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An efficient synthesis of a new class of spiroheterocycles: diastereoselective synthesis of dihydropyrrolo[2,1-*a*]isoquinolines

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Abstract—Isoquinoline reacts with diaroylacetylenes in the presence of 1,3-dicarbonyl compounds in a one-pot reaction to afford functionalized spiropyrroloisoquinolines in 90–96% yields.

The pyrroloisoquinoline ring system is found as a major structural motif of the *Erythrina* alkaloids.[1,2] A variety of pharmacological effects are associated with pyrroloisoquinoline derivatives including sedative, hypotensive, neuromuscular blocking and CNS activities.[3] In recent years, there has been significant interest in the synthesis of these compounds and many approaches involving *N*-acyliminium cyclization, as a key ring-forming step, have been reported.[4]

As part of our current studies on the development of new routes in heterocyclic synthesis,[5] we report an efficient one-pot synthesis of spiropyrroloisoquinolines via reaction of diaroylacetylenes and isoquinoline in the presence of 1,3-dicarbonyl compounds such as acetylacetone, 1,3-dimethylbarbituric acid, 1,3-indandione, Meldrum's acid or dimedone which leads to the introduction of asymmetry during the key ring-forming step.

The reaction between isoquinoline and dibenzoylacetylene in the presence of acetylacetone at ambient temperature in CH_2Cl_2 led to the corresponding pyrroloisoquinoline derivative in high yield[6] (Table 1).

Table 1 contains the results of our study. The structures of compounds **1a**–**1g** were deduced from their elemental analyses and their IR, ^{1}H NMR and ^{13}C NMR spectral data. For example, the ^{1}H NMR spectrum of **1a** exhibited five singlets identified as methyl (δ 2.07 and 2.19), olefinic (δ 6.13), methine (δ 6.21) and hydroxy (δ 9.42) protons, along with aromatic protons (δ 6.29–7.77). The ^{1}H-decoupled ^{13}C NMR spectrum of **1a** showed 26 distinct resonances in agreement with the proposed structure.

Although the mechanistic details of the reaction are not known, a plausible pathway may be proposed (Scheme 1). Presumably, the zwitterionic intermediate **2**, formed from the reaction of isoquinoline and dibenzoylacetylene,[7] is protonated by acetylacetone to furnish intermediate **3**, which is attacked by the anion of the CH-acid to produce the dihydroisoquinoline **4**. The latter can then undergo cyclization under the reaction conditions to afford the pyrroloisoquinoline system **1a**.

Unambiguous evidence for the structure of **1a** was obtained from single-crystal X-ray analysis. An ORTEP[8] diagram of **1a** is shown in Figure 1. Details of the structure determination and refinements are described in the experimental section.

In summary, we have reported an efficient and highly diastereoselective approach to the pyrroloisoquinoline ring system from readily available substrates. The advantage of the present procedure is that the reaction is performed under neutral conditions by simple mixing of the starting materials.

Keywords: Pyrroloisoquinoline; 1,3-Dicarbonyl compounds; Diaroylacetylenes; Isoquinoline.
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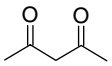
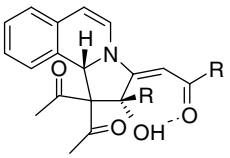
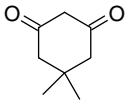
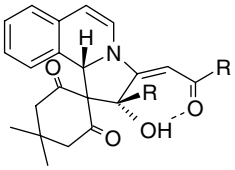
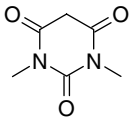
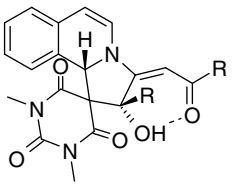
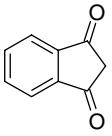
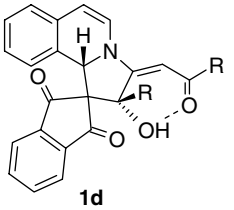
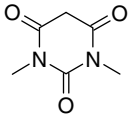
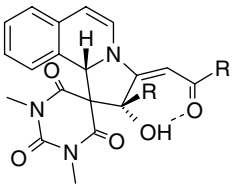
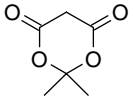
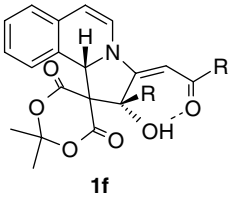
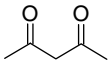
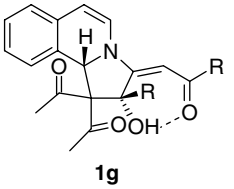
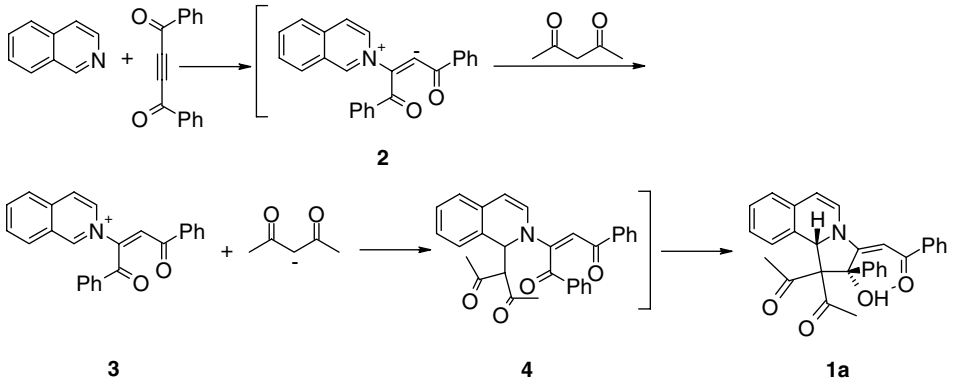
Table 1. Reaction of isoquinoline with diaroylacetylenes in the presence of 1,3-diones

