A New Synthetic Approach to the Benzo[*c*]phenanthridine Ring System

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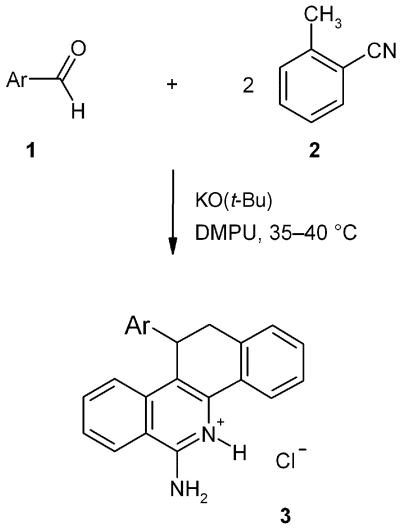
Abstract: The base-catalyzed reaction of 2-methylbenzonitrile and paraformaldehyde provided 6-amino-11,12-dihydrobenzo[*c*]phenanthridine, which was converted via the corresponding 6-oxo- and 6-thioxo-derivatives into benzo[*c*]phenanthridine.

Key words: aldehydes, nitriles, ring closure, dehydrogenation, heterocycles

The benzo[*c*]phenanthridine ring system is found in a number of alkaloids such as fagaronine, chelerythrine, sanguinarine, and nitidine. These naturally occurring alkaloids are of interest because of the cytotoxic activity associated with this class of compounds.[1] We have recently developed a highly efficient and versatile synthesis of 11-substituted 6-amino-11,12-dihydrobenzo[*c*]phenanthridines. The synthesis is based upon a condensation of 2 equivalents of 2-methylbenzonitrile (**2**) and various aromatic aldehydes **1**, which is catalyzed by potassium *t*-butoxide in DMPU as solvent (Scheme 1).[2]



Scheme 1 Synthesis of 11-substituted 6-amino-11,12-dihydrobenzo[*c*]phenanthridines

All of these newly synthesized derivatives possess adequate to remarkable antitumor activity against several human tumor cell lines.[2]

In our quest to explore the synthetic potential of this condensation we investigated the applicability of aliphatic aldehydes instead of aromatic aldehydes in the above mentioned reaction sequence. Therefore, through the condensation of paraformaldehyde (**4**) with 2-methylbenzonitrile (**2**) we were able to apply this new reaction method to the synthesis of the benzo[*c*]phenanthridine ring system. Various synthetic pathways for the benzo[*c*]phenanthridine skeleton are reported in the literature and most of them are summarized in Table 1.

Table 1 Published Syntheses of Benzo[*c*]phenanthridine

Author	Date of Publication	Steps	Yield
Graebe[3]	1904	5	–
Späth and Kuffner[4]	1931	5	–
Ritchie[5]	1944	8	6.6
Badger and Seidler[6]	1954	5	–
Wahley and Meadow[7]	1954	5	< 2.7[a]
Arcus et al.[8]	1957	5	< 10.8[a]
Abramovitch and Tertzakian[9]	1963	9	1.3
Tilak et al.[10]	1968	4	< 5.3[a]
Bhargava and Saharia[11]	1972	6	12
Ninomiya et al.[12]	1973	5	< 28[a]
Boyer and Patel[13]	1979	6	< 10.7[a]
Beugelmans et al.[14]	1985	3	< 34[a]
Kessar et al.[15]	1988	4	< 39[a]
Grimshaw and Hewitt[16]	1990	5	< 36[a]

[a] Yield not given for each individual reaction step.

