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A synthesis of pyrrolo[2,1-*a*]isoquinolines through the reaction of activated acetylenes and isoquinoline in the presence of ethyl bromopyruvate

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Abstract—Isoquinoline reacts with ethyl bromopyruvate in the presence of dialkyl acetylenedicarboxylates or diaryloylacetylenes to produce dialkyl 1-(2-ethoxy-2-oxoacetyl)pyrrolo[2,1-*a*]isoquinoline-2,3-dicarboxylates or ethyl 2-[2,3-diaryloylpyrrolo[2,1-*a*]isoquinoline-1-yl]-2-oxoacetates in good yields.

Bridgehead nitrogen heterocycles are of interest because they constitute an important class of natural products, many of which exhibit useful biological activity.[1,2] The reaction of nucleophiles, nitrogen-containing heterocycles in particular, with activated acetylenes has been the subject of significant research.[3] An example is the interesting reaction between pyridine and dimethyl acetylenedicarboxylate (DMAD) in methanol, in which the corresponding indolizine-1,2,3-tricarboxylate is isolated.[4] As part of our current studies on the development of new routes to heterocyclic systems,[5] in this letter we describe a simple synthesis of functionalized pyrrolo[2,1-*a*]isoquinolines, pyrrolo[1,2-*a*]quinoline and indolizine.

The reaction of isoquinoline (**1**) with dialkyl acetylenedicarboxylates (**2a**–**d**) or diaryloylacetylenes[6] (**2e** and **2f**) in the presence of ethyl bromopyruvate (**3**) proceeded smoothly 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[7] of dialkyl 1-(2-ethoxy-2-oxoacetyl)pyrrolo[2,1-*a*]isoquinoline-2,3-dicarboxylates (**4a**–**d**) or ethyl 2-[2,3-diaryloylpyrrolo[2,1-*a*]isoquinoline-1-yl]-2-oxoacetates (**4e** and **4f**) in 90–94% yields (Scheme 1).

The ^1H NMR spectrum of **4a** exhibited signals for the methyl (δ 1.38 ppm), methoxy (δ 3.90 and 3.99 ppm), and methylene (δ 4.36 ppm) protons, along with multiplets at δ 7.54–9.31 ppm for the isoquinoline moiety. The proton-decoupled ^{13}C NMR spectrum of **4a** showed 20 distinct resonances in agreement with the proposed structure.

Mechanistically, it is conceivable that the reaction involves the initial formation of a 1:1 zwitterionic intermediate[8] **5** between isoquinoline and the activated acetylene, which undergoes reaction with **3** to produce **6**. Cyclization of intermediate **6** via enolate **7** leads to **8**, which then yields **4** by oxidation (see Scheme 2).

Under similar conditions, the reaction of quinoline or pyridine with DMAD in the presence of **3** led to dimethyl 3-(2-ethoxy-2-oxoacetyl)pyrrolo[1,2-*a*]quinoline-1,2-dicarboxylate (**9**) or dimethyl 1-(2-ethoxy-2-oxoacetyl)-2,3-indolizine dicarboxylate (**10**) in excellent yields (Scheme 3).

In conclusion, we report a novel transformation involving activated acetylenes and isoquinoline, quinoline, or pyridine in the presence of ethyl bromopyruvate, which affords bridgehead nitrogen-containing heterocycles. The present procedure has the advantage that, not only is the reaction performed under neutral conditions, but also the reactants can be mixed without any prior activation or modification. The simplicity of the present procedure makes it an interesting alternative to other approaches.

