Stereoselective synthesis of dialkyl 2-benzoyloxy-3-(*N*-alkyl-*N′*-arylcarbamimidoyl)succinates: a four component reaction

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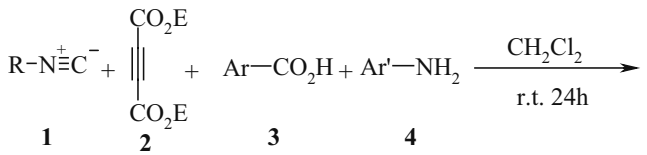
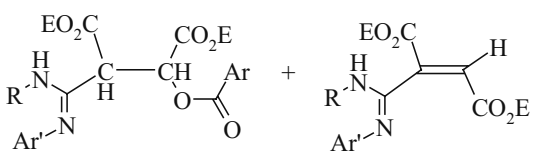
An improved four-component reaction of isocyanides is described. The reaction between alkyl isocyanides, dialkyl acetylenedicarboxylates, aromatic amines and benzoic acid in dichloromethane at room temperature leads to dialkyl 2-benzoyloxy-3-(*N*-alkyl-*N′*-arylcarbamimidoyl)succinates in good yields

Keywords: alkyl isocyanides, four-component reaction, dialkyl acetylenedicarboxylates, aromatic amines, benzoic acid

Multi-component reactions (MCRs) have attracted great attention from synthetic chemists because they can be employed for the synthesis of complex molecules from simply available starting materials in one pot. These processes consist of two or more synthetic steps, which are performed without isolation of any intermediates thus reducing time and saving both energy and raw materials. These reactions have provided simple and short synthetic routs for the synthesis of biologically active and industrially valuable products.[1-9] An important class of MCRs is isocyanide based multi component reactions (IMCRs), including Passerini three-component reaction (P-3CR) and Ugi four-component reaction (U-4CR).[6-8] A recently investigated IMCR is the reaction of isocyanides with electron-deficient acetylenic esters in the presence of a proton source such as an alcohol. The addition of isocyanides on acetylenic esters produces a reactive zwitterionic intermediate, which may then be trapped by a compound containing an acidic NH or OH proton. The three-component reaction of isocyanides, acetylenic esters and a proton source such as pyrrole,[10] naphthols,[11] phenols[12] and 4-hydroxycoumarin has been investigated.[13] Most of these rections were reported to produce keteneimines as intermediate or the final product.[11-13] However, the reaction of isocyanides with acetylenic esters in the presecnce of pyrrole, indole, carbazole,[10] and *N*-phenylacetamide[14] has been reported to produce amidine derivatives as the major product. In contination of our previous works[7,9-11] on the IMCRs, we report here the four-component reaction between alkyl isocyanides, dialkyl acetylenedicarboxylates, aromatic amines and benzoic acid in dichloromethane to afford dialkyl 2-benzoyloxy-3-(*N*-alkyl-*N′*-arylcarbamimidoyl)succinates in good yields. Thus, the reaction between cyclohexyl isocyanide, dimethyl acetylenedicarbixylate (DMAD), benzoic acid and aniline leads to dimethyl 2-benzoyloxy-3-(*N*-cyclohexyl-*N′*-phenylcarbamimidoyl)succinate **5a** in 70% yield (Scheme 1). Compound **5a** possesses two steriogenic centres and may exist as two diastereomers. However, the ^{1}H NMR spectrum of **5a** showed the existence of only one isomer. Two products were isolated from the reaction between cyclohexyl isocyanide, diethyl acetylenedicarboxylate, benzoic acid and aniline. The tetraadduct diethyl 2-benzoyloxy-3-(*N*-cyclohexyl-*N′*-phenylcarbamimidoyl)succinate **5b** in 65% yield and the triadduct diethyl 2-(*N*-cyclohexyl-*N′*-phenylcarbamimidoyl) fumarate **6b** in 15% yield. When 4-nitrobenzoic acid was used instead of benzoic acid, the product of four-component addition was not isolated and the triadduct **6f** was the major



1 **2** **3** **4**



5 **6**

5, 6	R	E	Ar	Ar'	6%*	5%*
a	Cy	Me	C_6H_5	Ph	—	70%
b	Cy	Et	C_6H_5	Ph	15%	65%
c	Cy	Me	C_6H_5	4-BrC_6H_4	—	70%
d	Cy	Et	C_6H_5	4-BrC_6H_4	—	75%
e	^{t}Bu	Me	C_6H_5	4-BrC_6H_4	—	70%
f	Cy	Me	4-$O_2NC_6H_4$	Ph	70%	—

* Isolated yield.

