Three-component reaction between alkyl isocyanides, dialkyl acetylenedicarboxylates, and carboxylic acids

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Protonation of the reactive intermediates produced in the reaction between alkyl isocyanides and dialkyl acetylenedicarboxylates by carboxylic acids leads to vinylnitrilium cations which then undergo nucleophilic addition of the conjugate bases of the carboxylic acids. This intermediate rearranges to produce dialkyl *(E)*2-{[(aryl)acetyl(alkylamino)]carbonyl}-2-butenedioate derivatives.

Keywords: multicomponent reaction, alkyl isocyanide, dialkyl acetylene dicarboxylate, carboxylic acids

Isocyanide based reactions have been the most studied multi-component reactions, by organic chemists. The Ugi four component reaction[1–3] and the Passerini three component reaction[4] are among the most important isocyanide based multi-component reactions. The Ugi four component reaction and the Passerini three component reaction involve the reaction of isocyanides with carboxylic acids in the presence of imines or aldehydes, respectively. Recently another type of isocyanide based multi-component reaction has been developed and extensively investigated. Isocyanides react easily with electron-deficient acetylene diesters such as dimethyl acetylenedicarboxylate (DMAD) to produce a reactive zwitterionic intermediate which can be trapped by an electrophile. A wide variety of electrophiles have been applied to trap the isocyanide-DMAD intermediate, among them are carbon electrophiles such as aldehydes, imines, quinones,[5] 1,2-diketones,[6] 1,2,3-tricarbonyl compounds,[7] isocyanates,[8] and hydrogen electrophiles such as pyrrole,[9] amides,[10] hydroxy-coumarin,[11] phenols,[12] phthalic anhydride,[13] and isatoic anhydride.[14] Reaction of the isocyanide-DMAD adduct with aromatic-substituted acetic acids has been reported to afford 2,5-diaminofuran derivatives in the presence of two equivalents of an isocyanide.[15] In the context of our previous works on isocyanide based multi-component reactions,[9–11,16,17] we now report the results of our investigations on the reaction of carboxylic acids and dialkyl acetylenedicarboxylates in the presence of alkyl isocyanides.

Results and discussion

Reaction of carboxylic acid **3** and dialkyl acetylenedicarboxylate **2** in the presence of alkyl isocyanide **1** affords dialkyl *(E)*2-{[(aryl)acetyl(alkylamino)]carbonyl}-2-butenedioate derivatives **4** in excellent yields (Scheme 1).

The structures of compounds **4a–f** were deduced from their elemental analyses, IR and ^{1}H, ^{13}C and ^{19}F NMR.

The ^{1}H NMR spectra of products **4a–f** revealed the restricted rotation around the carbon–carbon double bond. The stereochemistry of the double bond has the *E*-configuration in **4**.

The vinyl proton of the *E* isomer is expected to resonate at lower field than the proton of the Z isomer.[18]

The mass spectrum of compound **4a** showed the molecular ion peak at 429.

^{19}F NMR spectrum of compound **4a** displayed a signal at –63.31 ppm.

The ^{1}H NMR spectrum of compound **4a** was simple and exhibited two sharp signals at 3.74 and 3.79 ppm for two methoxy groups. The protons of methylene were observed as a singlet at δ = 3.81 ppm and vinylic proton at δ = 6.86. The aromatic protons resonated at δ = 7.31–7.57 ppm. One sharp singlet signal was assigned to the methyls of the t-Bu (δ = 1.31). The ^{13}C NMR spectrum of compound **4a** showed 18 distinct resonances in agreement with the proposed structure. The IR spectrum of **4a** exhibited absorption of the vinylic moiety at 1645 cm^{-1} and of the carbonyl groups at 1726 and 1675 cm^{-1}.

On the basis of the well established chemistry of isocyanides[19–24] it is reasonable to assume that the compound **4** arises from initial addition of the isocyanide **1** to the acetylenic ester **2** and subsequent protonation of the 1:1 adduct **5** by compound **3**. This is followed by attack of the carboxylate anion **7** on the positively charged ion **6** to form an imidoyl carboxylate **8**, which undergoes rearrangement[25–27] under these reaction conditions to produce compound **4** (Scheme 2).

In conclusion, we report that the three-component reaction between alkyl isocyanides, dialkyl acetylenedicarboxylates and carboxylic acids is a simple and efficient route for the synthesis of dialkyl *(E)*2-{[(aryl)acetyl(alkylamino)]carbonyl}-2-butenedioate derivatives. The advantages of this method are the inexpensive and easily available starting materials, neutral reaction conditions, high yields, single-product reaction and simple work-up processes.

