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Reaction between alkyl isocyanides, acetylenic esters and dicyclohexylcarbodiimide, a novel synthesis of highly substituted pyrroles

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Abstract: Alkyl isocyanides react with dicyclohexylcarbodiimide and dialkyl acetylenedicarboxylates, in one-pot, to afford highly substituted 1, 3-dihydro-2*H*-pyrrole derivatives in good yields.

Keywords: Four-component reaction, Isocyanides, DCC, Pyrroles, Ketenimines.

Introduction

Isocyanides are the only class of stable organic compounds with a formally divalent carbon. One of the classic themes in the chemistry of isocyanides is heterocyclic synthesis [1, 2]. Formation of pyrrole containing compounds is of particular interest in organic synthesis since this ring system is often embedded in important natural products and medicinally active compounds [3]. In particular fully substituted pyrrole derivatives are biologically active and have been proven to display antibacterial, antiviral, anti-inflammatory, and antioxidant activities [4]. In connection with our interest in heterocyclic synthesis [5] herein we report an efficient synthesis of highly substituted pyrroles from alkyl isocyanides, dicyclohexylcarbodiimide, and acetylenic esters.

Results and discussion

The reaction of alkyl isocynides **1**, dialkyl acetylene dicarboxylates **2**, and dicyclohexylcarbodiimide (**3**), proceeded spontaneously in CH_2Cl_2, and was complete within a few hours. The ^1H and ^{13}C NMR spectra of the crude products clearly indicated the formation of product **4** (Scheme **1**).

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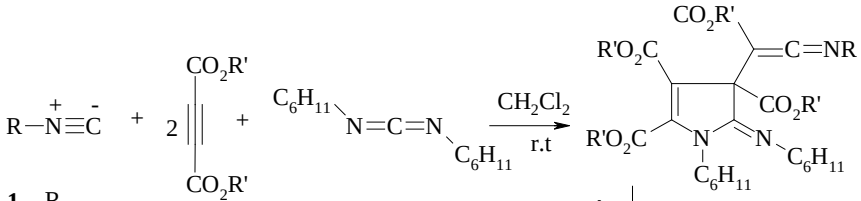
The structures of compounds **4a-f** were deduced from their IR, ^1H and ^{13}C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at the appropriate *m/z* values. The ^1H NMR spectrum of **4a** exhibited a single sharp line readily recognized as arising from *tert*-butyl (δ 1.14 ppm) and four single sharp lines from methoxy groups (δ 3.62, 3.72, 3.75 and 3.93 ppm) protons along with multiplets (δ 2.50 and 5.01 ppm) for the CHN protons of DCC. The ^1H decoupled ^{13}C NMR spectrum of **4a** showed 28 distinct resonances in agreement with the proposed structure. The ^1H and ^{13}C NMR spectra of **4b-f** are similar to those of **4a** except for the alkoxy and alkyl moieties, which exhibited characteristic signals with appropriate chemical shifts.

Although the mechanistic details of the reaction are not clearly known, a plausible rationalization may be advanced to explain the product formation. Presumably, the zwitterion **5** formed from isocyanide and the acetylenic compound [6, 7], adds to dicyclocarbodiimide to furnish intermediate **6**, which is added to another molecule of acetylenic ester to produce **7**. This intermediate undergoes cyclization to furnish the fused structure **4** (Scheme **2**).

Conclusion

In summary, we have found that the reaction of alkyl isocyanides, dialkyl acetylenedicarboxylates, and DCC provides a simple entry to the one-pot synthesis of trialkyl 3-[2-(alkylimino)-1-(alkoxycarbonyl)vinyl]-1-cyclohexyl-2-(cyclohexylimino)-1,3-dihydro-2*H*-pyrrole-3,4,5-tricarboxylates of potential synthetic interest. The present procedure carries the advantage that, not only is the reaction performed under neutral conditions, but also the substances can be mixed without any activation or modification.

