Four-component reaction of cyclohexyl isocyanide, acetylenic esters, carboxylic acids and pyrrole. Synthesis of dialkyl 2-alkanoyloxy (or benzoyloxy)-3-[cyclohexylimino(1*H*-pyrrol-2-yl)methyl]succinates

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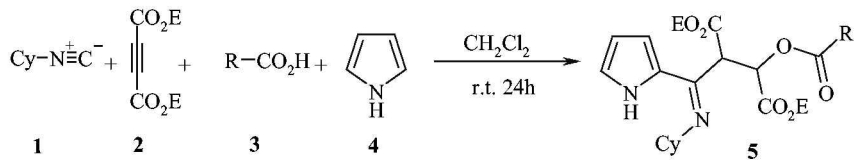
An improved four-component reaction of isocyanides is described. The reaction between cyclohexyl isocyanide, dialkyl acetylenedicarboxylates, carboxylic acids and pyrrole in dichloromethane at room temperature leads to 2-alkanoyloxy (or benzoyloxy)-3-[cyclohexylamino(1*H*-pyrrol-2-yl)methyl]succinates in good yields.

Keywords: isocyanide, four-component reaction, dialkyl acetylenedicarboxylates, pyrrole

A multicomponent reaction (MCR) is a process in which three or more easily accessible components are combined together in a single reaction vessel to produce a final product displaying features of all inputs and thus offers greater possibilities for molecular diversity per step with a minimum of synthetic time and effort. MCRs constitute an especially attractive synthetic strategy since they provide easy and rapid access to large libraries of organic compounds with diverse substitution patterns. As MCRs are one-pot reactions, they are easier to carry out than multistep syntheses. Coupled with high-throughput library screening, this strategy was an important development in the drug discovery in the context of rapid identification and optimisation of biologically active lead compounds.[1-9]

A large and important class of MCRs are the isocyanide based multicomponent reactions (IMCRs), first of them was introduced in 1921 by Passerini.[10] One of the most utilised multicomponent reactions is the Ugi reaction. Synthesis of α-acylamino amides is achieved by reacting aldehydes, primary amines, carboxylic acids and isocyanides.[6-8] Recently, three-component reactions between isocyanides, electron-deficient acetylenic esters and organic compounds containing at least one acidic NH, OH or CH group have been reported.[11-15] These reactions usually passed through a zwiterionic intermediate to produce keteneimines which may be isolated as stable products or cyclise to heterocyclic compounds. Isocyanides have been reported to react with acetylenic esters in the presence of pyrrole or indole to produce unsaturated amidines.[11] We have reported a four-component reaction between alkyl isocyanides, acetylenic esters, carboxylic acids and anilines to produce dialkyl 2-benzoyloxy-3-(*N*-alkyl-*N*′-arylcarbamimidoyl)succinates.[16] In the course of our work on the reaction between isocyanides and acetylenic esters, we report here the four-component reaction between cyclohexyl isocyanide, acetylenic esters, carboxylic acids and pyrrole. Thus, the reaction between cyclohexyl isocyanide **1**, dialkyl acetylenedicarboxylate (DAAD) **2**, carboxylic acid **3** and pyrrole **4** leads to addacts **5** in good yields (Scheme 1). A similar reaction was examined between indole, dimethyl acetylenedicarboxylate (DMAD), cyclohexyl isocyanide and acetic acid, but the only isolated compound was the product of three-component addition of indole, DMAD and cyclohexyl isocyanide. The structure of this compound was proved by comparision of its IR and NMR spectral data with the previously reported sample.[11]

The structure of compounds **5a–e** was deduced by elemental and spectral analysis. The mass spectrum of compound **5a** showed a molecular ion peak at 355 confirming that compound **5a** is an adduct of cyclohexyl isocyanide, pyrrole, dimethyl acetylenedicarboxylate and propionic acid. The NMR spectra of compound **5a** showed the presence of two diastereomers; we could not distinguish their relative configuration by NMR spectral data. The quantitative ratio of diastereoisomers was obtained from the ^{1}H NMR spectrum to be 63:37. The ^{1}H NMR spectrum of compound **5a** showed multiplets between 1.08 and 2.57 ppm for cyclohexyl and ethyl protons. Two single signals were observed at 3.65 and 3.68 ppm for methoxy protons of major diastereoisomer. The two methine protons of major diastereoisomer resonated at 4.44 and 4.81 ppm as two doublets ($^3J_{HH}$ = 9.9 H_Z). Three multiplets were observed at 5.97, 6.08 and 6.68 ppm for pyrrole protons. The NH proton resonated at 8.92 ppm as a broad single line. The characteristic signals related to the minor isomer were observed at 3.55 and 3.66 ppm (for methoxy protons), 4.51 and 4.63 ppm (two doublets with $^3J_{HH}$ = 9.8 H_Z for methine protons) and 8.64 ppm for NH proton. The ^{13}C NMR spectrum of compound