Entry	Acetylenic compound	1,3-Dicarbonyl compound	Product	Yield[a] (%)
a	ROC—≡—COR R= Ph		 **1a**	92
b	ROC—≡—COR R= Ph		 **1b**	90
c	ROC—≡—COR R= Ph		 **1c**	93
d	ROC—≡—COR R= Ph		 **1d**	91
e	ROC—≡—COR R= 4-MePh		 **1e**	93
f	ROC—≡—COR R= Ph		 **1f**	90
g	ROC—≡—COR R= 4-MePh		 **1g**	96

[a] Isolated yields.



Scheme 1. Proposed mechanism.

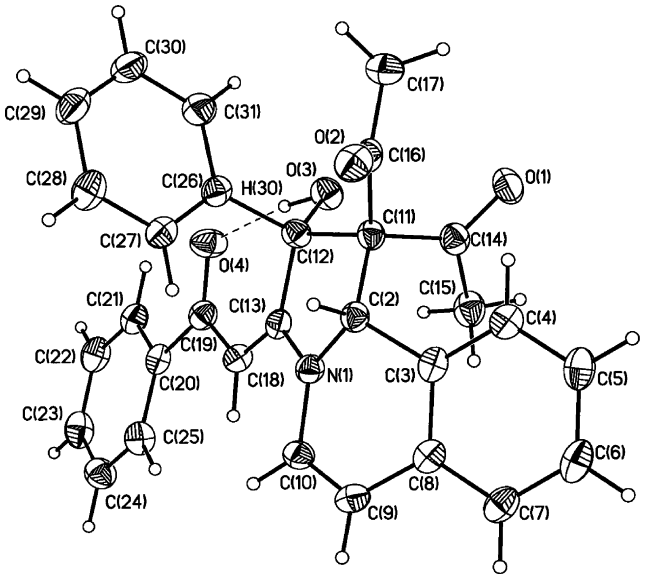


Figure 1. X-ray crystal structure of **1a**.

Supplementary data

Selected physical and spectral data for compounds **1b** and **1d**–**1g** are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.07.135.

