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NOTE

One-Pot Synthesis of 2*H*-Quinolizine and 1*H*-Pyrido[1,2-a]qinoline Derivatives by Using Dialkylcarbodiimides

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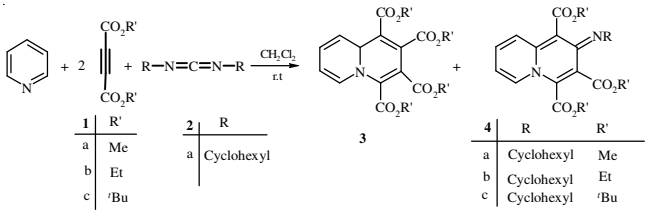
Reaction of the zwitter ions generated from pyridine and dialkylacetylene dicarboxylate with electron-deficient dialkylcarbodiimides lead to substituted 2*H*-quinolizines.

Key Words: 2*H*-Quinolizine, Synthesis, Zwitter ion, Electron-deficient.

Quinolizines are of considerable interest due to their widespread occurrence in natural products, particularly in the field of alkaloids[1]. A large variety of nitrogen heterocycles are known to form zwitter ionic species on addition of activated olefins or acetylenes. The earliest work in the area was reported by Diels and Alder and their study[2] and subsequently the structure elucidation of Acheson[3] showed that pyridine reacts smoothly with dimethyl acetylene dicarboxylate (DMAD) to form 4*H*-quinolizine.

Herein we report the reaction of pyridine with dialkylacetylene dicarboxylates **1** in the presence of dialkylcarbodiimides **2** in dry dichloromethane at ambient temperature to produce 4*H*-quinolizine-1,2,3,4-tetracarboxylate (**Scheme-I**).



Scheme-I

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 BrukerAvance DRX-300 spectrometer using $CDCl_3$ as applied solvent and TMS as internal standard at 300 and 75 MHz, respectively.

To a stirred solution of dimethyl acetylenedicarboxylate (0.48 mL, 4 mmol) and pyridine (0.16 g, 2 mmol) in 10 mL CH_2Cl_2 was added drop wise at -10 ºC over 10 min dicyclocarbodiimide (DCC) (0.41 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 residual products were purified by recrystallized from diethyl ether as yellow powder; yield: 0.44 g (55 %), m.p. 154 ºC. IR (KBr, ν_{max}, cm^{-1}): 1740, 1715 and 1666 (3 C=O), 1632 (C=N). ^{1}H NRM δ 1.21-1.96 (m, 10H, 5CH_2), 3.43-3.51 (m, 1H, CHN), 3.91 (s, 3H, OCH_3), 3.97 (s, 6H, 2OCH_3), 7.51 (t, 1H, *J* = 7.0 Hz, CH), 8.01 (t, 1H, *J* = 8.6 Hz, CH), 8.83 (d, 1H, *J* = 9.1 Hz, CH), 9.46 (d, 1H, *J* = 7.1 Hz, CH) ppm. ^{13}C NMR δ 24.8 (2CH_2), 25.5 (CH_2), 33.6 (2CH_2), 49.4 (CHN), 52.2 (OCH_3), 52.5 (2OCH_3), 103.9 (C), 115.0 (C), 118.8 (CH), 124.8 (CH), 129.6 (CH), 138.1 (CH), 145.3 (C), 146.8 (C), 156.6 (N-C=N), 163.9 (C=O), 164.5 (C=O), 165.9 (C=O) ppm. Anal. calcd. (%) for $C_{21}H_{24}N_2O_6$ (400): C, 62.99; H, 6.04; N, 7.00; Found (%): C, 63.08; H, 5.98; N, 7.15.

Triethyl 2-(cyclohexylimino)-2*H*-quinolizine-1,3,4-tricaboxylate (4b): Yellow powder; yield: 0.51 g (58 %), m.p. 165 ºC. IR (KBr, ν_{max}, cm^{-1}): 1741, 1710 and 1666 (3C=O), 1619 (C=N). ^{1}H NMR δ 1.08-1.96 (m, 10H, 5CH_2), 1.19 (t, 3H, *J* = 7.1 Hz, CH_3), 1.35 (t, 3H, *J* = 7.1 Hz, CH_3), 1.38 (t,