Experimental

Elemental analyses were performed using a Costech ECS 4010 CHNS-O analyser at the analytical laboratory of Islamic Azad University Yazd branch. IR spectra were recorded on a Shimadzu IR-470 spectrometer.^{1}H, ^{19}F and ^{13}C NMR spectra were recorded on a Bruker DRX-500 Avance spectrometer at solution in $CDCl_3$ using TMS as internal standard. The chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification.

General procedure

A mixture of alkyl isocyanide (1 mmol) in 2 mL acetone was added to a magnetically stirred solution of carboxylic acid (1 mmol) and dialkyl acetylenedicarboxylate (1 mmol) in 10 mL acetone at room temperature. The reaction mixture was then stirred for 24 hours. The solvent was removed and the residue was purified by silica gel column chromatography using hexane-ethyl acetate (3:1) as eluent. The solvent was removed under reduced pressure to afford the product.

Dimethyl (E)2-{[(3-trifluoromethyl-phenyl)acetyl (tert-butylamino)] carbonyl}-2-butenedioate **(4a):** Yellow oil, yield 90%; IR (KBr) (ν_{max}, cm^{-1}): 1726 (OCNCO), 1675 (CO_2Me), 1645 (C=C). Anal.Calcd for $C_{20}H_{22}F_3NO_6$: C, 55.94; H, 5.16; N, 3.26. Found: C, 55.78; H, 5.31; N, 3.39%. MS (*m/z*, %): 429 (M^+, 7). ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.31 (9H, s, CMe_3), 3.74 and 3.79 (6H, 2s, 2 OCH_3), 3.81 (2H, s, CH_2), 6.86 (1H, s, CH), 7.42 (1H, t, $^{3}J_{HH}$ = 7.8 Hz, HAr), 7.47 (1H, d, $^{3}J_{HH}$ = 7.4 Hz, HAr), 7.51 (1H, d, $^{3}J_{HH}$ = 7.9 Hz, HAr), 7.57 (1H, s, HAr). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ = 28.21(methyl groups of *tert*-butyl), 42.28 (CH_2), 52.07 and 52.53 (2 OCH_3), 59.37 (C of t-butyl), 123.96 (q, $^{1}J_{FC}$ = 272 Hz, CF_3), [125.85 (q, $^{3}J_{FC}$ = 3.7 Hz), 128.59, 130.46 (q, $^{2}J_{FC}$ = 32 Hz,), 132.67, 135.89 and 138.59 6C aromatic], 129.43 and 141.57 (C=CH), 163.01 (NCO), 164.79 (CO_2CH_3), 167.25 (CO_2CH_3), 171.82 (CH_2CON). ^{19}F NMR (470.56 MHz, $CDCl_3$) δ = –63.31 (CF_3) ppm.

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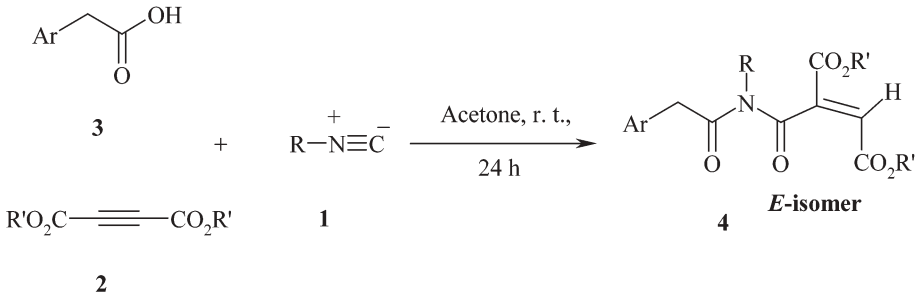
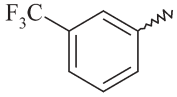
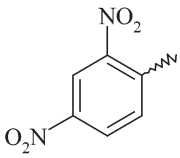
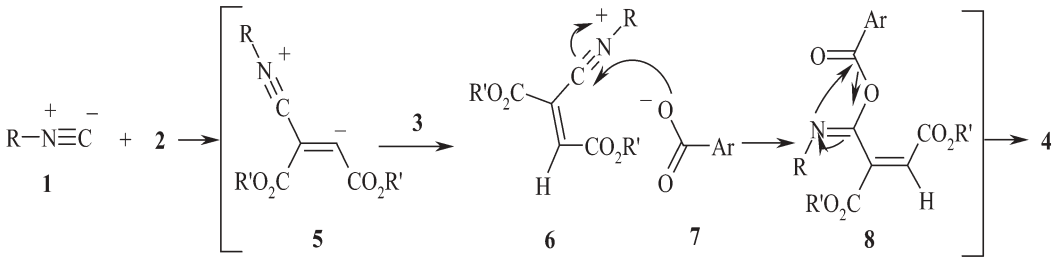


Entry	Ar	R	R'	Product	Yield (%)*
1		tert-Bu	Me	**4a**	90
2		Cy	Me	**4b**	88
3		tert-Bu	Et	**4c**	85
4		tert-Bu	Me	**4d**	91
5		Cy	Me	**4e**	88
6		tert-Bu	Et	**4f**	87

*Isolated Yields

Scheme 1 Reaction between carboxylic acids and dialkyl acetylenedicarboxylates in the presence of alkyl isocyanides.