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6. *General procedure for the preparation of compounds* **1**. To a stirred solution of the diaroylacetylene (2 mmol) and 1,3-dicarbonyl compound (2 mmol) in 10 mL of dry CH_2Cl_2 was added a solution of isoquinoline (2 mmol) in 5 mL of dry CH_2Cl_2 at room temperature. The reaction mixture was then allowed to stir for 24 h. The solvent was removed under reduced pressure and the residue was recrystallized from MeOH/EtOAc (1:9) mixture. *2-[1,1-Diacetyl-2-hydroxy-2-phenyl-1,10b-dihydropyrrolo[2,1-a]isoquinoline-3(2H)-yliden]-1-phenyl-1-ethanone* (**1a**). Yellow crystals; yield: 0.84 g (92%), mp 196–198 °C. IR ν/cm^{-1} (KBr): 3365 (OH), 1693 (C=O), 1501, 1214, 874; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.07 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 6.13 (s, 1H, CH), 6.21 (s, 1H, CH), 6.29 (d, $^3J = 7.4$ Hz, 1H, CH), 6.70 (d, $^3J = 7.6$ Hz, 1H, CH), 6.86 (d, $^3J = 7.4$ Hz, 1H, CH), 7.07–7.10 (m, 2H, CH), 7.18 (t, $^3J = 7.5$ Hz, 1H, CH), 7.20–7.23 (m, 1H, CH), 7.25 (t, $^3J = 7.5$ Hz, 2H, CH), 7.32 (t, $^3J = 7.5$ Hz, 2H, CH), 7.40 (t, $^3J = 7.5$ Hz, 1H, CH), 7.47–7.49 (m, 2H, CH), 7.77 (d, $^3J = 7.5$ Hz, 2H, CH), 9.42 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 125.6 MHz) δ 30.2 (CH_3), 31.1 (CH_3), 63.4 (C–O), 82.7 (C), 84.9 (CH), 89.1 (CH), 116.6 (CH), 121.4 (CH), 125.7 (CH), 126.0 (CH), 126.2 (CH), 127.9 (2 CH), 128.2 (CH), 128.3 (2 CH), 128.4 (2 CH), 128.5 (CH), 129.0 (2 CH), 129.8 (C), 130.1 (C), 132.0 (CH), 137.8 (C), 139.8 (C), 166.8 (C–N), 188.9 (C=O), 203.3 (C=O), 205.0 (C=O). MS (EI) *m/z* (%) 463 (M^+, 18), 420 (40), 340 (100), 105 (44), 77 (16), 43 (100). Anal. Calcd for $C_{30}H_{25}NO_4$ (463.53): C, 77.74; H, 5.44; N, 3.02. Found: C, 77.42; H, 5.53; N, 3.09. *X-ray crystal-structure determination of* **1a**. Structure-determination and refinement data: formula, $C_{30}H_{25}NO_4$, M_r 463.53; crystal size, $0.45 \times 0.23 \times 0.20$ mm^3, crystal system, monoclinic, $a = 9.9313(8)$, $b = 8.3117(7)$, $c = 28.341(2)$ Å, $\beta = 91.257(5)$, space group $P2_1/n$; $Z = 4$, $V = 2338.9(3)$ Å^3, $D_{calcd} = 1.316$ g cm^{-3}; $R = 0.0474$ (for 5280 reflections), $R_w = 0.0884$; $-12 \leqslant h \leqslant 12$; $-10 \leqslant k \leqslant 10$; $-22 \leqslant l \leqslant 36$; Mo K_α radiation ($\lambda = 0.71073$ Å); $T = 120(2)$ K. The crystallographic data of **1a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-628361. Copies of these data can be obtained, free of charge, via the internet (http://www.ccdc.cam.ac.uk/data_request/cif), e-mail (data_request@ccdc.cam.ac.uk), or fax (+44 1223 336033). *Compound* **1c**: Yellow crystals; yield: 0.96 g (93%), mp 166–168°C. IR ν/cm^{-1} (KBr): 3342 (OH), 1686 (C=O), 1591, 1479, 1376, 1221; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.24 (s,

3H, NCH_3), 3.31 (s, 3H, NCH_3), 6.25 (d, $^3J = 7.7$ Hz, 1H, CH), 6.28 (s, 1H, CH), 6.30 (s, 1H, CH), 6.48 (d, $^3J = 7.5$ Hz, 1H, CH), 6.92 (d, $^3J = 7.7$ Hz, 1H, CH), 7.09 (t, $^3J = 7.3$ Hz, 1H, CH), 7.15 (d, $^3J = 7.2$ Hz, 1H, CH), 7.20 (t, $^3J = 7.3$ Hz, 1H, CH), 7.34–7.38 (m, 7H, CH), 7.44 (t, $^3J = 7.1$ Hz, 1H, CH), 7.79 (d, $^3J = 7.5$ Hz, 2H, CH), 9.58 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 125.6 MHz) δ 28.7 (NCH_3), 29.4 (NCH_3), 63.5 (C), 70.2 (C–O), 90.1 (C), 90.2 (CH), 114.9 (CH), 121.0 (CH), 122.3 (CH), 125.3 (2 CH), 126.5 (CH), 127.8 (2 CH), 128.1 (CH), 128.2 (2 CH), 128.3 (CH), 128.5 (CH), 128.7 (CH), 129.4 (CH), 130.0 (C), 130.2 (C), 131.9 (CH), 137.6 (C), 139.8 (C), 151.6 (C–N), 163.0 (C═O), 165.6 (C═O), 165.8 (C═O), 189.0 (C═O). MS (EI) *m/z* (%) 519 (M^+, 8), 390 (3), 285 (100), 207 (20), 105 (58), 77 (80). Anal. Calcd for $C_{31}H_{25}N_3O_5$ (519.55): C, 71.67; H, 4.85; N, 8.09. Found: C, 71.37; H, 4.78; N, 8.15.

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