1 **2** **3** **4** **5**

5	R	E	Yield%*
a	Et	Me	60%
b	Me	Et	65%
c	Me	Me	60%
d	Ph	Et	65%
e	Ph	Me	60%

*Isolated yield.

Scheme 1

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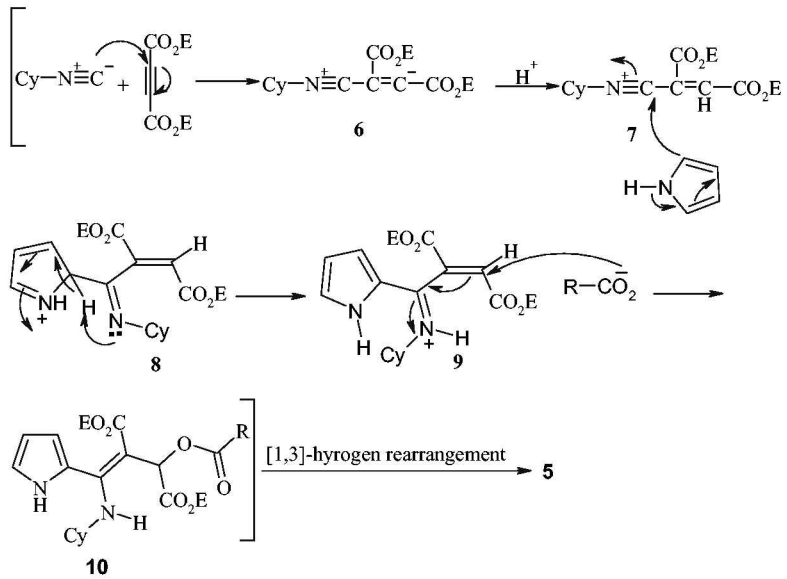

Scheme 2

5a showed 20 distinct signal for each isomer which is consistent with the proposed structure. The structure assigned for compound **5a** based on the mass spectrometry and NMR spectral data was also supported by the IR spectroscopy. The IR spectrum of compound **5a** exhibited an absorption bond at 3355 cm^{-1} for NH group and strong, broad absorptions about 1731 cm^{-1} for carbonyl ester groups. The NMR spectra of compounds **5b**, **5d** and **5f** also showed the presence of two diastereomers (see Experimental). The ^1H NMR spectrum of the crude product of compound **5c** showed the presence of two diastereomers in 88:12 ratio, but after chromatography only the major isomer was isolated in 60% yield.

A reasonable mechanism for the formation of compounds **5** is presented in Scheme 2. The zwitterionic intermediate **6** formed from the addition of cyclohexyl isocyanide to acetylenic ester is protonoted by carboxylic acid to afford the nitrilium cation **7** which then converted to cation **8** by the addition of pyrrole. The aromatisation of pyrrole ring by rearrangement of a proton leads to iminium cation **9** that undergoes the conjugate addition of carboxylate anion to produce enamine **10**, which then tautomerises to the product **5**.

In summary, we have reported a simple and efficient one-pot synthesis of 2-alkanoyloxy (or benzoyloxy)-3-[cyclohexylimino(1*H*-pyrrol-2-yl)methyl]succinates by four-component reaction between cyclohexyl isocyanide, dialkyl acetylenedicarboxylates, pyrrole and carboxylic acids. 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.

