

NOTE

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

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(Received: 20 March 2012;

Accepted: 30 January 2013)

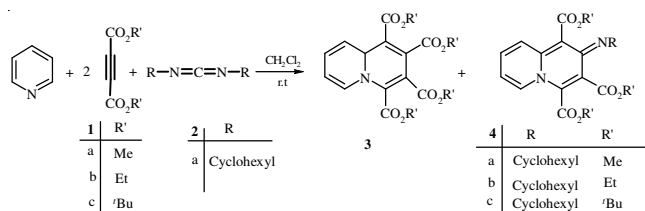
AJC-12770

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 alkaloids¹. 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 study² and subsequently the structure elucidation of Acheson³ 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 spectro-

meter operating at an ionization potential of 70 eV. IR spectra were measured on a Shimadzu IR-460 spectrometer. ¹H and ¹³C NMR spectra were measured on a BrukerAvance DRX-300 spectrometer using CDCl₃ 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 CH₂Cl₂ was added drop wise at -10 °C over 10 min dicyclo-carbodiimide (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 °C. IR (KBr, ν_{max}, cm⁻¹): 1740, 1715 and 1666 (3 C=O), 1632 (C=N). ¹H NMR δ 1.21-1.96 (m, 10H, 5CH₂), 3.43-3.51 (m, 1H, CHN), 3.91 (s, 3H, OCH₃), 3.97 (s, 6H, 2OCH₃), 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. ¹³C NMR δ 24.8 (2CH₂), 25.5 (CH₂), 33.6 (2CH₂), 49.4 (CHN), 52.2 (OCH₃), 52.5 (2OCH₃), 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 C₂₁H₂₄N₂O₆ (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-tricarboxylate (4b**):** Yellow powder; yield: 0.51 g (58 %), m.p. 165 °C. IR (KBr, ν_{max}, cm⁻¹): 1741, 1710 and 1666 (3C=O), 1619 (C=N). ¹H NMR δ 1.08-1.96 (m, 10H, 5CH₂), 1.19 (t, 3H, *J* = 7.1 Hz, CH₃), 1.35 (t, 3H, *J* = 7.1 Hz, CH₃), 1.38 (t,

3H, $J = 7.1$ Hz, CH₃), 3.37-3.45 (m, 1H, CH), 4.14 (q, 2H, $J = 7.1$ Hz, OCH₂), 4.39 (q, 2H, $J = 7.1$ Hz, OCH₂), 4.44 (q, 2H, $J = 7.1$ Hz, OCH₂), 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. ¹³C NMR $\delta = 13.3$ (CH₃), 13.4 (CH₃), 13.8 (CH₃), 24.3 (2CH₂), 25.0 (CH₂), 33.2 (2CH₂), 49.0 (CHN), 61.6, (OCH₂), 61.8 (OCH₂), 61.9 (OCH₂), 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 C₂₄H₃₀N₂O₆ (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-tricarboxylate (4c): Yellow powder; yield: 0.50 g (48 %), m.p. 157-159 °C. IR (KBr, $\nu_{\max}$, cm⁻¹): 1739, 1712 and 1660 (3C=O), 1625 (C=N). ¹H NMR $\delta = 1.21$ -1.95 (10 H, m, 5 CH₂), 1.57 (s, 9H, CMe₃), 1.62 (s, 9H, CMe₃), 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. ¹³C NMR $\delta = 24.9$ (2CH₂), 25.5 (CH₂), 33.8 (2CH₂), 27.9 (CMe₃), 28.1 (CMe₃), 28.2 (CMe₃), 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 C₃₀H₄₂N₂O₆ (526): C, 68.42; H, 8.04; N, 5.32; Found (%): C, 68.49; H, 7.98; N, 5.26