Keywords: Activated acetylenes; Isoquinoline; Quinoline; Pyridine; Indolizine.
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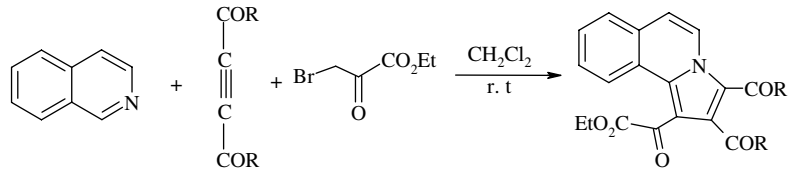
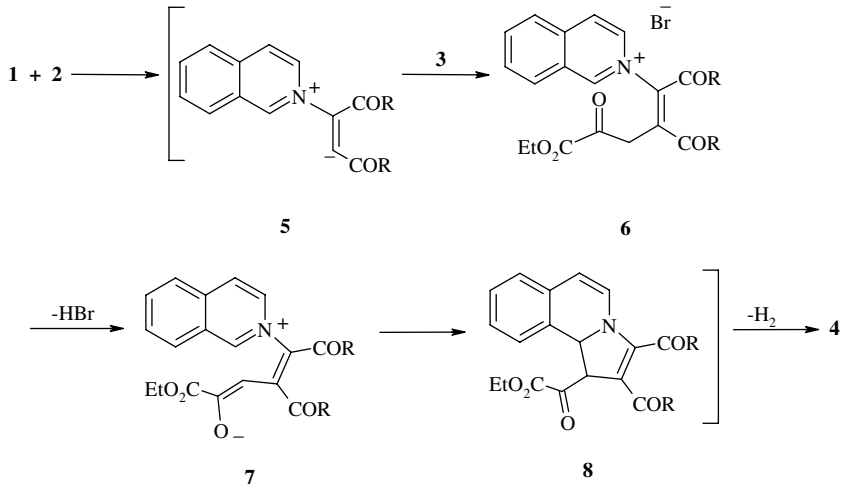
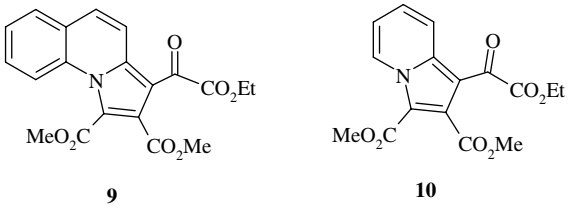


2, 4	R	Yield (%) of 4
a	MeO	91
b	EtO	94
c	^{i}PrO	91
d	^{t}BuO	92
e	C_6H_5	93
f	4-CH_3-C_6H_4	93

Scheme 1.



Scheme 2.



Scheme 3.

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7. A typical procedure for the synthesis of dimethyl 1-(2-ethoxy-2-oxoacetyl)pyrrolo[2,1-*a*]isoquinoline-2,3-dicarboxylate (**4a**): To a stirred solution of 0.28 g of DMAD (2 mmol) and 0.39 g of **3** (2 mmol) in 10 mL of CH_2Cl_2 was added 0.26 g of **1** (2 mmol) at room temperature. The reaction mixture was then stirred for 24 h. The solvent was removed under reduced pressure and the viscous residue was purified by column chromatography (Merck 230–400 mesh) using *n*-hexane–EtOAc (4:1) as eluent to give **4a**. Pale yellow crystals, yield: 0.70 g (91%), mp 102–104 °C. IR ν/cm^{-1} (KBr): 1729, 1713, 1700 and 1632 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.38$ (3H, t, $^3J_{HH} = 7.2$ Hz, CH_3),

3.90 (3H, s, OCH_3), 3.99 (3H, s, OCH_3), 4.36 (2H, q, $^3J_{HH} = 7.2$ Hz, OCH_2), 7.54 (1H, d, $^3J_{HH} = 7.6$ Hz, CH), 7.69 (1H, t, $^3J_{HH} = 7.2$ Hz, CH), 7.73 (1H, t, $^3J_{HH} = 7.2$ Hz, CH), 7.93 (1H, d, $^3J_{HH} = 7.5$ Hz, CH), 8.69 (1H, d, $^3J_{HH} = 7.5$ Hz, CH), 9.31 (1H, d, $^3J_{HH} = 7.6$ Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 14.1$ (CH_3), 53.0 (OCH_3), 53.1 (OCH_3), 63.1 (OCH_2), 112.5 (C), 117.9 (CH), 119.9 (C), 124.4 (C), 124.9 (CH), 126.1 (CH), 128.4 (CH), 129.5 (CH), 129.9 (C), 130.7 (CH), 131.0 (C), 133.8 (C), 163.7 (C=O), 164.7 (C=O), 166.1 (C=O), 177.4 (C=O) ppm. MS (EI, 70 eV): m/z (%) = 383 (M^+, 10), 324 (18), 310 (78), 167 (46), 149 (84), 129 (82), 59 (100). Anal. Calcd for $C_{20}H_{17}NO_7$ (383.4): C, 62.66; H, 4.47; N, 3.65. Found: C, 62.62; H, 4.49; N, 3.66.