Experimental

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.^1H 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 pyrrole (2 mmol), isocyanide (2 mmol) and 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-propanoyloxy-3-[cyclohexylimino(1H-pyrrol-2-yl)methyl] succinate **(5a):** Yellow oil, Yield 0.47 g (60%); IR (KBr) (ν_{max}, cm^{-1}): 3355 (NH), 1731, 1704 (C=O, ester). Anal. Calcd for $C_{20}H_{28}N_2O_6$: C, 61.21; H, 7.19; N, 7.14. Found: C, 61.32; H, 7.25; N, 7.05%. MS (*m/z*, %): 392 (M^+, 9). Major isomer (63%) ^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.09 (3 H, m, CH_3), 1.14–2.17 (10 H, m, 5 CH_2 of cyclohexyl), 2.37 (2 H, m, CH_2), 3.62 (1 H, m, CH of cyclohexyl), 3.65 (3 H, s, OCH_3), 3.68 (3 H, s, OCH_3), 4.44 (1 H, d, $^3J_{HH}$ = 9.92 H_Z, CH), 4.81 (1 H, d, $^3J_{HH}$ = 9.92 H_Z, CH), 5.97 (1 H, m, CH of pyrrole), 6.08 (1 H, m, CH of pyrrole), 6.68 (1 H, m, CH of pyrrole), 8.92 (1 H, s, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): 9.71 (CH_3), 25.77, 26.98, 27.04, 30.09 and 30.26 (5 CH_2 of cyclohexyl), 31.80 (CH_2) 45.21 (CH), 53.06 (OCH_3), 53.11 (OCH_3), 56.32 (CH of cyclohexyl), 59.53 (OCH), 108.75, 108.93, 118.81 and 124.44 (4CH, pyrrole), 168.95 (C=N), 171.23, 172.48 and 179.29 (3 C, CO_2). Minor isomer (37%): ^1H NMR δ = 1.11 (3 H, m, CH_3), 1.14–2.17 (10 H, m, 5 CH_2 of cyclohexyl), 3.55 (3 H, s, OCH_3), 3.66 (3 H, s, OCH_3), 3.62 (1 H, m, CH of cyclohexyl), 4.51 (1 H, d, $^3J_{HH}$ = 9.81 H_Z, CH), 4.63 (1 H, d, $^3J_{HH}$ = 9.81 H_Z, CH), 5.97 (1 H, m, CH of pyrrole), 6.08 (1 H, m, CH of pyrrole), 6.68 (1 H, m, CH of pyrrole), 8.64 (1 H, s, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): 9.77 (CH_3), 25.50, 26.99, 27.51, 30.23 and 30.30 (5 CH_2 of cyclohexyl), 31.83 (CH_2), 45.26 (CH), 53.01 (OCH_3), 53.04 (OCH_3), 58.03 (CH of cyclohexyl), 59.51 (OCH), 108.31, 108.85, 118.91 and 124.68 (pyrrole), 169.16 (C=N), 171.18, 172.58 and 179.01 (3 C, CO2).

Diethyl 2-ethanoyloxy-3-[cyclohexylimino(1H-pyrrol-2-yl)methyl] succinate (**5b**): Yellow oil, Yield 0.52 g (65%); IR (KBr) (ν_{max}, cm^{-1}): 3390 (NH), 1725 (C=O, ester). Anal. Calcd for $C_{21}H_{30}N_2O_6$: C, 62.05; H, 7.44; N, 6.89. Found: C, 62.22; H, 7.32; N, 6.81%. MS (*m/z*, %): 406 (M^+, 9). Major isomer (64%) ^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.11 (6 H, m, 2 OCH_2CH_3), 1.20–2.02 (10 H, m, 5 CH_2 of cyclohexyl), 2.17 (3 H, s, CH_3), 3.99 (1 H, m, CH of cyclohexyl), 4.12 (4 H, m, 2 OCH_2CH_3), 4.38 (1 H, d, $^3J_{HH}$ = 9.75 H_Z, CH), 4.78 (1 H, d, $^3J_{HH}$ = 9.75 H_Z, CH), 6.00 (1 H, m, CH of pyrrole), 6.06 (1 H, m, CH of pyrrole), 6.67 (1 H, m, CH of pyrrole), 8.85 (1 H, s, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): 14.34, 14.40 (2 C, OCH_2CH_3), 25.26, 26.59, 27.01, 29.84 and 30.12 (5 CH_2 of cyclohexyl), 30.00 (CH_3), 45.35 (CH), 56.42 (CH of cyclohexyl), 60.10 (OCH), 61.94, 62.22 (2 C, OCH_2CH_3), 108.34, 108.84, 118.71 and 124.52 (4 CH, pyrrole), 168.22 (C=N), 171.82, 171.97 and 175.02 (3 C, CO2). Minor isomer (36%): ^1H NMR δ = 1.16 (3 H, m, OCH_2CH_3), 1.20–2.02 (10 H, m, 5 CH_2 of cyclohexyl), 2.28 (3 H, s, CH_3), 3.99 (1 H, m, CH of cyclohexyl), 4.12 (2 H, m, OCH_2CH_3), 4.49 (1 H, d, $^3J_{HH}$