Scheme 1

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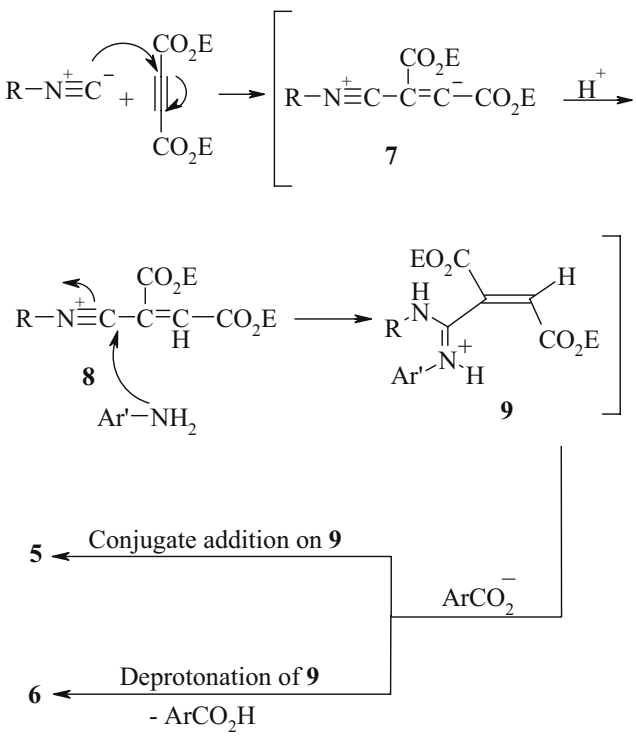
product obtained in 70% yield. This is probably due to the low nucleophilicity of 4-nitrobenzoic acid towards the addition on unsaturated amidine **6f**.

The structure of new compounds was deduced by elemental and spectral analysis. The ^{1}H NMR spectrum of **5a** exhibited two sharp lines at δ = 3.77 and 3.81 ppm for the protons of two methoxy groups. Two doublets ($^3J_{HH}$ = 10 H_Z) were observed at δ = 4.57 and 5.11 ppm for the protons of two methine groups. Cyclohexyl protons were observed as multiplets between δ = 1.07–1.80 and at δ = 3.65 ppm. Multiplets observed between δ = 7.15–7.34 ppm are related to the aromatic protons. The NH proton resonated at δ = 5.91 ppm as a doublet ($^3J_{HH}$ = 7 H_Z) which disappeared after addition of some D_2O to $CDCl_3$ solution of **5a**. This proton is coupled with the CH proton of cyclohexyl moiety. When cyclohexyl group is replaced by *tert*-butyl in **5e**, the NH proton is observed as a singlet. The ^{13}C NMR spectrum of compound **5a** showed 20 distinct signals in consistent with the proposed structure. The suggested structure was also supported by the IR spectrum. The strong absorption bonds at 3270, 1733 and 1635 are respectively related to NH, ester and amidine groups.

A reasonable mechanism for the formation of compounds **5** and **6** is presented in Scheme 2. The zwitterionic intermediate **7** formed from the addition of isocyanide on acetylenic ester is protonoted by benzoic acid to afford the nitrilium cation **8** which then converted to amidinium cation **9** by the addition of amine. The conjugate addition of carboxylate anion on amidinium cation **9** affords the product **5**. Carboxylate anion may also depronate intermediate **9** to yield the product **6**.

In summary, we report here a simple and efficient one-pot synthesis of dialkyl 2-benzoyloxy-3-(*N*-alkyl-*N'*-arylcarbamimidoyl)succinates by four-component reaction between alkyl isocyanides, dialkyl acetylenedicarboxylates, aromatic amines and benzoic acid. The advantage of this method is that the reaction is carried out under neutral conditions and simply available starting materials are used without any purification or modification.



Scheme 2

Experimental

Melting points were determined with an electrothermal 9100 apparatus. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyser. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionisation potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer.^{1}H and ^{13}C NMR spectra were recorded on Bruker DRX-500 Avance spectrometer at solution in $CDCl_3$ using TMS as internal standard. The chemicals used in this work purchased from fluka (Buchs, Switzerland) and were used without further purification.

General procedure

To a magnetically stirred solution of amine (2 mmol), isocyanide (2 mmol) and aryl carboxylic acid (2 mmol) in 10 ml dichloromethane was added a mixture of dialkyl acetylenedicarboxylate (2 mmol) in 5 ml dichloromethane at room temperature. The reaction mixture was then stirred for 24 h. The solvent was removed and the residue was purified by silica gel column chromatography using hexane–ethyl acetate as eluent. The solvent was removed under reduced pressure to afford the product.