Indeed, we synthesized 11,12-dihydrobenzo[*c*]phenanthridin-6-amine-hydrochloride (**5**) in moderate yield by reaction of paraformaldehyde (**4**) as the aliphatic aldehyde component with two equivalents of 2-methylbenzonitrile (**2**) (Scheme 2). The starting materials are readily available from commercial suppliers. The reaction sequence to the target molecule **8** proceeded by diazotisation of the amino group in the 6-position with *t*-butylnitrite in dimethyl formamide leading to the 6-oxo derivative **6**. Un-

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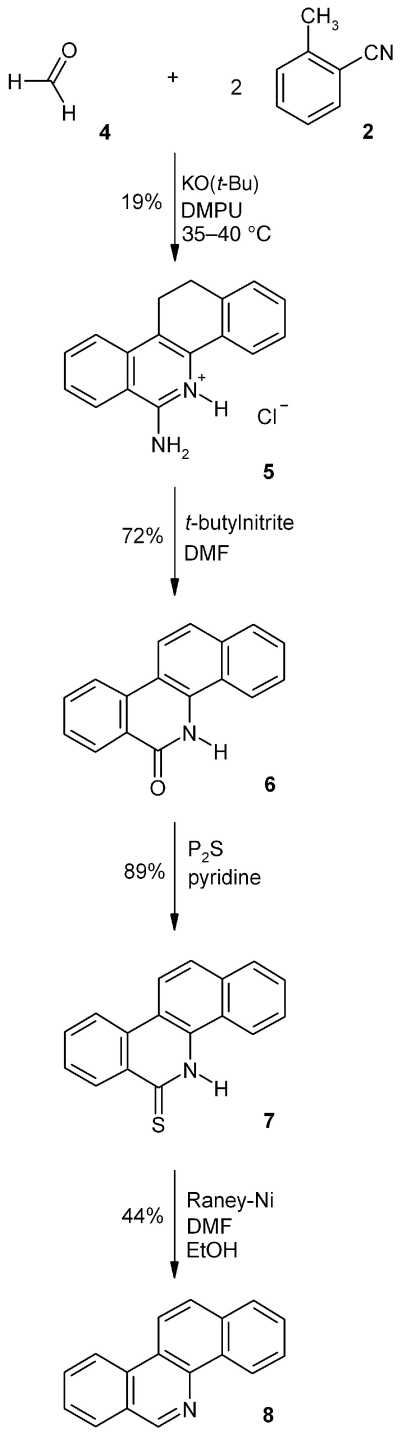
expectedly, also dehydrogenation to the fully aromatic ring system occurred. If the aromatic amine **5** was treated with nitrite and a reducing agent instead of *t*-butylnitrite and dimethyl formamide hydrolysis to 5,6,11,12-tetrahydrobenzo[*c*]phenanthridin-6-one was observed.

Accordingly, in both cases the expected classical exchange of the amino group by hydrogen did not take place. In accordance with our results a similar behaviour during diazotisation was reported for 6-aminophenanthridine by Keene and Tissington.[17] The 6-oxo derivative **6** was reacted with phosphorus pentasulfide in pyridine under reflux to obtain the 6-thioxo derivative **7** in very good yield, followed by efficient desulfurization with Raney nickel in dimethyl formamide–ethanol to afford benzo[*c*]phenanthridine (**8**) in an overall yield of 6.3%. The last two reaction steps have been reported by Taylor and Martin for the conversion of 5,6-dihydrophenanthridin-6-one via the 6-thioxo derivative into phenanthridine.[18]



Scheme 2 Synthesis of the benzo[*c*]phenanthridine skeleton

Although the benzo[*c*]phenanthridine skeleton has been prepared previously, this new and facile reaction sequence is superior in point of convenience. The overall yield is limited to 6.3% by the first step, while the consecutive steps gave yields of at least 89%. An increase of the yield of the reaction product **5** in this new synthetic route to the benzo[*c*]phenanthridine ring system is the objective of further investigation.

Melting points were determined with a Büchi 510 melting point apparatus and on a Thermowar microhotstage and are reported uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ARX 300 spectrometer at 300 K in DMSO-d_6/TMS. IR spectra were obtained using a Perkin-Elmer FT-IR 16 PC spectrometer. Electron impact mass spectra (70 eV) were recorded on a Hewlett-Packard 5989 A mass spectrometer. High resolution mass spectra were performed on a Finnigan MAT 8230 MS (70 eV). Elemental analyses were carried out by the Microanalytical laboratory of Ilse Beetz, Germany.

