An Efficient Synthesis of Functionalized 6,10-Dioxo-6,10-dihydro-5*H*-pyrido[1,2-*a*]quinoxalines and 6,10-Dioxo-6,10-dihydropyrido[2,1-*c*][1,4]benzoxazines

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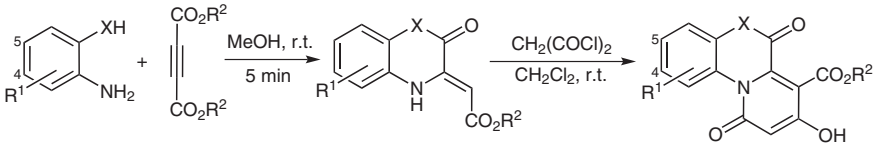
Abstract: An efficient synthesis of alkyl 8-hydroxy-6,10-dioxo-6,10-dihydro-5*H*-pyrido[1,2-*a*]quinoxaline-7-carboxylates and alkyl 8-hydroxy-6,10-dioxo-6,10-dihydropyrido[2,1-*c*][1,4]benzoxazine-7-carboxylates is described. This involves the reaction between malonyl dichloride and alkyl 2-[3,4-dihydro-3-oxoquinoxaline 2(1*H*)-ylidene]acetates or alkyl 2-(2-oxo-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ylidene)acetates in CH_2Cl_2 at room temperature.

Key words: malonyl dichloride, pyrido[1,2-*a*]quinoxaline, pyrido[2,1-*c*][1,4]benzoxazine, benzene-1,2-diamine, 2-aminophenol, acetylenic ester

Quinoxalines and benzoxazines are privileged ring systems. Their derivatives have broad biological activities and have been used as anticancer,[1] antiviral,[2] antibacterial agents,[3] and kinase inhibition agents.[4,5] In addition to the medicinal applications, quinoxalines and benzoxazines have been used as dyes[6,7] and key intermediates in the synthesis of organic semiconductors.[8,9] Quinoxalines also play an important role as a basic skeleton for the design of a number of antibiotics such as echinomycin, actinomycin, and leromycin. It has been reported that these compounds inhibit the growth of gram-positive bacteria, and are active against various transplantable tumors.[10,11] The majority of quinoxaline and benzoxazine derivatives are prepared by the reaction of benzene-1,2-diamine or 2-aminophenol with a 1,2-dicarbonyl compound.[12,13]

As part of our current studies on the development of new routes in heterocyclic synthesis,[14–16] we report[17] an efficient and convenient synthetic route to alkyl 8-hydroxy-6,10-dioxo-6,10-dihydro-5*H*-pyrido[1,2-*a*]quinoxaline-7-carboxylates **4a–c** and alkyl 8-hydroxy-6,10-dioxo-6,10-dihydropyrido[2,1-*c*][1,4]benzoxazine-7-carboxylates **4d–h** from the reaction between malonyl dichloride and alkyl 2-[3,4-dihydro-3-oxoquinoxaline-2(1*H*)-ylidene]acetates **3a–c** or alkyl 2-[2-oxo-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ylidene]acetates **3d–h** in CH_2Cl_2 at room temperature (Scheme 1). Compounds **3** were prepared from the reaction of dialkyl acetylenedicarboxylates **2a–c** with benzene-1,2-diamine (**1a**) and 2-aminophenol (**1b**).[18,19] A number of compounds closely related to **4** have been prepared by reaction of compounds related to **3** with bis(2,4,6-trichlorophenyl)malonate.[20]

The structures of compounds **4a–h** were apparent from their mass spectra, which displayed in each case the molecular ion peak at the appropriate *m/z* values. The ^{1}H NMR and ^{13}C NMR spectroscopic data, as well as IR spectra, are in agreement with the proposed structures. The ^{1}H NMR spectrum of **4a** in DMSO-d_6 showed four singlets for methoxy (δ = 3.74 ppm), CH (δ = 6.08 ppm), OH (δ = 11.76 ppm), and NH (δ = 11.84 ppm) protons. The ^{13}C NMR spectrum of **4a** exhibited 14 signals in agreement with the proposed structure. Partial assignments of these resonances are given in the experimental data. The ^{1}H NMR and ^{13}C NMR spectra of **4b–h** are sim-



1	X
a	NH
b	O

2	R^2
a	Me
b	Et
c	*t*-Bu

3	X	R^1	R^2	Yield (%)
a	NH	H	Me	98
b	NH	H	Et	95
c	NH	H	*t*-Bu	98
d	O	H	Me	97
e	O	4-Me	Me	96
f	O	4-Cl	Me	95
g	O	5-Me	Me	98
h	O	5-Cl	Me	95

4	X	R^1	R^2	Yield (%)
a	NH	H	Me	98
b	NH	H	Et	95
c	NH	H	*t*-Bu	98
d	O	H	Me	97
e	O	4-Me	Me	96
f	O	4-Cl	Me	95
g	O	5-Me	Me	98
h	O	5-Cl	Me	95

Scheme 1

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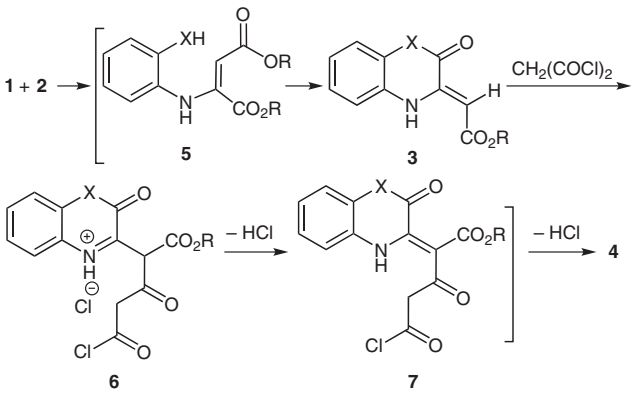
ilar to those for **4a**, except for the ester moieties, which showed characteristic resonances in appropriate regions of the spectra.