Dimethyl 2-benzoyloxy-3-(N-cyclohexyl-N'-phenylcarbamimidoyl) succinate **5a:** White powder, m.p. 182–184°C, yield 70%, IR (KBr) (ν_{max}, cm^{-1}): 3270 (NH), 1733, 1635 (C=O and C=N). Anal. Calcd for $C_{26}H_{30}N_2O_6$: C, 66.9; H, 6.5; N, 6.0. Found: C, 66.7; H, 6.5; N, 6.1%. MS, *m/z* (%): 466 ($M^{+\cdot}$, 8). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.07–1.89 (10 H, m, 5 CH_2), 3.74 (1 H, m, CH of cyclohexyl), 3.77 and 3.81 (6 H, 2 s, 2 OCH_3), 4.57 and 5.11 (2 H, 2 d $^3J_{HH}$ = 10 Hz, 2 CH), 5.91 (1 H, d $^3J_{HH}$ = 8 Hz, NH), 7.15–7.34 (10 H, m, aromatic). ^{13}C NMR (128.5 MHz, $CDCl_3$): δ 24.08, 25.03, 25.70, 33.03, 33.12 and 49.40 (5 CH_2 and CH of cyclohexyl), 53.18 and 53.29 (2 OCH_3), 54.32 and 64.79 (2 CH), 127.43, 129.11, 128.23, 129.52, 129.61, 130.90, 134.92 and 145.21 (aromatic), 165.27 (C=N), 169.18, 170.48, 171.99 (3 C=O).

Diethyl 2-benzoyloxy-3-(N-cyclohexyl-N'-phenylcarbamimidoyl) succinate **5b:** White powder, m.p. 179–180°C, yield 65%, IR (KBr) (ν_{max}, cm^{-1}): 3290 (NH), 1734, 1641 (C=O and C=N). Anal. Calcd for $C_{28}H_{34}N_2O_6$: C, 68.0; H, 6.9; N, 5.7. Found: C, 68.8; H, 6.7; N, 5.5%. MS, *m/z* (%): 494 ($M^{+\cdot}$, 3) ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.09–1.89 (10 H, m, 5 CH_2), 3.75 (1 H, m, CH of cyclohexyl), 1.31 and 1.33 (6 H, 2 t $^3J_{HH}$ = 7 Hz, 2 CH_3), 4.19–4.60 (4 H, m, 2 OCH_2), 4.59 and 5.20 (2 H, d $^3J_{HH}$ = 10 Hz, 2 CH), 5.84 (H, d $^3J_{HH}$ = 8 Hz, NH), 7.17–7.37 (10 H, m, aromatic). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 25.01, 25.10, 25.75, 33.03, 34.00 and 49.33 (5 CH_2 and CH of cyclohexyl), 14.48 and 14.50 (2 CH_3), 62.14 and 62.19 (2 OCH_2), 54.60 and 64.79 (2 CH), 127.37, 128.14, 128.24, 129.40, 129.43, 130.78, 135.24 and 145.20 (aromatic), 165.49 (C=N), 168.74, 169.91, 171.96 (3 C=O).

Dimethyl2-benzoyloxy-3-[N-cyclohexyl-N'-(4-bromophenyl)carbamimidoyl]succinate **5c:** White powder, m.p. 158–159°C, yield 70%, IR (KBr) (ν_{max}, cm^{-1}): 3285 (NH), 1738, 1664, 1640 (C=O and C=N). Anal. Calcd for $C_{26}H_{29}BrN_2O_6$: C, 57.25; H, 5.4; N, 5.1. Found: C, 57.1; H, 5.5; N, 5.4%. MS, *m/z* (%): 544 ($M^{+\cdot}$, 5) ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.06–1.90 (10 H, m, 5 CH_2), 3.70 (1 H, m, CH of cyclohexyl), 3.78 and 3.82 (6 H, s, 2 OCH_3), 4.58 and 5.13 (2 H, d $^3J_{HH}$ = 10 Hz, 2 CH), 6.01 (H, d $^3J_{HH}$ = 8 Hz, NH), 7.18–7.37 (9 H, m, aromatic). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 25.05, 25.69, 32.98, 33.03 and 49.49 (5 CH_2 and CH of cyclohexyl), 53.21 and 53.31 (2 OCH_3), 54.24 and 64.82 (2 CH), 121.22, 128.35, 129.50, 129.76, 131.17, 132.65, 134.61 and 144.48 (aromatic), 165.27 (C=N), 168.98, 170.24, 171.82 (3 C=O).

