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A novel annelation to quinolines and isoquinolines under Friedel–Crafts conditions: a one-step synthesis of functionalized pyridoquinolines and pyridoisoquinolines

Shashi B. Mahato,*[a] Subhadra Garai,[a] Manuela Weber[b] and Peter Luger[b]

[a] *Indian Institute of Chemical Biology, 4, Raja S.C. Mullick Road, Jadavpur, Calcutta-700032, India*
[b] *Institut für Kristallographie, Freie Universität Berlin, Takustr. 6, 14195, Germany*

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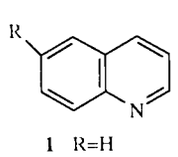
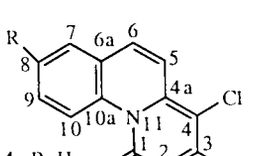
A novel one-step synthesis of pyridoquinolines and pyridoisoquinolines from quinoline, 6-methyl-, and 6-methoxyquinolines and isoquinoline under Friedel–Crafts conditions is reported. The complete structures of the pyridoquinoline and pyridoisoquinoline analogues obtained by using 6-methylquinoline and isoquinoline as substrates were established by single-crystal X-ray analysis.

Our recent synthesis of polyaryl compounds[1–4] as well as that of Roberts *et al.*[5,6] employing excess amounts of substrates and catalyst, and sometimes elevated temperatures under Friedel–Crafts conditions revealed the synthetic utility of the technique. These results and our subsequent one-pot syntheses of novel indolylquinolines[7] of biological interest[8,9] and new indole analogues[10] from indoles have added a new dimension to Friedel–Crafts chemistry.[11–14] Our next target was using quinolines and isoquinolines as substrates. These heterocycles are in general resistant to Friedel–Crafts acylation.[15] Surprisingly, under our experimental conditions good yields of novel functionalized pyridoquinolines and pyridoisoquinolines were obtained in one step. This new synthetic approach to such unique pyridoquinolines is attractive for its simplicity and possible general applicability.

The initial study involved the use of quinoline (**1**), 6-methyl-, and 6-methoxyquinolines (**2**,**3**) as substrates, dichloroacetyl chloride as acylating agent and anhydrous aluminium chloride as the catalyst. The use of excess amounts of the substrates and the catalyst and application of elevated temperature were obligatory for the success of the synthesis. Nitrobenzene was used as the solvent and the ratio 1 : 1 : 0.4 was maintained for the substrate, the catalyst and the acylating agent.[16] Purification by column chromatography over silica gel yielded the compounds (**4**–**6**) as single isolable products in good yields (66–75%). Elemental analysis, UV, IR, NMR and mass spectral data[16] of the products disclosed that these were not usual acylated products but novel compounds generated through a unique way of formation. However, the spectral data appeared to be inadequate for unambiguous determination of the structures. Single-crystal X-ray analysis was performed for unambiguous elucidation of the structure of **5**,[17] and the compounds **4** and **6** which are similar to **5** in their spectral characteristics, could also be described as shown. The ORTEP[18] drawing of the molecular structure of compound **5** is shown in Fig. 1.



1 R=H
2 R=Me
3 R=OMe



4 R=H
5 R=Me
6 R=OMe

Thus the reaction producing the compounds 2,4-dichloro-3-hydroxy-1*H*-pyrido[1,2-*a*]quinolin-1-one (**4**), 2,4-dichloro-3-hydroxy-8-methyl-1*H*-pyrido[1,2-*a*]quinolin-1-one (**5**) and 2,4-dichloro-3-hydroxy-8-methoxy-1*H*-pyrido[1,2-*a*]quinolin-1-one (**6**) seemed to be an attractive method for the synthesis of such heterocycles.

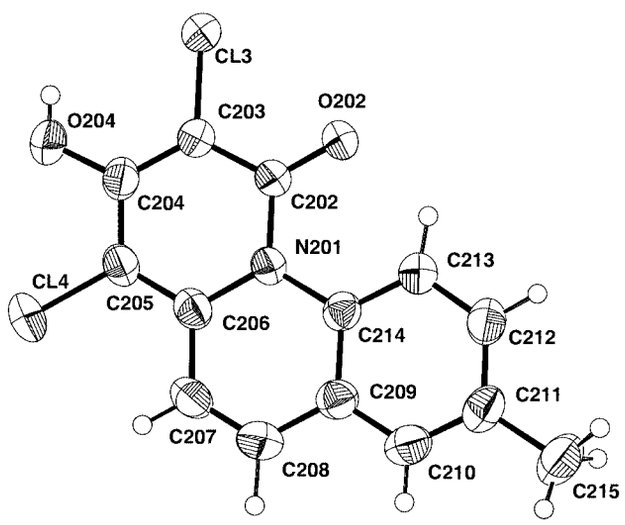
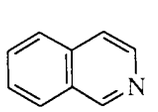
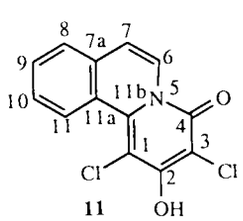


Fig. 1 The ORTEP drawing of the molecular structure of 2,4-dichloro-3-hydroxy-8-methyl-1*H*-pyrido[1,2-*a*]quinolin-4-one (**5**).