11,12-Dihydrobenzo[*c*]phenanthridin-6-amine Hydrochloride (5)

A solution of 2-methylbenzonitrile (**2**; 9.4 g, 80 mmol) and paraformaldehyde (**4**; 1.2 g, 40 mmol) in DMPU (60 mL) was added dropwise to a stirred solution of *t*-BuOK (9.9 g, 88 mmol) in DMPU (90 mL) at 35 °C under an atmosphere of nitrogen. The resulting mixture was stirred for 4 h at 35–40 °C and then quenched with ice water (400 mL) containing NH_4Cl (8.6 g, 160 mmol). The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). After evaporation of the solvent, HCl (5 N, 10 mL) was added under vigorous stirring to obtain **5** as the hydrochloride. The precipitate was collected and washed with CH_2Cl_2 (10 mL) to give 2.19 g (19%) of **5**; mp 289 °C.

IR (KBr): 3100, 2946, 1654, 1628, 1616, 1570, 1554, 1496 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.96–3.02 (m, 2 H, CH_2), 3.05–3.10 (m, 2 H, CH_2), 7.41–7.44 (m, 3 H, ArH), 7.76 (t, *J* = 7.7 Hz, 1 H, ArH), 8.01 (t, *J* = 7.7 Hz, 1 H, ArH), 8.14 (d, *J* = 8.0 Hz, 1 H, ArH), 8.28–8.32 (m, 1 H, ArH), 8.61 (d, *J* = 8.3 Hz, 1 H, ArH), 9.55 (br s, 2 H, NH_2), 13.85 (br s, 1 H, ≡N$^+$H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 20.8, 26.8, 116.1, 116.9, 123.4, 124.2, 125.9, 126.9, 127.3, 128.0, 128.2, 129.7, 131.6, 134.9, 136.0, 137.3, 154.7.

MS (EI): *m*/*z* (%) = 246 (M^+, 100), 245 (M^+ – 1, 77), 123 (M^{2+}, 16).

Anal. Calcd for $C_{17}H_{15}N_2Cl$: C, 72.21; H, 5.35; N, 9.91. Found: C, 72.13; H, 5.35; N, 9.99.

5,6-Dihydrobenzo[*c*]phenanthridin-6-one (6)

A solution of *t*-butylnitrite (4.3 g, 42 mmol) in DMF (10 mL) was added dropwise to a stirred solution of **5** (1.4 g, 5.7 mmol) in DMF (20 mL). The resulting mixture was stirred for 1 h at 55 °C, cooled to r.t., quenched with ice water and stirred for 0.5 h. The precipitate was collected, washed with H_2O (20 mL) and petroleum ether (bp 50–70 °C, 10 mL) and crystallized from MeOH–H_2O (3:1) to give 1.0 g (72%) of **6**; mp 327 °C (Lit.[19] 325 °C).

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IR (KBr): 3166, 3060, 2358, 1654, 1610, 1558, 1490 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 7.63–7.71 (m, 3 H, ArH), 7.81 (d, *J* = 8.8 Hz, 1 H, ArH), 7.92 (t, *J* = 7.6 Hz, 1 H, ArH), 8.01–8.04 (m, 1 H, ArH), 8.42 (d, *J* = 7.5 Hz, 1 H, ArH), 8.49 (d, *J* = 8.8 Hz, 1 H, ArH), 8.63 (d, *J* = 8.2 Hz, 1 H, Ar-H), 8.90–8.93 (m, 1 H, ArH), 11.90 (br s, 1 H, =NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 113.2, 120.7, 122.2 (2 C), 122.6, 123.1, 125.5, 126.5, 127.3, 127.5, 127.7, 128.3, 132.3, 133.1, 133.4, 134.8, 161.6.

