), 7.21 (d, *J* = 7.3 Hz, 2 H), 6.71 (d, *J* = 11.8 Hz, 1 H), 5.90 (d, *J* = 11.8 Hz, 1 H), 5.03 (s, 2 H), 4.16 (q, *J* = 7.1 Hz, 2 H), 3.19–3.07 (m, 1 H), 1.25 (t, *J* = 7.1 Hz, 3 H), 1.11 (d, *J* = 6.8 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.8, 169.6, 164.9, 139.1, 136.8, 128.7, 127.4, 126.4, 120.0, 60.8, 47.1, 34.4, 19.0, 14.0.

MS: *m*/*z* (%) = 304 [$(M + 1)^+$, 27], 106 (100).

Anal. Calcd for $C_{17}H_{21}NO_4$ (303.15): C, 67.31; H, 6.98; N, 4.62. Found: C, 67.27; H, 7.06; N, 4.68.

4c

Mp 37–39 °C.

IR (KBr): 3342, 2983, 1715, 1684, 1601, 1516, 1268, 1159 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 7.6 Hz, 2 H), 7.27–7.22 (m, 4 H), 7.11 (t, *J* = 7.6 Hz, 3 H), 6.85 (d, *J* = 11.9 Hz, 1 H), 5.92 (d, *J* = 11.9 Hz, 1 H), 4.21 (q, *J* = 7.2 Hz, 2 H), 2.28 (s, 3 H), 1.26 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.6, 169.4, 165.2, 139.0, 138.0, 135.2, 133.9, 131.9, 129.8, 129.6, 128.0, 127.9, 120.3, 60.8, 21.0, 14.0.

MS: *m*/*z* (%) = 337 (M^+, 24), 105 (100).

Anal. Calcd for $C_{20}H_{19}NO_4$ (337.13): C, 71.20; H, 5.68; N, 4.15. Found: C, 71.15; H, 5.62; N, 4.19.

4d

Oil.

IR (neat): 3296, 2982, 1719, 1694, 1661, 1342, 1220, 1174 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.56–7.46 (m, 3 H), 7.41–7.35 (m, 2 H), 7.31–7.18 (m, 5 H), 6.28 (d, *J* = 11.9 Hz, 1 H), 5.64 (d, *J* = 11.9 Hz, 1 H), 5.12 (s, 2 H), 4.19 (q, *J* = 7.1 Hz, 2 H), 1.27 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.5, 168.8, 164.6, 137.5, 136.9, 135.5, 132.5, 128.7, 128.5, 128.5, 128.1, 127.5, 121.4, 61.0, 48.6, 14.0.

MS: *m*/*z* (%) = 337 (M^+, 4), 105 (100).

Anal. Calcd for $C_{20}H_{19}NO_4$ (337.13): C, 71.20; H, 5.68; N, 4.15. Found: C, 71.23; H, 5.75; N, 4.14.

4e

Oil.

IR (neat): 3412, 2958, 1723, 1698, 1643, 1202, 1156 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.24 (m, 4 H), 5.65–5.63 (m, 1 H), 3.70 (s, 3 H), 2.69–2.56 (m, 1 H), 2.47 (t, *J* = 7.4 Hz, 2 H), 2.41 (s, 3 H), 1.63–1.53 (m, 2 H), 1.44–1.36 (m, 2 H), 1.03 (d, *J* = 6.8 Hz, 6 H), 0.93 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.8, 172.0, 166.0, 157.7, 138.9, 135.0, 130.2, 128.5, 113.1, 51.4, 34.3, 33.9, 28.7, 22.2, 21.2, 19.0, 13.8.

MS: *m*/*z* (%) = 345 (M^+, 10), 169 (100).

Anal. Calcd for $C_{20}H_{27}NO_4$ (345.19): C, 69.54; H, 7.88; N, 4.05. Found: C, 69.51; H, 7.93; N, 4.09.

4f

Oil.