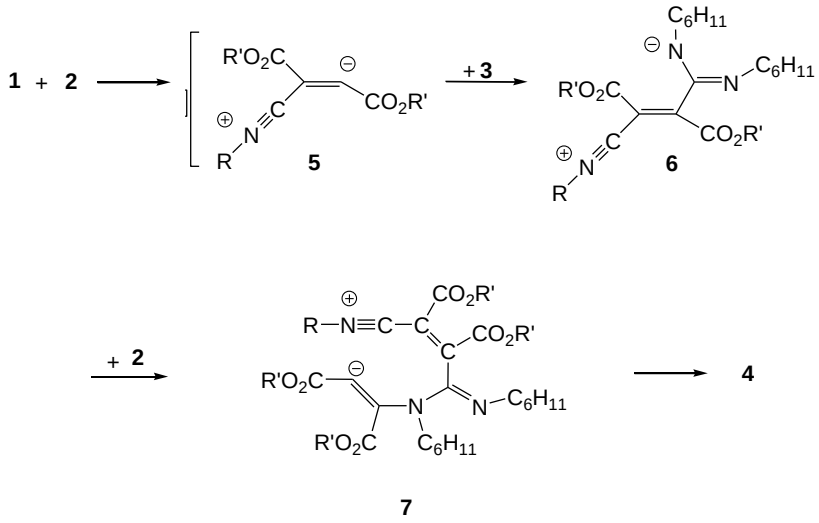


1	R
a	^{t}Bu
b	Cyclohexyl

2	R'
a	Me
b	Et
c	^{t}Bu

4	R	R'	Yield (%)
a	^{t}Bu	Me	88
b	^{t}Bu	Et	80
c	^{t}Bu	^{t}Bu	85
d	Cyclohexyl	Me	75
e	Cyclohexyl	Et	80
f	Cyclohexyl	^{t}Bu	80

Scheme 1: Synthesis of highly substituted pyrrole.



Scheme 2: A plausible mechanism for the product.

Experimental

Chemicals were purchased from Fluka and used without further purification. Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer, and the results agreed favorably with the calculated values. Mass spectra were recorded on a Finnigan MAT 8430 spectrometer operating at an ionization potential of 70 eV. IR spectra were measured on a Shimadzu IR-460 spectrometer. ^{1}H and ^{13}C NMR spectra were measured on a Bruker Avance DRX-300 spectrometer using $CDCl_3$ as applied solvent and TMS as internal standard at 300 and 75 MHz, respectively.

General procedure for the preparation of trialkyl 3-[2-(alkylimino)-1-(alkoxycarbonyl)vinyl]-1-cyclohexyl-2-(cyclohexylimino)-1,3-dihydro-2H-pyrrole-3,4,5-tricarboxylates **4:**

To a stirred solution of **3** (DCC) (0.41 g, 2 mmol) and dimethyl acetylenedicarboxylate **2** (0.96 ml, 4 mmol) in 10 mL CH_2Cl_2 was added dropwise at -10°C

over 10 min *tert*-butyl isocyanide **1** (0.16 g, 2 mmol). The reaction mixture was then allowed to warm up to room temperature and stand for 24 h. The solvent was removed under reduced pressure and the residue was washed from diethyl ether to produce the pure desired products.

Trimethyl 3-[2-(tert-butylimino)-1-(methoxy carbonyl) vinyl]-1-cyclohexyl-2-(cyclohexylimino)-1,3-dihydro-2H-pyrrole-3,4,5-tricarboxylate **4a**:

Yield: 0.48 g (85%) of yellow powder; mp 152-153°C, IR (KBr) (ν_{max}/cm^{-1}) : 2120 (C=C=N), 1749-1700 (C=O). ^{1H} NMR ($CDCl_3$): δ 1.14 (9H, s, CMe_3), 1.24-1.91 (20H, m, 10 CH2), 2.49 (1H, m, CHN), 3.62 (3H, s, COOMe), 3.72 (3H, s, COOMe), 3.75 (3H, s, COOMe), 3.93 (3H, s, COOMe), 5.04 (1H, m, CHN). ^{13}C NMR($CDCl_3$): δ 24.4, 25.7, 26.3, 26.4, 26.6, 29.0, 30.3, 33.6, 34.2 and 35.3 (10 CH_2), 30.1 (CMe_3), 51.9, 52.0, 52.8 and 54.10 (4 OMe), 58.7 (CHN), 59.5 (CMe_3), 60.3 (CHN), 84.2 (C=C=N), 98.2 (C), 117.0 (C), 150.8 (C), 159.0 (N-C=N), 162.5, 163.4, 166.2 and 166.6 (4 C=O), 170.7 (C=C=N). Found: C, 62.78; H, 7.53; N, 7.35. $C_{30}H_{43}N_3O_8$ requires: C, 62.81; H, 7.55; N, 7.32. EIMS: m/z = 573 (M^+, 5), 449 (100), 394(60).