= 9.97 H_Z, CH), 4.59 (1 H, d, $^3J_{HH}$ = 9.97 H_Z, CH), 6.00 (1 H, m, CH of pyrrole), 6.06 (1 H, m, CH of pyrrole), 6.67 (1 H, m, CH of pyrrole), 8.63 (1 H, s, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): 14.29, 14.38 (2 C, OCH_2CH_3), 25.04, 26.73, 27.03, 29.75 and 30.13 (5 CH_2 of cyclohexyl), 30.09 (CH_3), 45.52 (CH), 58.01 (CH of cyclohexyl), 60.08 (OCH), 61.99, 62.11 (2 C, OCH_2CH_3), 108.79, 108.96, 118.72 and 124.84 (4CH, pyrrole), 168.47 (C=N), 171.57, 172.07 and 174.95 (3 C, CO_2).

Dimthyl 2-ethanoyloxy-3-[cyclohexylimino(1H-pyrrol-2-yl)methyl] succinate (**5c**): Yellow oil, Yield 0.45 g (60%); IR (KBr) (ν_{max}, cm^{-1}): 3385 (NH), 1737, 1711 (C=O, ester). Anal. Calcd for $C_{19}H_{26}N_2O_6$: C, 60.30; H, 6.93; N, 7.40. Found: C, 60.35; H, 6.87; N, 7.54%. MS (*m/z*, %): 378 (M^+, 10). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.05–1.84 (10 H, m, 5 CH_2 of cyclohexyl), 2.15 (3 H, s, CH_3), 3.65 (3 H, s, OCH_3), 3.66 (3 H, s, OCH_3), 3.70 (1 H, m, CH of cyclohexyl), 4.43 (1 H, d, $^3J_{HH}$ = 9.72 H_Z, CH), 4.85 (1 H, d, $^3J_{HH}$ = 9.72 H_Z, CH), 5.99 (1 H, m, CH of pyrrole), 6.03 (1 H, m, CH of pyrrole), 6.66 (1 H, m, CH of pyrrole), 9.05 (1 H, s, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): 25.02, 26.51, 26.55, 29.64 and 29.70 (5 CH_2 of cyclohexyl), 29.19 (CH_3), 44.79 (CH), 52.60, 52.70 (2 C, OCH_3), 55.99 (CH of cyclohexyl), 59.79 (OCH), 108.34, 108.36, 118.45 and 123.88 (pyrrole), 168.46 (C=N), 171.18, 171.99 and 174.75 (3 C, CO_2).

Diethyl 2-benzoyloxy-3-[cyclohexylimino(1H-pyrrol-2-yl)methyl] succinate (**5d**): Yellow oil, Yield 0.60 g (65%); IR (KBr) (ν_{max}, cm^{-1}): 3360 (NH), 1726, 1700 (C=O, ester). Anal. Calcd for $C_{26}H_{32}N_2O_6$: C, 66.65; H, 6.88; N, 5.98. Found: C, 66.52; H, 6.82; N, 5.74%. MS (*m/z*, %): 468 (M^+, 4). Major isomer (70%) ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.12 (6 H, m, 2 OCH_2CH_3), 1.24–2.02 (10 H, m, 5 CH_2 of cyclohexyl), 3.94 (1 H, m, CH of cyclohexyl), 4.11 (4 H, m, 2 OCH_2CH_3), 4.35 (1 H, d, $^3J_{HH}$ = 10.35 H_Z, CH), 4.45 (1 H, d, $^3J_{HH}$ = 10.35 H_Z, CH), 5.92 (1 H, m, CH of pyrrole), 6.00 (1 H, m, CH of pyrrole), 6.68 (1H, m, CH of pyrrole), 7.27–7.77 (5 H, m, arom), 8.92 (1 H, s, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): 13.86, 13.89 (2 C, OCH_2CH_3), 24.92, 25.52, 26.18, 29.73 and 30.37 (5 CH2 of cyclohexyl), 44.65 (CH), 55.26 (CH of cyclohexyl), 59.42 (OCH), 61.43, 61.95 (2 C, OCH_2CH_3), 107.47, 108.29, 118.18 and 124.15 (4 CH, pyrrole), 128.83, 129.38, 133.27 and 135.21 (aromatic), 166.89 (C=N), 168.63, 171.54 and 174.81 (3 C, CO2). Minor isomer (30%): δ = 1.18 (6 H, m, 2 OCH_2CH_3), 1.24–2.02 (10 H, m, 5 CH_2 of cyclohexyl), 3.94 (1 H, m, CH of cyclohexyl), 4.11 (4 H, m, 2 OCH_2CH_3), 4.38 (1 H, d, $^3J_{HH}$ = 10.22 H_Z, CH), 4.48 (1 H, d, $^3J_{HH}$ = 10.22 H_Z, CH), 5.82 (1H, m, CH of pyrrole), 5.99 (1 H, m, CH of pyrrole), 6.67 (1 H, m, CH of pyrrole), 7.27–7.77 (5 H, m, arom), 8.71 (1 H, s, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): 13.80, 13.94 (2 C, OCH_2CH_3), 24.92, 25.09, 26.12, 29,75 and 30.37 (5 CH_2 of cyclohexyl), 44.69 (CH), 56.39 (CH of cyclohexyl), 59.30 (OCH), 61.48, 61.82 (2 C, OCH_2CH_3), 107.47, 108.24, 118.18 and 124.19 (pyrrole), 128.76, 129.47, 133.24 and 134.92 (aromatic), 166.89 (C=N), 168.81, 171.46 and 174.92 (3 C, CO_2).