IR (neat): 3448, 2964, 1711, 1693, 1681, 1274, 1169 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.56 (d, *J* = 7.3 Hz, 2 H), 7.35–7.18 (m, 5 H), 7.08 (d, *J* = 8.1 Hz, 2 H), 5.71 (s, 1 H), 3.68 (s, 3 H), 2.62 (t, *J* = 3.8 Hz, 2 H), 2.26 (s, 3 H), 1.69–1.57 (m, 2 H), 1.49–1.38 (m, 2 H), 0.94 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.2, 172.0, 166.0, 157.0, 137.9, 135.4, 134.2, 131.6, 129.7, 129.6, 128.2, 127.9, 114.3, 51.5, 34.8, 29.0, 22.3, 21.1, 13.8.

MS: *m*/*z* (%) = 379 (M^+, 4), 169 (100).

Anal. Calcd for $C_{23}H_{25}NO_4$ (379.18): C, 72.80; H, 6.64; N, 3.69. Found: C, 72.83; H, 6.69; N, 3.74.

4g

Mp 140–142 °C.

IR (KBr): 3398, 2990, 1714, 1686, 1619, 1353, 1197, 1175 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.57–7.45 (m, 2 H), 7.44–7.35 (m, 3 H), 7.34–7.12 (m, 4 H), 6.12 (s, 1 H), 3.77 (s, 3 H), 3.07–2.48 (m, 1 H), 2.40 (s, 3 H), 1.18–0.75 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.3, 167.9, 166.1, 153.7, 139.0, 134.9, 134.2, 130.1, 130.0, 128.8, 128.6, 126.8, 113.5, 51.7, 34.1, 21.2, 18.8.

MS: *m*/*z* (%) = 365 (M^+, 20), 189 (100).

Anal. Calcd for $C_{22}H_{23}NO_4$ (365.16): C, 72.31; H, 6.34; N, 3.83. Found: C, 72.28; H, 6.41; N, 3.78.

4h

Oil.

IR (neat): 3447, 2973, 1718, 1677, 1621, 1179, 1156 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.56–7.44 (m, 2 H), 7.43–7.35 (m, 3 H), 7.34–7.19 (m, 5 H), 6.16 (s, 1 H), 4.89 (s, 2 H), 3.68 (s, 3 H), 3.06–2.94 (m, 1 H), 1.25–1.15 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.4, 165.7, 162.3, 137.0, 130.3, 129.0, 128.6, 128.5, 128.1, 127.5, 127.3, 126.9, 126.7, 51.8, 43.1, 32.8, 19.2.

MS: *m*/*z* (%) = 365 (M^+, 24), 106 (100).

Anal. Calcd for $C_{22}H_{23}NO_4$ (365.16): C, 72.31; H, 6.34; N, 3.83. Found: C, 72.27; H, 6.38; N, 3.89.

4i
Mp 72–75 °C.

IR (KBr): 2924, 1688, 1655, 1594, 1236, 1091 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.93 (t, *J* = 8.4 Hz, 2 H), 7.61 (d, *J* = 8.2 Hz, 2 H), 7.43 (d, *J* = 8.2 Hz, 2 H), 7.13 (t, *J* = 8.4 Hz, 2 H), 6.63 (d, *J* = 11.8 Hz, 1 H), 6.43 (d, *J* = 11.8 Hz, 1 H), 3.78 (t, *J* = 7.3 Hz, 2 H), 1.65–1.44 (m, 2 H), 1.38–0.99 (m, 16 H), 0.87 (t, *J* = 6.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.9, 172.9, 168.6, 167.2, 164.7, 138.9, 134.4, 133.6, 132.7, 132.6, 131.3, 131.2, 130.1, 129.5, 129.0, 116.0, 115.7, 46.2, 31.8, 29.5, 29.4, 29.4, 29.4, 29.0, 28.5, 26.7, 22.6, 14.1.

MS: *m*/*z* (%) = 485 (M^+, 43), 139 (100).

Anal. Calcd for $C_{27}H_{33}ClFNO_3$ (485.21): C, 69.19; H, 6.84; N, 2.88. Found: C, 69.23; H, 6.91; N, 2.83.

4j
Oil.