A tentative mechanism for this transformation is proposed in Scheme 2. It is conceivable that the initial event is the formation of intermediate **5** from **1** and the acetylenic ester,[18,19] which is converted to alkylidene quinoxaline **3**. Compound **3** is subsequently attacked by malonyl dichloride to produce **6**. Intermediate **6** undergoes cyclization reaction, HCl elimination, and keto–enol tautomerism to generate compounds **4**.



Scheme 2

In conclusion, we have described a convenient route to 6,10-dioxo-6,10-dihydro-5*H*-pyrido[1,2-*a*]quinoxalines and 6,10-dioxo-6,10-dihydropyrido[2,1-*c*][1,4]benzoxazines from malonyl dichloride and alkyl 2-[3,4-dihydro-3-oxoquinoxaline-2(1*H*)-ylidene]acetates or alkyl 2-[2-oxo-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ylidene]acetates in CH_2Cl_2 at room temperature. The advantage of the present procedure is that the reaction is performed in the absence of added base by simple mixing of the starting materials.

References and Notes

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(17) **General Procedure for the Synthesis of Compounds 4**
To a suspension of **3** (2 mmol)[18] in CH_2Cl_2 (10 mL) was added of malonyl dichloride (0.29 g, 2.1 mmol) at r.t. The reaction mixture was then stirred for 15 min. The formed precipitate was filtered off and washed with CH_2Cl_2 to afford the pure product.
Compound **4a**: pale yellow powder; mp 300–304 °C (dec.); yield 0.56 g (98%). IR (KBr): ν_{max} = 3450, 1729, 1693, 1655, 1490, 1418, 1365, 1306, 1258, 1106, 757 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.74 (3 H, s, OMe), 6.08 (1 H, s, CH), 7.12 (1 H, d, ^3J = 7.8 Hz, CH), 7.20 (1 H, t, ^3J = 7.9 Hz, CH), 7.30 (1 H, t, ^3J = 8.0 Hz, CH), 9.19 (1 H, d, ^3J = 7.8 Hz, CH), 11.76 (1 H, s, OH), 11.84 (1 H, s, NH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 52.6 (OMe), 102.9 (CH), 112.4 (C), 116.4 (CH), 121.5 (CH), 122.8 (CH), 123.9 (C), 127.3 (CH), 128.1 (C), 133.0 (C), 156.2 (COH), 162.1 (CO), 162.9 (CO), 165.3 (CO_2) ppm. MS: *m/z* (%) = 285 (20) [M – 1^+], 262 (20), 236 (35), 179 (10), 123 (40), 97 (50), 83 (55), 69 (60), 57 (100), 43 (90). Anal. Calcd (%) for $C_{14}H_{10}N_2O_5$ (286.24): C, 58.75; H, 3.52; N, 9.79. Found: C, 58.60; H, 3.44; N, 9.65.
Compound **4d**: pale yellow powder; mp 298–300 °C (dec.); yield 0.55 g (97%). IR (KBr) ν_{max} = 3505, 1764, 1721, 1661, 1618, 1499, 1408, 1333, 1304, 1294, 1106, 759 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.79 (3 H, s, OMe), 6.12 (1 H, s, CH), 7.27 (1 H, t, ^3J = 7.0 Hz, CH), 7.30 (1 H, d, ^3J = 7.9 Hz, CH), 7.33 (1 H, t, ^3J = 8.0 Hz, CH), 9.18 (1 H, d, ^3J = 8.6 Hz, CH), 12.01 (1 H, s, OH) ppm.^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 52.5 (OMe), 104.1 (CH), 114.8 (C), 116.8 (CH), 120.6 (CH), 123.1 (C), 124.3 (CH), 127.0 (CH), 127.9 (C), 141.1 (C), 154.2 (COH), 161.4 (CO), 161.5 (CO), 164.1 (CO_2) ppm. Anal. Calcd (%) for $C_{14}H_9NO_6$ (287.22): C, 58.54; H, 3.16; N, 4.88. Found: C, 58.60; H, 3.14; N, 4.85.
Compound **4g**: yellow powder; mp 298–301 °C (dec.); yield 0.58 g (98%). IR (KBr) ν_{max} = 3440, 1764, 1722, 1665, 1621, 1455, 1324, 1286, 1250, 1107, 765 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.32 (3 H, s, Me), 3.78 (3 H, s, OMe), 6.10 (1 H, s, CH), 7.15 (1 H, d, ^3J = 8.3 Hz, CH), 7.19 (1 H, d, ^3J = 8.3 Hz), 9.03 (1 H, s, CH), 11.99 (1 H, s, OH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 20.9 (Me), 52.4 (OMe), 104.1 (CH), 114.8 (C), 116.5 (CH), 120.7 (CH), 122.6 (C), 127.4 (CH), 127.9 (C), 133.5 (C), 139.0 (C), 154.3 (C-OH), 161.3 (CO), 161.4 (CO), 164.1 (CO_2) ppm. Anal. Calcd (%) for $C_{15}H_{11}NO_6$ (301.25): C, 59.81; H, 3.68; N, 4.65. Found: C, 59.80; H, 3.65; N, 4.65.
All other novel compounds isolated possessed spectroscopic and analytical data in keeping with their proposed structures.

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