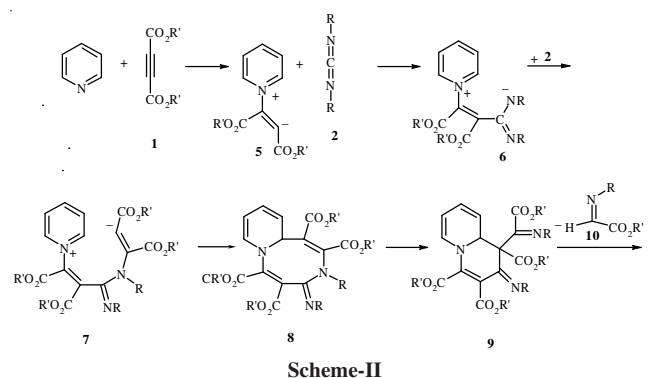
Trimethyl 1-(cyclohexylimino)-1*H*-pyrido[1,2-*a*]-quinoline-2,3,4-tricarboxylate (11): Yellow powder; yield: 0.54 g (60 %), m.p. 162 °C. IR (KBr, $\nu_{\max}$, cm⁻¹): 1738, 1714 and 1660 (3 C=O), 1624 (C=N). ¹H NMR δ : 0.87-1.36 (m, 10H, 5CH₂), 3.58-3.76 (m, 1H, CHN), 3.88 (s, 3H, OCH₃), 3.94 (s, 6H, 2OCH₃), 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, $J = 7.8$ Hz 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. ¹³C NMR δ : 24.4 (2CH₂), 25.6 (CH₂), 31.1 (2CH₂), 49.8 (CHN), 51.8 (OCH₃), 52.8 (2OCH₃), 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 C₂₅H₂₆N₂O₆ (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-tricarboxylate (12): Yellow powder; yield: 0.58 g (65 %), m.p. 178 °C. IR (KBr, $\nu_{\max}$, cm⁻¹): 1739, 1720 and 1665 (3C=O), 1619 (C=N). ¹H NMR δ : 1.01-1.84 (m, 10H, 5CH₂), 3.54-3.65 (m, 1H, CHN), 3.90 (s, 3H, OCH₃), 3.92 (s, 3H, OCH₃), 3.93 (s, 3H, OCH₃), 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. ¹³C NMR δ : 23.6 (2CH₂), 25.2 (CH₂), 30.8 (CH₂), 31.0 (CH₂), 49.2 (CHN), 52.4 (2OCH₃), 52.8 (OCH₃), 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.

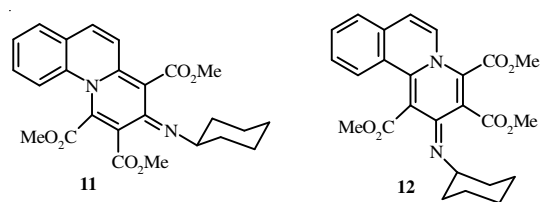
calcd. (%) for C₂₅H₂₆N₂O₆ (450): C, 66.66; H, 5.82; N, 6.22; Found (%): C, 66.74; H, 5.68; N, 6.15.

The reactions proceeded spontaneously in CH₂Cl₂ and were completed within a few hours. The ¹H and ¹³C 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, ¹H and ¹³C 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 compound⁴⁻⁷ 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).



Quinoline and isoquinoline were employed to react with dimethyl acetylenedicarboxylates **1** and dicyclohexylcarbodiimide **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*]isoquinoline-1,3,4-tricarboxylates **12**, respectively (Scheme-III).



Scheme-III

REFERENCES

1. W. Eberbach and W. Maier, *Tetrahedron Lett.*, **30**, 5591 (1989).
2. F.J. Swinbourne, J.H. Hunt and G. Klinkert, *Adv. Heterocycl. Chem.*, **23**, 103 (1978).
3. O. Diels and K. Alder, *Justus Liebigs Ann. Chem.*, **498**, 16 (1932).
4. R.M. Acheson and J. Woollard, *J. Chem. Soc. Perkin Trans. I*, 438 (1975).
5. R.M. Acheson and A.O. Plunkett, *J. Chem. Soc.*, 2676 (1964).
6. R.M. Acheson and B.J. Jones, *J. Chem. Soc.*, 748 (1962).
7. R.M. Acheson, M.W. Foxton and A.R. Hands, *J. Chem. Soc.*, 387 (1968).