Diethyl 2-benzoyloxy-3-[N-cyclohexyl-N'-(4-bromophenyl)carbamimidoyl]succinate **5d:** White powder, m.p. 140–142°C, yield 75%, IR (KBr) (ν_{max}, cm^{-1}): 3275 (NH), 1731, 1649 (C=O and C=N). Anal. Calcd for $C_{28}H_{33}BrN_2O_6$: C, 58.6; H, 5.8; N, 4.9. Found: C, 58.6; H, 6.0; N, 4.6%. MS, *m/z* (%): 572 ($M^{+\cdot}$, 11) ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.06–1.92 (10 H, m, 5 CH_2), 3.74 (1 H, m, CH of cyclohexyl), 1.30 and 1.32 (6 H, 2 t $^3J_{HH}$ = 7 Hz, 2 CH_3), 4.18–4.64 (4 H, m, 2 OCH_2), 4.63 and 5.13 (2 H, 2 d $^3J_{HH}$ = 10 Hz, 2 CH), 6.36 (H, d $^3J_{HH}$ = 8 Hz, NH), 7.20–8.14 (9 H, m, aromatic). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 25.05, 25.74, 32.95, 33.05 and 49.45 (5 CH_2 and CH of cyclohexyl), 14.47 and 14.50 (2 CH_3), 62.14 and 62.30 (2 OCH_2), 54.41 and 64.97 (2 CH), 121.27, 128.42, 129.15, 129.88, 131.25, 132.44, 133.56 and 144.50 (aromatic), 165.58 (C=N), 169.64, 171.27, 172.18 (3 C=O).

Dimethyl 2-benzoyloxy-3-[N-tert-butyl-N'-(4-bromophenyl)carbamimidoyl]succinate **5e:** White powder, m.p. 148–150°C, yield 70%, IR (KBr) (ν_{max}, cm^{-1}): 3283 (NH), 1735, 1645 (C=O). Anal. Calcd

for $C_{24}H_{27}BrN_2O_6$: C, 55.5; H, 5.2; N, 5.4. Found: C, 55.6; H, 5.4; N, 5.3%. MS, *m/z* (%): 518 ($M^{+\cdot}$, 9). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.30 (9 H, s, 3 CH_3), 3.69 and 3.84 (6 H, 2 s, 2 OCH_3), 4.54 and 5.14 (2 H, 2 d, $^3J_{HH}$ = 10 Hz, 2 CH), 5.84 (1 H, s, NH), 7.20–7.39 (9 H, m, aromatic). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 28.20 (3 CH_3), 52.04 and 53.20 (2 OCH_3), 53.32 (C), 55.10 and 64.80 (2 CH), 121.22, 128.332, 129.21, 129.79, 131.23, 132.40, 133.45 and 144.48 (aromatic), 165.40 (C=N), 168.90, 170.30, 171.70 (3 C=O).

Diethyl 2-(N-cyclohexyl-N′-phenylcarbamimidoyl)fumarate **6b:** Viscose oil, yield 15%, IR (KBr) (ν_{max}, cm^{-1}): 3325 (NH), 1725, 1696, 1675 (C=O and C=N). Anal. Calcd for $C_{21}H_{28}N_2O_4$: C, 67.7; H, 7.6; N, 7.5. Found: C, 67.6; H, 7.6; N, 7.3%. MS, *m/z* (%): 372 ($M^{+\cdot}$, 27). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.08–1.99 (10 H, m, 5 CH_2), 3.87 (1 H, tt $^3J_{HH}$ = 12 Hz, J_{HH} = 3 Hz, CH of cyclohexyl), 1.27 and 1.33 (6 H, 2 t $^3J_{HH}$ = 7 Hz, 2 CH_3), 4.20 and 4.26 (4 H, 2 q $^3J_{HH}$ = 7 Hz, 2 OCH_2), 6.52 (H, s, CH), 7.38–7.66 (5 H, m, aromatic). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 25.60, 25.74, 29.67 and 60.74 (5 CH_2 and CH of cyclohexyl), 61.80 and 62.56 (2 OCH_2), 14.34 and 14.44 (2 CH_3), 125.92, 128.84, 128.93, 132.90, 135.86, and 143.07 (aromatic and olefinic carbons), 164.61 (C=N), 166.32 and 175.45 (2 C=O).

Dimethyl 2-[N-cyclohexyl-N′-phenylcarbamimidoyl]fumarate **6f:** Viscose oil, yield 70%, IR (KBr) (ν_{max}, cm^{-1}): 3320 (NH), 1723, 1662 (C=O and C=N). Anal. Calcd for $C_{19}H_{24}N_2O_4$: C, 66.3; H, 7.0; N, 8.1. Found: C, 68.4; H, 7.0; N, 8.25%. MS, *m/z* (%): 344 ($M^{+\cdot}$, 20). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.08–1.93 (10 H, m, 5 CH_2), 3.60 (1 H, m, CH of cyclohexyl), 3.67 and 3.74 (6 H, 2 s, 2 OCH_3), 6.69 (1 H, s, CH), 7.56–7.92 (5 H, m, aromatic). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 25.55, 25.67, 29.64 and 60.37 (5 CH_2 and CH of cyclohexyl), 51.38 and 52.77 (2 OCH_3), 125.90, 128.76, 128.88, 132.91, 135.27, and 143.17 (aromatic and olefinic carbons), 164.35 (C=N), 166.72 and 175.91 (2 C=O).

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