Compound **4b**: Yellow powder, yield: 0.78 g (94%), mp 140–142 °C. IR ν/cm^{-1} (KBr): 1722, 1715, 1710 and 1630 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.37$ (3H, t, $^3J_{HH} = 7.2$ Hz, CH_3), 1.38 (3H, t, $^3J_{HH} = 7.2$ Hz, CH_3), 1.41 (3H, t, $^3J_{HH} = 7.2$ Hz, CH_3), 4.35 (2H, q, $^3J_{HH} = 7.2$ Hz, OCH_2), 4.36 (2H, q, $^3J_{HH} = 7.2$ Hz, OCH_2), 4.48 (2H, q, $^3J_{HH} = 7.2$ Hz, OCH_2), 7.49 (1H, d, $^3J_{HH} = 7.6$ Hz, CH), 7.65 (1H, t, $^3J_{HH} = 7.3$ Hz, CH), 7.68 (1H, t, $^3J_{HH} = 7.3$ Hz, CH), 7.88 (1H, d, $^3J_{HH} = 7.5$ Hz, CH), 8.65 (1H, d, $^3J_{HH} = 7.5$ Hz, CH), 9.27 (1H, d, $^3J_{HH} = 7.6$ Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 14.1$ (CH_3), 14.2 (CH_3), 14.3 (CH_3), 62.5 (OCH_2), 62.7 (OCH_2), 63.0 (OCH_2), 112.9 (C), 117.8 (CH), 119.9 (C), 124.4 (C), 124.9 (CH), 125.1 (CH), 128.4 (CH), 129.4 (CH), 129.9 (C), 130.5 (CH), 131.0 (C), 133.6 (C), 163.7 (C=O), 164.3 (C=O), 165.7 (C=O), 177.4 (C=O) ppm. MS (EI, 70 eV): m/z (%) = 411 (M^+, 14), 338 (100), 310 (32), 264 (78), 164 (32), 101 (23), 73 (16). Anal. Calcd for $C_{22}H_{21}NO_7$ (411.4): C, 64.23; H, 5.14; N, 3.40. Found: C, 64.20; H, 5.12; N, 3.41.

Compound **4c**: Yellow powder, yield: 0.80 g (91%), mp 138–140 °C. IR ν/cm^{-1} (KBr): 1739, 1714, 1710 and 1620 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.23$ (3H, t, $^3J_{HH} = 7.2$ Hz, CH_3), 1.38 (6H, d, $^3J_{HH} = 6.8$ Hz, $2CH_3$), 1.44 (6H, d, $^3J_{HH} = 6.8$ Hz, $2CH_3$), 4.36 (2H, q, $^3J_{HH} = 7.2$ Hz, OCH_2), 5.18 (1H, m, CH), 5.36 (1H, m, CH), 7.19 (1H, d, $^3J_{HH} = 7.7$ Hz, CH), 7.54 (1H, t, $^3J_{HH} = 7.4$ Hz, CH), 7.59 (1H, t, $^3J_{HH} = 7.4$ Hz, CH), 7.70 (1H, d, $^3J_{HH} = 7.5$ Hz, CH), 8.44 (1H, d, $^3J_{HH} = 7.5$ Hz, CH), 9.23 (1H, d, $^3J_{HH} = 7.7$ Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 13.9$ (CH_3), 21.7 (2 CH_3), 21.8 (2 CH_3), 62.5 (OCH_2), 69.9 (*C*HMe$_2$), 70.2 (*C*HMe$_2$), 113.0 (C), 116.9 (CH), 119.4 (C), 123.9 (C), 124.2 (CH), 125.0 (CH), 127.3 (CH), 128.3 (CH), 128.7 (C), 129.5 (CH), 129.9 (C), 132.5 (C), 163.1 (C=O), 163.2 (C=O), 165.0 (C=O), 176.7 (C=O) ppm. MS (EI, 70 eV): m/z (%) = 439 (M^+, 5), 257 (36), 215 (64), 173 (100), 141 (98), 58 (68). Anal. Calcd for $C_{24}H_{25}NO_7$ (439.5): C, 65.59; H, 5.73; N, 3.19. Found: C, 65.62; H, 5.70; N, 3.21.