Scheme 2 Suggested mechanism for formation compound **4**.

Dimethyl (E)2-{[(3-trifluoromethyl-phenyl)acetyl (cyclohexylamin o)]carbonyl}-2-butenedioate **(4b):** Yellow oil, yield 88%; IR (KBr) (ν_{max}, cm^{-1}): 1723 (OCNCO), 1683 (CO_2Me), 1644, (C=C). Anal. Calcd for $C_{22}H_{24}F_3NO_6$: C, 58.02; H, 5.31; N, 3.08. Found: C, 58.19; H, 5.44; N, 3.27%. MS (*m/z*, %): 455 (M^+, 3). ^1H NMR (500.13 MHz, $CDCl_3$): δ = 1.13–1.78 (10H, $5CH_2$ of cyclohexyl), 3.70 and 3.77 (6H, 2 s, 2 OCH_3), 3.79 (1H, m, CH of cyclohexyl), 4.05 (2H, s, CH_2), 6.62 (1H, s, CH), 7.40 (1H, t, $^3J_{HH}$ = 7.8 Hz, HAr), 7.44 (1H, d, $^3J_{HH}$ = 7.4 Hz, HAr), 7.49 (1H, d, $^3J_{HH}$ = 7.9 Hz, HAr), 7.52 (1H, s, HAr). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ = 25.12, 25.31, 26.40, 31.20 and 32.51 (5 CH_2 of cyclohexyl), 43.70 (CH_2), 48.73 (CH of cyclohexyl), 52.08 and 52.81 (2 OCH_3), 123.93 (q, $^1J_{FC}$ = 272 Hz, *C*F_3), [125.92 (q, $^3J_{FC}$ = 3.7 Hz), 128.92, 130.71(q, $^2J_{FC}$ = 32 Hz,), 132.76, 134.71 and 138.43 6C aromatic], 128.54 and 143.18 (C=CH), 162.83 (NCO), 164.64 (CO_2CH_3), 166.84 (CO_2CH_3), 174.13 (CH_2CON). ^{19}F NMR (470.56 MHz, $CDCl_3$) δ = –63.35 (CF_3) ppm.

Diethyl (E)2-{[(3-trifluoromethyl-phenyl)acetyl (tert-butylamino)] carbonyl}-2-butenedioate **(4c):** Yellow oil, yield 85%; IR (KBr) (ν_{max}, cm^{-1}): 1719 (OCNCO), 1672 (CO_2Me), 1639, (C=C). Anal.Calcd for $C_{22}H_{26}F_3NO_6$: C, 57.76; H, 5.73; N, 3.06. Found: C, 57.59; H, 5.61; N, 3.23%. MS (*m/z*, %): 457 (M^+, 5). ^1H NMR (500.13 MHz, $CDCl_3$): δ = 1.25 and 1.34 (6H, 2t, $^3J_{HH}$ = 7 Hz, $2CH_3$), 1.28 (9H, s, CMe_3), 3.80 (2H, s, CH_2), 4.22 (4H, m, $2OCH_2$), 6.82 (1H, s, CH), 7.35 (1H, t, $^3J_{HH}$ = 7.8 Hz, HAr), 7.42 (1H, d, $^3J_{HH}$ = 7.4 Hz, HAr), 7.47 (1H, d, $^3J_{HH}$ = 7.9 Hz, HAr), 7.51 (1H, s, HAr). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ = 13.61 and 14.07 (2 *C*H_3), 27.88 (methyl groups of *tert*-butyl), 42.25 (CH_2), 59.61 (C of t-butyl), 60.71 and 61.26 (2 *OC*H_2), 123.95 (q, $^1J_{FC}$ = 272 Hz, *C*F_3), [125.84 (q, $^3J_{FC}$ = 3.7 Hz), 128.53, 130.38 (q, $^2J_{FC}$ = 32 Hz,), 132.71, 135.94 and 138.01 6C aromatic], 129.02 and 141.38 (C=CH), 162.78 (NCO), 164.36 (CO_2CH_3), 166.81 (CO_2CH_3), 171.86 (CH_2CON). ^{19}F NMR (470.56 MHz, $CDCl_3$) δ = –63.38 (CF_3) ppm.