Dimethyl2-benzoyloxy-3-[cyclohexylimino(1H-pyrrol-2-yl)methyl] succinate (**5e**): Yellow oil, Yield 0.52 g (60%); IR (KBr) (ν_{max}, cm^{-1}): 3365 (NH), 1733, 1699(C=O, ester). Anal. Calcd for $C_{24}H_{28}N_2O_6$: C, 65.44; H, 6.41; N, 6.36. Found: C, 65.61; H, 6.35; N, 6.44%. MS (*m/z*, %): 440 (M^+, 6). Major isomer (65%) ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.12–2.03 (10 H, m, 5 CH_2 of cyclohexyl), 3.64 (3 H, s, OCH_3), 3.67 (3 H, s, OCH_3), 3.88 (1 H, m, CH of cyclohexyl), 4.41 (1 H, d, $^3J_{HH}$ = 10.34 H_Z, CH), 4.52 (1 H, d, $^3J_{HH}$ = 10.34 H_Z, CH), 5.95 (1 H, m, CH of pyrrole), 6.12 (1 H, m, CH of pyrrole), 6.71 (1 H, m, CH of pyrrole), 7.24–7.77 (5 H, m, arom), 8.87 (1 H, s, NH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): 25.09, 26.14, 26.26, 29.86 and 30.12 (5 CH_2 of cyclohexyl), 44.70 (CH), 52.59, 52.75 (2 C, OCH_3), 55.18 (CH of cyclohexyl), 59.65 (OCH), 107.61, 108.42, 118.36 and 123.96 (4 CH, pyrrole), 128.49, 129.38, 133.33 and 135.08 (aromatic), 168.24 (C=N), 168.69, 172.02 and 174.97 (3 C, CO2). Minor isomer (35%): ^{1}H NMR δ = 1.12–2.03 (10 H, m, 5 CH_2 of cyclohexyl), 3.65 (3 H, s, OCH_3), 3.66 (3 H, s, OCH_3), 3.92 (1 H, m, CH of cyclohexyl), 4.12 (1 H, d, $^3J_{HH}$ = 10.24 H_Z, CH), 4.25 (1 H, d, $^3J_{HH}$ = 10.24 H_Z, CH), 5.85 (1H, m, CH of pyrrole), 6.02 (1 H, m, CH of pyrrole), 6.64 (1 H, m, CH of pyrrole), 8.60 (1 H, s, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): 25.12, 26.14, 26.21, 29.64 and 30.49 (5CH2 of cyclohexyl), 44.67 (CH), 52.57, 52.75 (2 C, OCH_3), 56.45 (CH of cyclohexyl), 59.47 (OCH), 107.61, 108.44, 118.36 and 124.02 (pyrrole), 128.82, 129.44, 133.33 and 135.43 (aromatic), 168.12 (C=N), 168.79, 171.88 and 174.95 (3 C, CO_2).

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