Compound **4d**: Pale yellow crystals, yield: 0.86 g (92%), mp 193–195 °C. IR ν/cm^{-1} (KBr): 1736, 1715, 1714 and 1615 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.38$ (3H, t, $^3J_{HH} = 7.2$ Hz, CH_3), 1.59 (9H, s, 3 CH_3), 1.71 (9H, s, 3 CH_3), 4.39 (2H, q, $^3J_{HH} = 7.2$ Hz, OCH_2), 7.50 (1H, d, $^3J_{HH} = 7.7$ Hz, CH), 7.71 (1H, d, $^3J_{HH} = 7.2$ Hz, CH), 7.73 (1H, t, $^3J_{HH} = 7.2$ Hz, CH), 7.93 (1H, t, $^3J_{HH} = 7.5$ Hz, CH), 8.55 (1H, d, $^3J_{HH} = 7.5$ Hz, 1CH), 9.21 (1H, d, $^3J_{HH} = 7.7$ Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 14.2$ (CH_3), 28.3 (3 CH_3), 28.4 (3 CH_3), 62.9 (OCH_2), 83.4 (*C*Me$_3$), 84.0 (*C*Me$_3$), 114.9 (C), 117.3 (CH), 119.8 (C), 124.6 (C), 124.9 (CH), 125.6 (CH), 128.5 (CH), 129.1 (CH), 130.2 (C), 130.3 (CH), 131.8 (C), 132.4 (C), 163.5 (C=O), 163.8 (C=O), 165.0 (C=O), 177.3 (C=O) ppm. MS (EI, 70 eV): m/z (%) = 467 (M^+, 9), 356 (52), 265 (58), 264 (100), 58 (38). Anal. Calcd for $C_{26}H_{29}NO_7$ (467.5): C, 66.80; H, 6.25; N, 3.00. Found: C, 66.84; H, 6.28; N, 3.04.

Compound **4e**: Yellow powder, yield: 0.88 g (93%), mp 190–192 °C. IR ν/cm^{-1} (KBr): 1741, 1714, 1690 and 1631 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.97$ (3H, t, $^3J_{HH} = 7.2$ Hz, CH_3), 3.85 (2H, q, $^3J_{HH} = 7.2$ Hz, OCH_2), 7.31 (1H, d, $^3J_{HH} = 7.6$ Hz, CH), 7.34 (4H, m, 4 CH of C_6H_5), 7.50 (1H, d, $^3J_{HH} = 7.2$ Hz, CH of C_6H_5), 7.54 (1H, t, $^3J_{HH} = 7.2$ Hz, CH), 7.56 (1H, t, $^3J_{HH} = 7.2$ Hz, CH), 7.64 (4H, m, 4 CH of C_6H_5), 7.67 (1H, d, $^3J_{HH} = 7.2$ Hz, CH of C_6H_5), 8.00 (1H, t, $^3J_{HH} = 7.9$ Hz, CH), 8.06 (1H, d, $^3J_{HH} = 7.9$ Hz, CH), 9.58 (1H, d, $^3J_{HH} = 7.6$ Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 13.6$ (CH_3), 62.8 (OCH_2), 117.8 (CH), 120.2 (C), 120.7 (C), 124.5 (C), 125.5 (CH), 126.3 (CH), 128.1 (CH), 129.1 (2CH), 129.2 (CH), 129.4 (2CH), 130.4 (2CH), 130.5 (C), 130.7 (2CH), 131.4 (CH), 134.2 (CH), 134.3 (C), 134.5 (CH), 137.6 (C), 138.9 (C), 139.3 (C), 163.7 (C=O), 177.2 (C=O), 192.2 (C=O), 193.8 (C=O) ppm. MS (EI, 70 eV): m/z (%) = 475 (M^+, 12), 402 (75), 324 (86), 105 (100), 77 (68). Anal. Calcd for $C_{30}H_{21}NO_5$ (475.8): C, 75.78; H, 4.45; N, 2.95. Found: C, 75.82; H, 4.42; N, 3.02.