IR (neat): 3321, 2996, 1703, 1652, 1611, 1248, 1179, 843 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, *J* = 8.8 Hz, 2 H), 7.53 (d, *J* = 8.4 Hz, 2 H), 7.37 (d, *J* = 8.4 Hz, 2 H), 7.11 (d, *J* = 7.9 Hz, 2 H), 7.06 (d, *J* = 7.9 Hz, 2 H), 6.94 (d, *J* = 8.8 Hz, 2 H), 6.66 (d, *J* = 11.8 Hz, 1 H), 6.30 (d, *J* = 11.8 Hz, 1 H), 4.99 (s, 2 H), 3.88 (s, 3 H), 2.29 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.5, 172.5, 169.1, 164.1, 138.8, 137.2, 134.0, 133.9, 133.8, 131.0, 130.2, 129.9, 129.4, 129.2, 128.9, 128.1, 114.0, 55.5, 48.7, 21.1.

MS: *m*/*z* (%) = 447 (M^+, 3), 139 (100).

Anal. Calcd for $C_{26}H_{22}ClNO_4$ (447.12): C, 69.72; H, 4.95; N, 3.13. Found: C, 69.74; H, 5.07; N, 3.10.

4k
Oil.

IR (neat): 3675, 2972, 1697, 1661, 1605, 1204, 1173, 1077 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.88 (d, *J* = 8.2 Hz, 2 H), 7.39–7.24 (m, 6 H), 6.89 (d, *J* = 11.8 Hz, 1 H), 6.82 (d, *J* = 11.8 Hz, 1 H), 2.89–2.76 (m, 1 H), 2.43 (s, 3 H), 2.42 (s, 3 H), 1.09 (d, *J* = 6.7 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.9, 180.8, 170.0, 144.2, 139.0, 137.4, 135.0, 134.3, 130.3, 129.3, 128.7, 128.5, 125.2, 34.2, 21.6, 21.2, 19.0.

MS: *m*/*z* (%) = 349 (M^+, 8), 71 (100).

Anal. Calcd for $C_{22}H_{23}NO_3$ (349.17): C, 75.62; H, 6.63; N, 4.01. Found: C, 75.61; H, 6.69; N, 4.03.

Multicomponent Reaction of Acetylenic Esters/Ketones, Isocyanides, and Carboxylic Acids Leading to 5a, c, f–i; General Procedure

To a stirred solution of alkyne **1** (1.0 mmol) and isocyanide **2** (1.0 mmol) in anhyd MeCN (4 mL) was added a solution of carboxylic acid **3** (1.0 mmol) in anhyd $CHCl_3$ (1 mL). The mixture was then allowed to stir at 75 °C for 3 d. The solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography (PE–EtOAc, 10:1) to afford **5** (Table 4).

(*E*)-Ethyl 4-(*N*-Benzylbenzamido)-4-oxobut-2-enoate (5a)
Oil.

IR (neat): 3064, 2982, 1724, 1696, 1661, 1301, 1173 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.59–7.50 (m, 3 H), 7.45–7.37 (m, 2 H), 7.36–7.22 (m, 5 H), 6.83 (d, *J* = 15.3 Hz, 1 H), 6.62 (d, *J* = 15.3 Hz, 1 H), 5.09 (s, 2 H), 4.10 (q, *J* = 7.1 Hz, 2 H), 1.20 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.2, 167.5, 164.6, 136.7, 135.5, 135.3, 133.0, 130.9, 128.9, 128.8, 128.5, 128.1, 127.6, 61.0, 49.2, 13.9.

MS: *m*/*z* (%) = 337 (M^+, 1), 105 (100).

Anal. Calcd for $C_{20}H_{19}NO_4$ (337.13): C, 71.20; H, 5.68; N, 4.15. Found: C, 71.24; H, 5.73; N, 4.13.

5c
Mp 36–38 °C.

IR (KBr): 2929, 1680, 1671, 1561, 1235, 1102 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.94–7.86 (m, 2 H), 7.70 (d, *J* = 15.1 Hz, 1 H), 7.59 (d, *J* = 8.4 Hz, 2 H), 7.42 (d, *J* = 8.4 Hz, 2 H), 7.13 (t, *J* = 8.6 Hz, 2 H), 6.93 (d, *J* = 15.1 Hz, 1 H), 3.86 (t, *J* = 7.4 Hz, 2 H), 1.71–1.60 (m, 2 H), 1.36–1.13 (m, 16 H), 0.86 (t, *J* = 6.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.6, 172.6, 167.8, 167.3, 164.7, 139.4, 134.7, 133.7, 133.6, 133.0, 132.9, 131.5, 131.4, 130.2, 129.2, 116.0, 115.9, 46.7, 31.8, 29.5, 29.5, 29.4, 29.2, 29.1, 28.9, 26.8, 22.6, 14.0.