MS (EI): *m*/*z* (%) = 245 (M^+, 100), 122.5 (M^{2+}, 5).

5,6-Dihydrobenzo[*c*]phenanthridin-6-thione (7)

A mixture of **6** (0.74 g, 3 mmol), phosphorus pentasulfide (0.89 g, 4 mmol), and pyridine (10 mL) was heated under reflux for 2 h. The resulting mixture was quenched with ice water (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The organic layer was dried ($MgSO_4$), the solvent was removed in vacuo and the residue was crystallized from DMF–H_2O (1:1) to give 0.7 g of **7** (89%), mp 279 °C. Compound **7** decomposed in solution. The decomposition products were not investigated.

IR (KBr): 3234, 3048, 2922, 1628, 1610, 1572, 1526, 1498, 1450, 1430 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 7.70–7.78 (m, 3 H, ArH), 7.96–8.01 (m, 2 H, ArH), 8.06–8.09 (m, 1 H, ArH), 8.60 (d, *J* = 9.0 Hz, 1 H, ArH), 8.73 (d, *J* = 7.9 Hz, 1 H, ArH), 9.04 (d, *J* = 7.5 Hz, 1 H, ArH), 9.19–9.22 (m, 1 H, ArH), 13.26 (br s, 1 H, =NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 117.0, 120.4, 121.6, 122.6, 123.3, 125.1, 127.0, 127.8, 128.3, 128.5*, 130.4, 130.8, 131.8, 133.2, 133.5 183.8; * two overlapping signals.

MS (EI): *m*/*z* (%) = 261 (M^+, 100), 260 (M^+ – 1, 13), 130.5 (M^{2+}, 11).

HRMS: *m*/*z* calcd for $C_{17}H_{11}NS$, 261.06122; found, 261.06110.

HRMS: *m*/*z* calcd for $C_{16}{}^{13}CH_{11}NS$, 262.06458; found, 262.06460.

Benzo[*c*]phenanthridine (8)

A mixture of **7** (0.5 g, 1.9 mmol) and Raney nickel (1.8 g, moistened with water) in DMF (5 mL) and EtOH (5 mL) was heated under reflux for 1 h. The resulting mixture was filtered and the filtrate acidified with HCl. The solvent was removed in vacuo, the resulting residue was dissolved in H_2O (5 mL) and alkalized with NH_3. The precipitate was collected and crystallized from MeOH–H_2O (1:1). Further purification was achieved by precipitation of **8** as the hydrochloride following by releasing of the free base to give 195 mg (44%) of **8**; mp 130 °C (Lit.[20] 130–133 °C).

IR (KBr): 1618, 1600, 1582, 1512, 1477 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 7.73–7.83 (m, 2 H, H-2, H-3), 7.86 (t, *J* = 7.5 Hz, 1 H, H-9), 8.03 (t, *J* = 7.9 Hz, 1 H, H-8), 8.13 (d, *J* = 7.2 Hz, 1H, H-4), 8.19 (d, *J* = 9.0 Hz, 1 H, H-12), 8.35 (d, *J* = 8.0 Hz, 1 H, H-10,), 8.83 (d, *J* = 9.0 Hz, 1 H, H-11,), 8.95 (d, *J* = 8.3 Hz, 1 H, H-7), 9.33 (d, *J* = 8.8 Hz, 1 H, H-1), 9.61 (s, 1 H, H-6).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 120.6 (C-11), 120.7 (C-10b), 122.6 (C-7), 124.2 (C-1), 126.5 (C-10a), 127.0 (C-2), 127.5 (C-3), 127.68 (C-9), 127.75 (C-12), 127.80 (C-4), 128.8 (C-10), 131.3 (C-4a), 131.4 (C-8), 132.1 (C-6a), 132.9 (C-12a), 140.5 (C-4b), 152.3 (C-6).

MS (EI): *m*/*z* (%) = 229 (M^+, 100), 228 (M^+ – 1, 25), 114.5 (M^{2+}, 21).

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