3H, *J* = 7.1 Hz, CH_3), 3.37-3.45 (m, 1H, CH), 4.14 (q, 2H, *J* = 7.1 Hz, OCH_2), 4.39 (q, 2H, *J* = 7.1 Hz, OCH_2), 4.44 (q, 2H, *J* = 7.1 Hz, OCH_2), 7.37 (t, 1H, *J* = 7.3 Hz, CH), 7.98 (t, 1H, *J* = 8.9 Hz, CH), 8.65 (d, 1H, *J* = 8.9 Hz, CH), 9.54 (d, 1H, *J* = 7.4 Hz, CH) ppm. ^{13}C NMR δ = 13.3 (CH3), 13.4 (CH_3), 13.8 (CH_3), 24.3 ($2CH_2$), 25.0 (CH_2), 33.2 ($2CH_2$), 49.0 (CHN), 61.6, (OCH_2), 61.8 (OCH_2), 61.9 (OCH_2), 104.0 (C), 114.8 (C), 118.6 (CH), 124.7 (CH), 129.5 (CH), 137.7 (CH), 145.7 (C), 148.9 (C), 156.7 (N-C=N), 164.2 (C=O), 165.0 (C=O), 165.2 (C=O) ppm. Anal. calcd. (%) for $C_{24}H_{30}N_2O_6$ (442): C, 62.67; H, 6.51; N, 6.96; Found (%): C, 62.23; H, 6.70; N, 7.12. MS (EI, 70 eV): m/z (%) = 442 (M^+, 5), 346 (90), 316 (90), 242 (100), 170 (60).

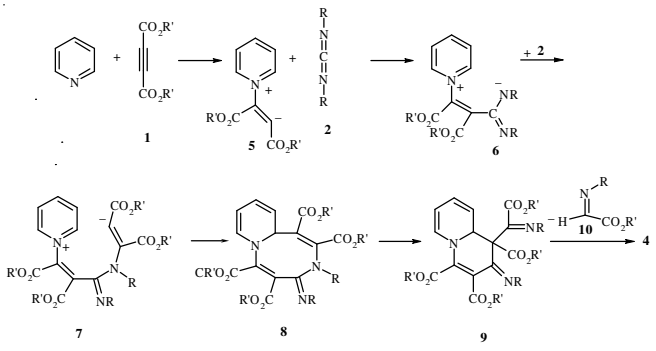
Tri(*tert*-butyl) 2-(cyclohexylimino)-2*H*-quinolizine-1,3,4-tricaboxylate (4c): Yellow powder; yield: 0.50 g (48 %), m.p. 157-159 ºC. IR (KBr, ν_{max}, cm^{-1}): 1739, 1712 and 1660 (3C=O), 1625 (C=N). ^{1}H NMR δ = 1.21-1.95 (10 H, m, 5 CH_2), 1.57 (s, 9H, CMe_3), 1.62 (s, 9H, CMe_3), 1.64 (s, 9H, CMe3), 3.34-3.42 (m, 1H, CH), 7.51 (t, 1H, *J* = 6.7 Hz, Hz, CH), 7.94 (t, 1H, *J* = 8.6 Hz, CH), 8.75 (d, 1H, *J* = 9.0 Hz, CH), 9.48 (d, 1H, *J* = 7.1 Hz, CH) ppm. ^{13}C NMR δ = 24.9 ($2CH_2$), 25.5 (CH_2), 33.8 ($2CH_2$), 27.9 (CMe_3), 28.1 (CMe_3), 28.2 (CMe_3), 49.4 (CHN), 81.2 (C), 82.8 (C), 83.2 (C), 103.9 (C), 115.0 (C), 118.8 (CH), 124.8 (CH), 129.6 (CH), 138.1 (CH), 145.3 (C), 145.7 (C), 156.6 (N-C=N), 162.1 (C=O), 164.3 (C=O), 164.8 (C=O) ppm. Anal. calcd. (%) for $C_{30}H_{42}N_2O_6$ (526): C, 68.42; H, 8.04; N, 5.32; Found (%): C, 68.49; H, 7.98; N, 5.26