MS: *m*/*z* (%) = 485 (M^+, 51), 139 (100).

Anal. Calcd for $C_{28}H_{33}ClFNO_3$ (485.21): C, 69.19; H, 6.84; N, 7.29. Found: C, 69.23; H, 6.91; N, 7.22.

5f
Oil.

IR (neat): 2970, 1700, 1658, 1653, 1239, 1152, 1010 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.11–8.06 (m, 2 H), 7.77 (d, *J* = 15.0 Hz, 1 H), 7.41 (d, *J* = 15.0 Hz, 1 H), 7.18 (t, *J* = 8.6 Hz, 2 H), 3.74 (t, *J* = 7.7 Hz, 2 H), 3.28–3.09 (m, 1 H), 1.67–1.54 (m, 2 H), 1.38–1.19 (m, 22 H), 0.88 (t, *J* = 6.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.0, 181.2, 168.4, 167.4, 164.8, 136.0, 133.3, 133.2, 133.0, 131.6, 131.5, 116.1, 115.9, 44.7, 34.5, 31.9, 29.6, 29.5, 29.5, 29.4, 29.3, 29.2, 26.8, 22.6, 19.4, 14.1.

MS: *m*/*z* (%) = 417 (M^+, 100).

Anal. Calcd for $C_{25}H_{36}FNO_3$ (417.27): C, 71.91; H, 8.69; N, 3.35. Found: C, 71.94; H, 8.76; N, 3.36.

5g
Mp 65–67 °C.

IR (KBr): 2974, 2932, 1704, 1661, 1604, 1294, 1152 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 7.6 Hz, 2 H), 7.84 (d, *J* = 15.0 Hz, 1 H), 7.46 (d, *J* = 15.0 Hz, 1 H), 7.33–7.22 (m, 5 H), 7.20 (d, *J* = 7.6 Hz, 2 H), 5.04 (s, 2 H), 3.23–3.10 (m, 1 H), 2.40 (s, 3 H), 1.15 (d, *J* = 6.8 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.7, 181.1, 168.7, 144.6, 136.6, 134.8, 134.1, 129.4, 128.8, 128.7, 128.4, 127.5, 126.3, 47.3, 34.8, 21.6, 19.2.

MS: *m*/*z* (%) = 349 (M^+, 42), 71 (100).

Anal. Calcd for $C_{22}H_{23}NO_3$ (349.17): C, 75.62; H, 6.63; N, 4.01. Found: C, 75.68; H, 6.71; N, 4.04.

5h
Oil.

IR (neat): 2959, 1699, 1658, 1257, 1161 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 8.8 Hz, 2 H), 7.85 (d, *J* = 15.0 Hz, 1 H), 7.49 (d, *J* = 15.0 Hz, 1 H), 7.37–7.25 (m, 3 H), 7.21 (d, *J* = 7.6 Hz, 2 H), 6.95 (d, *J* = 8.8 Hz, 2 H), 5.03 (s, 2 H),

3.87 (s, 3 H), 2.57 (d, *J* = 6.8 Hz, 2 H), 2.26–2.15 (m, 1 H), 0.93 (d, *J* = 6.6 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.5, 175.8, 168.7, 164.0, 136.5, 134.6, 134.3, 131.1, 129.6, 128.7, 127.5, 126.3, 113.9, 55.4, 47.3, 46.0, 25.1, 22.3.

MS: *m*/*z* (%) = 379 (M^+, 29), 106 (100).

Anal. Calcd for $C_{23}H_{25}NO_4$ (379.18): C, 72.80; H, 6.64; N, 3.69. Found: C, 72.74; H, 6.71; N, 3.73.

5i
Mp 80–82 °C.

IR (KBr): 3031, 2980, 1687, 1656, 1603, 1291, 1177 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 7.6 Hz, 2 H), 7.83 (d, *J* = 15.0 Hz, 1 H), 7.46 (d, *J* = 15.0 Hz, 1 H), 7.27 (d, *J* = 7.6 Hz, 2 H), 7.13 (d, *J* = 7.9 Hz, 2 H), 7.09 (d, *J* = 7.9 Hz, 2 H), 5.00 (s, 2 H), 3.20–3.09 (m, 1 H), 2.43 (s, 3 H), 2.32 (s, 3 H), 1.16 (d, *J* = 6.6 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.9, 181.3, 168.8, 144.7, 137.3, 135.0, 134.3, 134.2, 133.7, 129.5, 129.5, 129.0, 126.4, 47.3, 35.0, 21.7, 21.0, 19.4.