Dimethyl (E)2-{[(2,4-dinitrophenyl)acetyl (tert-butylamino)] carbonyl}-2-butenedioate **(4d):** Yellow oil, yield 91%; IR (KBr) (ν_{max}, cm^{-1}): 1728 (OCNCO), 1707 (CO_2Me), 1608, (C=C). Anal.Calcd for $C_{19}H_{21}N_3O_{10}$: C, 50.56; H, 4.69; N, 9.31. Found: C, 50.37; H, 4.80; N, 9.15%. MS (*m/z*, %): 451 (M^+, 7). ^1H NMR (500.13 MHz, $CDCl_3$): δ = 1.35 (9H, s, CMe_3), 3.72 and 3.80 (6H, 2s, 2 OCH_3), 3.83 (2H, s, CH_2), 6.96 (1H, s, CH), 7.50 (1H, d, $^3J_{HH}$ = 8.4 Hz, HAr), 8.39 (1H, m, HAr), 8.83 (1H, d, $^3J_{HH}$ = 7.9 Hz, HAr).^{13}C NMR (125.75 MHz, $CDCl_3$): δ = 28.08 (methyl groups of *tert*-butyl), 42.15 (CH_2), 52.64 and 53.08 (2 OCH_3), 59.48 (C of t-butyl), 120.51, 126.81, 128.64, 133.85, 140.64, 143.75, 146.31 and 159.11 (8C aromatic and olefinic), 161.32 (NCO), 165.63 (CO_2CH_3), 166.25 (CO_2CH_3), 172.43 (CH_2CON).

Dimethyl (E)2-{[(2,4-dinitrophenyl)acetyl (cyclohexylamino)]carb onyl}-2-butenedioate **(4e):** Yellow oil, yield 88%; IR (KBr) (ν_{max}, cm^{-1}): 1727 (OCNCO), 1705 (CO_2Me), 1603, (C=C). Anal.Calcd for

$C_{21}H_{23}N_3O_{10}$: C, 52.83; H, 4.86; N, 8.80. Found: C, 53.05; H, 4.64; N, 8.93%. MS (*m/z*, %): 477 (M^+, 3). ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.23–1.93 (10H, 5CH_2 of cyclohexyl), 3.67 and 3.80 (6H, 2 s, 2 OCH_3), 3.87 (1H, m, CH of cyclohexyl), 4.01 (2H, s, CH_2), 6.66 (1H, s, CH), 7.59 (1H, d, $^3J_{HH}$ = 8.4 Hz, HAr), 8.34 (1H, m, HAr), 8.78 (1H, d, $^3J_{HH}$ = 7.9 Hz, HAr). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ = 24.97, 25.52, 25.68, 31.31 and 33.26 (5 CH_2 of cyclohexyl), 43.35 (CH_2), 48.64 (CH of cyclohexyl), 52.16 and 52.97 (2 OCH_3), 120.06, 126.89, 128.86, 133.98, 140.65, 143.70, 146.32 and 159.05 (8C aromatic and olefinic), 161.52 (NCO), 164.88 (CO_2CH_3), 166.48 (CO_2CH_3), 171.76 (CH_2CON).

Diethyl (E)2-{[(2,4-dinitrophenyl)acetyl (tert-butylamino)] carbonyl}-2-butenedioate **(4f):** Yellow oil, yield 87%; IR (KBr) (ν_{max}, cm^{-1}): 1728 (OCNCO), 1705 (CO_2Me), 1602, (C=C). Anal.Calcd for $C_{21}H_{25}N_3O_{10}$: C, 52.61; H, 5.26; N, 8.76. Found: C, 52.50; H, 5.43; N, 8.56%. MS (*m/z*, %): 479 (M^+, 4). ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.18 and 1.31 (6H, 2t, $^3J_{HH}$ = 7 Hz, 2CH_3), 1.21 (9H, s, CMe_3), 3.83 (2H, s, CH_2), 4.18 (4H, m, 2OCH_2), 6.74 (1H, s, CH), 7.58 (1H, d, $^3J_{HH}$ = 8.4 Hz, HAr), 8.32 (1H, m, HAr), 8.72 (1H, d, $^3J_{HH}$ = 7.9 Hz, HAr).^{13}C NMR (125.75 MHz, $CDCl_3$): δ = 13.45 and 14.05 (2 CH_3), 29.33 (methyl groups of *tert*-butyl), 42.17 (CH_2), 58.14 (C of t-butyl), 61.91 and 62.15 (2 OCH_2), 119.87, 126.82, 128.51, 133.99, 140.55, 143.71, 146.22 and 159.04 (8C aromatic and olefinic), 161.02 (NCO), 164.97 (CO_2CH_3), 166.37 (CO_2CH_3), 172.58 (CH_2CON).

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