Trimethyl 1-(cyclohexylimino)-1*H*-pyrido-[1,2-a]-quinoline-2,3,4-tricaboxylate (11): Yellow powder; yield: 0.54 g (60 %), m.p. 162 ºC. IR (KBr, ν_{max}, cm^{-1}): 1738, 1714 and 1660 (3 C=O), 1624 (C=N). ^{1}H NMR δ: 0.87-1.36 (m, 10H, $5CH_2$), 3.58-3.76 (m, 1H, CHN), 3.88 (s, 3H, OCH_3), 3.94 (s, 6H, $2OCH_3$), 6.87 (dt, 1H, *J* = 6.7 Hz and *J* = 1.0 Hz, CH), 7.70 (dt, 1H, *J* = 8.6 Hz and *J* = 1.3 Hz, CH), 7.85 (d, 1H, *J* = 9.4 Hz, CH), 8.01 (dd, 1H, *J* = 7.8Hz and *J* = 1.5 Hz, CH), 8.15 (d, 1H, *J* = 8.6 Hz, CH), 8.25 (d, 1H, *J* = 9.4 Hz, CH) ppm. ^{13}C NMR δ: 24.4 ($2CH_2$), 25.6 (CH_2), 31.1 ($2CH_2$), 49.8 (CHN), 51.8 (OCH_3), 52.8 ($2OCH_3$), 104.3 (C), 118.2 (C), 120.3 (C), 126.2 (CH), 126.8 (CH), 129.3 (CH), 129.7 (CH), 129.9 (CH), 131.3 (C), 131.9 (C), 133.4 (C), 137.9 (CH), 155.2 (N-C=N), 162.7 (C=O), 163.6 (C=O), 165.7 (C=O) ppm. Anal. calcd. (%) for $C_{25}H_{26}N_2O_6$ (450): C, 66.66; H, 5.82; N, 6.22; Found (%): C, 66.58; H, 5.78; N, 6.17.

Trimethyl 4-(cyclohexylimino)-4*H*-pyrido[2,1-a]-isoquinoline-1,2,3-tricaboxylate (12): Yellow powder; yield: 0.58 g (65 %), m.p. 178 ºC. IR (KBr, ν_{max}, cm^{-1}): 1739, 1720 and 1665 (3C=O), 1619 (C=N). ^{1}H NMR δ: 1.01-1.84 (m, 10H, $5CH_2$), 3.54-3.65 (m, 1H, CHN), 3.90 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 7.50 (d, 1H, *J* = 7.5 Hz, CH), 7.66-7.76 (m, 3H, 3CH), 7.93 (dd, 1H, *J* = 7.5 Hz and *J* = 1.3 Hz, CH), 9.33 (d, 1H, *J* = 7.5 Hz) ppm. ^{13}C NMR δ: 23.6 ($2CH_2$), 25.2 (CH_2), 30.8 (CH_2), 31.0 (CH_2), 49.2 (CHN), 52.4 ($2OCH_3$), 52.8 (OCH_3), 105.1 (C), 116.8 (C), 124.8 (C), 125.1 (CH), 127.5 (CH), 128.2 (CH), 128.8 (CH), 130.2 (CH), 130.7 (C), 131.0 (C), 132.0 (C), 137.9 (CH), 156.4 (N-C=N), 162.5 (C=O), 163.3 (C=O), 166.1 (C=O) ppm. Anal. calcd. (%) for $C_{25}H_{26}N_2O_6$ (450): C, 66.66; H, 5.82; N, 6.22; Found (%): C, 66.74; H, 5.68; N, 6.15.

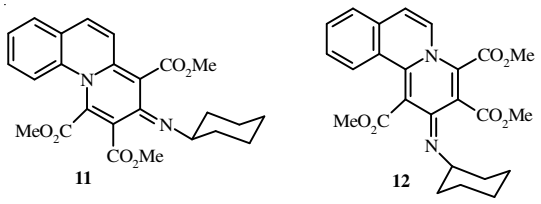
The reactions proceeded spontaneously in CH_2Cl_2 and were completed within a few hours. The ^{1}H and ^{13}C NMR spectra of the crude products clearly indicated the formation of **3** and **4**. The structures of compounds **4a-c** were deduced from their elemental analyses and their IR, ^{1}H and ^{13}C NMR spectra.

Although the mechanistic details of the reaction are not clearly known, a plausible rationalization may be advanced to explain the product formation. Presumably, the zwitter ion **5** formed from pyridine and the acetylenic compound[4-7] adds to the dicyclocarbodiimide to furnish intermediate **6**, which then adds to another molecule of acetylenic ester to produce **7**. This intermediate undergoes cyclization to furnish the fused structure **8**. Intermediate **8** is converted to **9** by recyclization and then by elimination of **10**, the product **4** is produced (**Scheme-II**).



Scheme-II

Quinoline and isoquinoline were employed to react with dimethyl acetylenedicarboxylates1 and dicyclohexylcarbo diimde **2** under above conditions produce trimethyl 3-(cyclohexylimino) 3*H*-pyrido[1,2-a]quinoline-1,2,4-tricarboxylates **11** and trimethyl 2-(cyclohexylimino) 2*H*-pyrido[2,1-a]isoqunoline-1,3,4-tricarboxylates **12**, respectively (**Scheme-III**).



Scheme-III

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