MS: *m*/*z* (%) = 363 (M^+, 10), 105 (100).

Anal. Calcd for $C_{23}H_{25}NO_3$ (363.18): C, 76.01; H, 6.93; N, 3.85. Found: C, 76.04; H, 6.99; N, 3.86.

Isomerization of 4 Leading to 5a–e; General Procedure
Compound **4** (0.3 mmol) and MeCN (2 mL) were mixed in $CHCl_3$ (0.5 mL). The mixture was then allowed to stir at 75 °C for 3 d and then concentrated in vacuo. The residue was purified by silica gel chromatography using PE–EtOAc (10:1) as eluent (Table 3).

5b
Oil.

IR (neat): 3032, 2994, 1698, 1673, 1675, 1501, 1193, 979 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.21 (m, 3 H), 7.08–6.99 (m, 2 H), 6.79 (d, *J* = 15.2 Hz, 1 H), 4.23 (q, *J* = 7.6 Hz, 2 H), 3.03–2.95 (m, 1 H), 2.40 (s, 3 H), 1.29 (t, *J* = 7.2 Hz, 3 H), 1.16 (d, *J* = 6.4 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.3, 165.2, 163.0, 139.2, 136.1, 135.0, 131.4, 130.6, 128.3, 61.2, 34.7, 21.2, 19.2, 14.1.

MS: *m*/*z* (%) = 303 (M^+, 3), 107 (100).

Anal. Calcd for $C_{17}H_{21}NO_4$ (303.15): C, 67.31; H, 6.98; N, 4.62. Found: C, 67.34; H, 7.08; N, 4.66.

5d
Mp 42–44 °C.

IR (KBr): 2971, 1683, 1658, 1595, 1250, 1170 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 8.8 Hz, 2 H), 7.72 (d, *J* = 15.0 Hz, 1 H), 7.52 (d, *J* = 8.4 Hz, 2 H), 7.37 (d, *J* = 8.4 Hz, 2 H), 7.22 (d, *J* = 7.9 Hz, 2 H), 7.11 (d, *J* = 7.9 Hz, 2 H), 6.92 (d, *J* = 8.8 Hz, 2 H), 6.87 (d, *J* = 15.0 Hz, 1 H), 5.06 (s, 2 H), 3.87 (s, 3 H), 2.31 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.3, 172.4, 168.2, 164.2, 139.5, 137.5, 134.8, 133.8, 133.7, 133.6, 131.2, 130.3, 129.5, 129.4, 129.3, 128.0, 114.0, 55.5, 49.3, 21.1.

MS: *m*/*z* (%) = 447 (M^+, 1), 139 (100).

Anal. Calcd for $C_{26}H_{22}ClNO_4$ (447.12): C, 69.72; H, 4.95; N, 7.92. Found: C, 69.76; H, 4.87; N, 7.94.

5e
Oil.

IR (neat): 2973, 1701, 1697, 1663, 1311, 1179 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95–7.81 (m, 3 H), 7.36–7.26 (m, 4 H), 7.22 (d, *J* = 15.1 Hz, 1 H), 7.07 (d, *J* = 8.0 Hz, 2 H), 3.19–3.08 (m, 1 H), 2.43 (s, 3 H), 2.42 (s, 3 H), 1.20 (d, *J* = 6.8 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.0, 181.0, 167.8, 144.7, 139.2, 135.1, 134.7, 134.5, 134.3, 130.6, 129.5, 129.0, 128.4, 34.9, 21.7, 21.2, 19.3.

MS: *m*/*z* (%) = 349 (M^+, 11), 173 (100).

Anal. Calcd for $C_{22}H_{23}NO_3$ (349.17): C, 75.62; H, 6.63; N, 4.01. Found: C, 75.66; H, 6.71; N, 3.97.

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(10) The crystal structure of **4f** has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 696375. The data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk].

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