Triethyl 3-[2-(tert-butylimino)-1-(ethoxycarbonyl) vinyl]-1-cyclohexyl-2-(cyclohexylimino)-1,3-dihydro-2H-pyrrole-3,4,5-tricarboxylate **4b:**

Yield: 0.50 g (80%) of yellow powder; mp183-185°C. IR (KBr) (ν_{max}/cm^{-1}): 1735-1700 (C=O), 2060 (C=C=N). ^{1}H NMR ($CDCl_3$): δ 1.14 (9H, s, CMe_3), 1.24 (3H, t, J = 6.7 Hz, Me), 1.30 (3H, t, J = 6.7 Hz, Me), 1.35 (3H, t, J = 6.7 Hz, Me), 1.40 (3H, t, J = 6.7 Hz, Me), 1.28-1.94 (20H, m, 10 CH_2), 2.52 (1H, m, CHN), 4.01 (q, J = 6.7 Hz, CH_2), 4.19 (q, J = 6.7 Hz, CH_2), 4.31 (q, J = 6.7 Hz, CH_2), 4.42 (q, J = 6.7 Hz, CH_2), 5.05 (1 H, m, CHN). ^{13}C NMR ($CDCl_3$): δ 13.3, 13.4, 13.5,and 13.7 (4 Me), 23.6, 24.5, 24.8, 25.1, 28.0, 29.2, 30.8, 32.7, 33.2 and 33.5 (10 CH_2), 29.3 (CMe_3), 55.1 (CHN), 57.6 (CMe_3), 59.3 (CHN), 59.8, 59.9, 60.7 and 61.9 (4 OCH_2), 83.4 (C=C=N), 97.7 (C), 116.7 (C), 150.7 (C), 158.1 (N-C=N), 161.5, 162.2, 164.9 and 165.0 (4 C=O), 169.7 (C=C=N). Found: C, 64.89; H, 8.12; N, 7.71. $C_{34}H_{51}N_3O_8$ requires: C, 64.84; H, 8.16; N, 6.67.

Tri(tert-butyl) 3-[1-(tert-butoxycarbonyl)-2-(tert-butylimino)vinyl]-1-cyclohexyl-2-(cyclohexylimino)-1,3-dihydro-2H-pyrrole-3,4,5-tricarboxylate **4c**:

Yield: 0.63 g (85%) of yellow powder; mp 144-146°C. IR (KBr) (ν_{max}/cm^{-1}): 2062 (C=C=N), 1730-1660 (C=O). ^{1}H NMR ($CDCl_3$): δ 1.08-1.96 (20H, m, 10 CH_2), 1.15 (s, CMe_3), 1.43 (9H, s, CMe_3), 1.48 (9H, s, CMe_3), 1.50 (9H, s, CMe_3), 1.62 (9H, s, CMe_3), 2.35 (1H, m, CHN), 5.30 (1H, m, CHN). ^{13}C NMR ($CDCl_3$): δ 25.0, 25.6, 26.5, 26.7, 26.9, 28.8, 30.6, 33.9, 34.7 and 35.5 (10 CH_2), 27.7, 28.3, 28.4, 28.8 and 29.6 (5 CMe_3), 58.5 (CHN), 59.6 (CMe_3), 60.7 (CHN), 79.1 ($OCMe_3$), 79.4 ($OCMe_3$), 80.9 ($OCMe_3$), 82.5 ($OCMe_3$), 83.4 (C=C=N), 97.8 (C), 115.4 (C), 151.0 (C), 159.5 (N-C=N), 162.9, 163.7, 166.3 and 166.9 (4 C=O), 169.8 (C=C=N). Found: C, 67.85; H, 9.15; N, 5.69. $C_{42}H_{67}N_3O_8$ requires: C, 67.99; H, 9.10; N, 5.66.

Trimethyl 1-cyclohexyl-2-(cyclohexylimino)-3-[2-(cyclohexylimino)-1-(methoxycarbonyl)vinyl]-1,3-dihydro-2H-pyrrole-3,4,5-tricarboxylate **4d**:

Yield: 0.45 g (75%) of yellow powder; mp 139-141°C. IR (KBr) (ν_{max}/cm^{-1}): 2080 (C=C=N), 1755-1710 (C=O). ^{1}H NMR ($CDCl_3$): δ 1.13-1.78 (30H, m, 15 CH_2), 2.50 (1H, m, CHN), 3.03 (1H, m, CHN), 3.66 (3H, s, OMe), 3.73 (6 H, s, 2 OMe), 3.93 (3H, s, OMe), 4.86 (1H, m, CHN). ^{13}C NMR($CDCl_3$): δ 23.7, 23.8, 24.8, 24.9, 25.4, 25.7, 26.2, 26.3, 28.2, 28.5, 31.0, 31.7, 33.6 and 34.0 (15 CH_2), 51.1, 51.2, 52.0 and 53.5 (4 OMe), 56.8 (CHN), 58.3 (CHN), 63.2 (CHN), 83.0 (C=C=N), 97.1 (C), 115.1 (C), 151.2 (C), 158.3 (N-C=N), 161.4, 162.1, 165.3 and 167.8 (4 C=O), 168.8 (C=C=N). Found: C, 64.21; H, 7.51; N, 7.14. $C_{32}H_{45}N_3O_8$ requires: C, 64.09; H, 7.56; N, 7.01. EIMS: m/z = 599 (M^+, 10), 517(40), 329(55), 55(100).

Triethyl 1-cyclohexyl-2-(cyclohexylimino)-3-[2-(cyclohexylimino)-1-(ethoxycarbonyl)vinyl]-1,3-dihydro-2H-pyrrole-3,4,5-tricarboxylate **4e**:

Yield: 0.52 g (80%) of yellow powder; mp 153-155°C. IR (KBr) (ν_{max}/cm^{-1}): 2100 (C=C=N), 1732-1715 (C=O). ^{1}H NMR ($CDCl_3$): δ 1.164 (3H, t, J = 6.7 Hz, Me), 1.23 (3H, t, J = 6.7 Hz, Me), 1.27 (3H, t, J = 6.7 Hz, Me), 1.34 (3H, t, J = 6.7 Hz, Me), 1.30-1.92 (30H, m, 15 CH2), 2.49 (m, CHN), 3.06 (1H, m, CHN), 4.00 (2H, q, J = 6.7 Hz, CH2), 4.21 (2H, q, J = 6.7 Hz, CH2), 4.28 (2H, q, J = 6.7 Hz, CH2), 4.37 (2H, q, J = 6.7 Hz, CH2), 4.90 (1H, m, CHN). ^{13}C NMR ($CDCl_3$): δ 13.8, 14.0, 14.2 and 14.3 (4 Me), 24.2, 25.3, 25.4, 25.8, 26.0, 26.1, 26.7, 28.7, 28.9, 28.5, 31.4, 32.1, 33.4, 34.1 and 34.6 (15 CH_2), 57.1 (CHN), 58.5 (CHN), 60.3 (CHN), 60.4, 61.3, 62.8 and 63.2 (4 OCH_2), 83.4 (C=C=N), 97.8 (C), 116.1 (C), 151.5 (C), 158.7 (N-C=N), 161.7, 162.3, 165.4 and 167.7 (4 C=O), 169.0 (C=C=N). Found: C, 65.89; H, 8.19; N, 6.34. $C_{36}H_{53}N_3O_8$ requires: C, 65.93; H, 8.15; N, 6.41.

Tri(tert-butyl) 3-[1-(tert-butoxycarbonyl)-2-(cyclohexyl imino)vinyl]-1-cyclohexyl-2-(cyclohexyl imino)-1,3-dihydro-2H-pyrrole-3,4,5-tricarboxylate **4f**:

Yield: 0.61 g (80%) of yellow powder; mp 161-163°C. IR (KBr) (ν_{max}/cm^{-1}): 2080 (C=C=N), 1740-1690 (C=O). ^{1}H NMR (CDCl3): δ 1.09-1.73 (30H, m,

15 CH2),1.47 (9H, s, CMe3), 1.51 (18H, 2s, 2 CMe3), 1.66 (9H, s, CMe3), 2.11 (1H, m, CHN), 3.78 (1H, m, CHN), 4.22 (1H, m, CHN). 13C NMR (CDCl3): δ 23.1, 23.4, 24.1, 24.9, 25.3, 25.8, 25.9, 26.0, 26.8, 28.2, 28.4, 30.7, 31.3, 33.2 and 34.3 (15 CH2), 28.1, 28.3, 28.4 and 28.7 (4 CMe3), 56.6 (CHN), 57.3 (CHN), 60.1 (CHN), 83.1 (C=C=N), 82.6, 82.7, 82.8 and 83.6 (4 OCMe3), 97.3 (C), 115.5 (C), 151.7 (C), 158.7 (N-C=N), 160.7, 162.0, 164.3 and 166.4 (4 C=O), 169.2 (C=C=N). Found: C, 68.62; H, 9.2; N, 5.39. $C_{44}H_{69}N_3O_8$ requires: C, 68.81; H, 9.05; N, 5.47.

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