Compound **4f**: Yellow crystals, yield: 0.94 g (93%), mp 181–183 °C. IR ν/cm^{-1} (KBr): 1725, 1716, 1669 and 1600 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.07$ (3H, t, $^3J_{HH} = 7.2$ Hz, CH_3), 2.33 (3H, s, Me), 2.35 (3H, s, Me), 3.98 (2H, q, $^3J_{HH} = 7.2$ Hz, OCH_2), 7.07 (1H, d, $^3J_{HH} = 7.5$ Hz, CH), 7.26 (1H, t, $^3J_{HH} = 7.3$ Hz, CH), 7.37 (1H, t, $^3J_{HH} = 7.3$ Hz, CH), 7.42 (2H, d, $^3J_{HH} = 7.3$ Hz, 2CH), 7.46 (1H, d, $^3J_{HH} = 7.3$ Hz, CH), 7.61 (2H, d, $^3J_{HH} = 7.6$ Hz, 2CH), 7.79 (2H, d, $^3J_{HH} = 7.5$ Hz, 2CH), 8.01 (2H, t, $^3J_{HH} = 7.9$ Hz, 2CH), 8.21 (1H, d, $^3J_{HH} = 7.9$ Hz, CH), 9.60 (1H, d, $^3J_{HH} = 7.5$ Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 14.1$ (CH_3), 21.7 (CH_3 of Ar), 21.8 (CH_3 of Ar), 62.5 (OCH_2), 116.9 (C), 119.2 (CH), 123.9 (C), 124.7 (C), 125.6 (CH), 127.4 (CH), 128.5 (2CH), 128.9 (CH), 129.1 (CH), 129.6 (C), 129.9 (CH), 130.2 (2CH), 130.4 (C), 133.7 (2CH), 135.5 (2CH), 136.0 (C), 137.3 (C_{ipso}), 144.5 (C_{ipso}), 144.8 (C_{ipso}), 145.6 (C_{ipso}), 163.2 (C=O), 176.4 (C=O), 191.8 (C=O), 193.5 (C=O) ppm. MS (EI, 70 eV): m/z (%) = 503 (M^+, 9), 430 (81), 402 (38), 383 (46), 282 (24), 120 (100), 91 (71), 73 (22). Anal. Calcd for $C_{32}H_{25}NO_5$ (503.6): C, 76.33; H, 5.00; N, 2.78. Found: C, 76.28; H, 5.04; N, 2.81.

Compound **9**: Yellow powder, yield: 0.70 g (91%), mp 105–107 °C. IR ν/cm^{-1} (KBr): 1719, 1712, 1710 and 1635 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.39$ (3H, t, $^3J_{HH} = 7.2$ Hz, CH_3), 3.91 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 4.30 (2H, q, $^3J_{HH} = 7.2$ Hz, OCH_2), 7.50 (1H, d, $^3J_{HH} = 7.5$ Hz, CH), 7.56 (1H, t, $^3J_{HH} = 7.2$ Hz, CH), 7.60 (1H, t, $^3J_{HH} = 7.2$ Hz, CH), 7.79 (1H, d, $^3J_{HH} = 7.7$ Hz, CH), 8.15 (1H, d, $^3J_{HH} = 7.2$ Hz, CH), 8.21 (1H, d, $^3J_{HH} = 7.7$ Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 13.7$ (CH_3), 51.9 (OCH_3), 52.8 (OCH_3), 63.0 (OCH_2), 117.0 (C), 117.6 (CH), 119.7 (CH), 124.2 (C), 125.4 (CH), 126.3 (C), 128.8 (CH), 129.2 (CH), 129.5 (C), 129.8 (CH), 132.4 (C), 132.8 (C), 163.0 (C=O), 163.7 (C=O), 165.1 (C=O), 175.2 (C=O) ppm. MS (EI, 70 eV): m/z (%) = 383 (M^+, 11), 324 (18), 310 (100), 167 (46), 149 (84), 129 (84), 59 (71). Anal. Calcd for $C_{20}H_{17}NO_7$ (383.4): C, 62.66; H, 4.47; N, 3.65. Found: C, 62.70; H, 4.50; N, 3.68.

Compound **10**: Yellow crystals, yield: 0.62 g (94%), mp 98–100 °C. IR ν/cm^{-1} (KBr): 1725, 1716, 1711 and 1642 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.40$ (3H, t, $^3J_{HH} = 7.2$ Hz, CH_3), 3.90 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 4.36 (2H, q, $^3J_{HH} = 7.2$ Hz, OCH_2), 7.14 (1H, t, $^3J_{HH} = 7.2$ Hz, CH), 7.47 (1H, t, $^3J_{HH} = 7.2$ Hz, CH), 8.47 (1H, d, $^3J_{HH} = 7.3$ Hz, CH), 9.51 (1H, d, $^3J_{HH} = 7.2$ Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 14.0$ (CH_3), 52.2 (OCH_3), 52.7 (OCH_3),

62.3 (OCH_2), 113.8 (C), 116.9 (CH), 120.1 (C), 120.4 (CH), 128.3 (CH), 129.4 (C), 130.2 (CH), 139.2 (C), 162.8 (C=O), 163.5 (C=O), 165.2 (C=O), 175.2 (C=O) ppm. MS (EI, 70 eV): m/z (%) = 333 (M^+, 12), 274 (38), 261 (100), 233 (76), 174 (18), 73 (24), 59 (83). Anal. Calcd for $C_{16}H_{15}NO_7$ (333.3): C, 57.66; H, 4.54; N, 4.20. Found: C, 57.61; H, 4.51; N, 4.23.

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