The mechanism for the formation of pyridoquinolines and pyridoisoquinolines is obscure. However, a mechanism for the formation of the pyridoquinolines may be proposed as exemplified for the substrate, 6–methylquinoline (**2**) (Scheme 1). Initial acylation of the quinoline nitrogen produces a species **7** which in its enolic form can undergo cycloaddition with dichloroketene (generated from the acid chloride and quinoline[19]) to produce the intermediate **8**. Loss of a proton and a molecule of HCl may subsequently generate **9** which presumably loses a Cl^+ ion with the assistance of $AlCl_3$ to form an extended conjugation, leading after hydrolysis to **5**. It may be noted that ketenes usually undergo [2 + 2] cycloadditions; however some examples of [4 + 2] cycloaddition are also known.[20,21]



10



11

To test the generality of the reaction the next substrate selected was isoquinoline **10** with the acylating agent, the catalyst as well as the solvent remaining the same. However,

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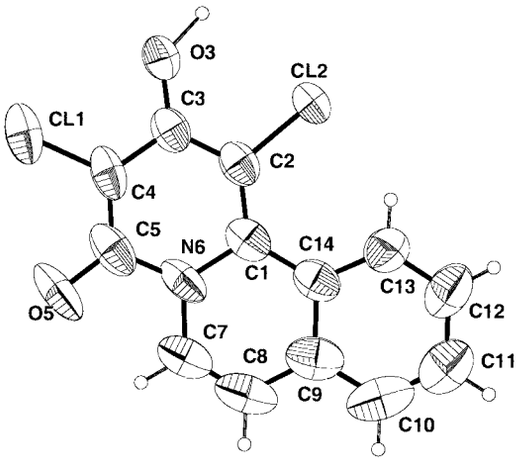
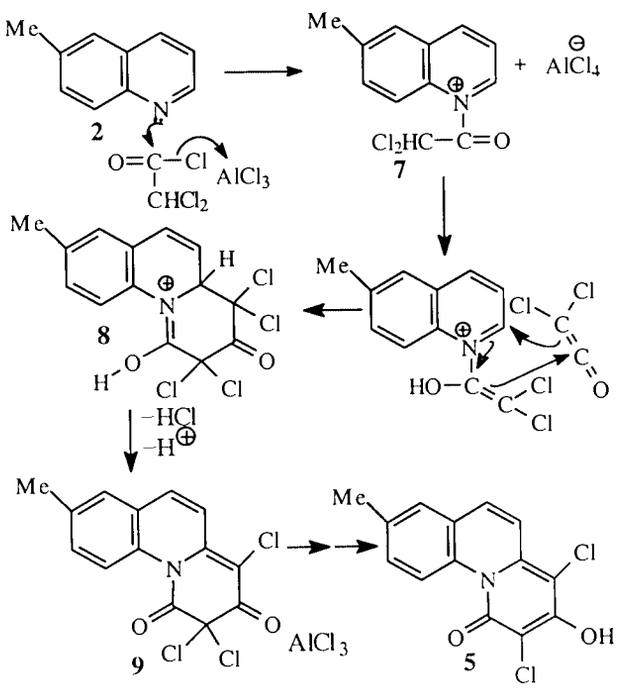


Fig. 2 The ORTEP drawing of the molecular structure of 1,3-dichloro-2-hydroxy-4*H*-pyrido[2,1-*a*]isoquinolin-4-one (**11**).



Scheme 1

unlike quinoline, isoquinoline has two sp^2 carbon atoms adjacent to the N-atom and as such two products, 1,3-dichloro-2-hydroxy-4*H*-pyrido[2,1-*a*]isoquinolin-4-one (**11**) and 1,3-dichloro-2-hydroxy-4*H*-pyrido[1,2-*b*]isoquinolin-4-one (**12**) would be expected to be formed. However, compound **11** was isolated as the major product (yield 66%)[22] and its structure was elucidated unambiguously by single-crystal X-ray analysis.[23] The ORTEP[18] drawing of the molecular structure of **11** is shown in Fig. 2.

The product **12** could not be isolated in a pure form although its formation could be inferred from the ^{1}H NMR characteristics of a very small impure fraction. The poor yield of **12** may probably be attributed to its structural instability.

In conclusion, we have developed a new method for the synthesis of functionalized pyridoquinolines from quinolines and pyridoisoquinolines from isoquinolines with the prospect of expanding it to other similar aromatic heterocycles as substrates. Thus this annelation to quinolines and isoquinolines provides an entirely new route for the one-step preparation of potential pyridoquinolines and pyridoisoquinolines.

It may be mentioned that the quinolizine ring system occurs in a number of bioactive alkaloids.[24] This method should provide an easy access to these alkaloids using suitable derivatives of quinoline and isoquinoline as substrates.

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16 The syntheses of the products were accomplished using the substrate, the catalyst and the acylating agent in the molar ratio 1:1:0.4. The substrate was dissolved in nitrobenzene, cooled to 15–18 °C followed by gradual addition of the catalyst. The acylating agent was slowly added with constant stirring. The reaction mixture was kept at ambient temperature (25 °C) for 1 h and then at 105 °C for 4 h. It was then kept overnight at ambient temperature, decomposed with ice–HCl mixture, extracted with ether or *n*-butanol, the solvent removed under reduced pressure and the product purified by column chromatography over silica gel followed by crystallization.
Compound 4. Mp 246–247 °C; yield 75%; λ_{max}(MeOH)/nm 401 (ε/dm^3 mol^{-1} cm^{-1} 27082); ν_{max}(KBr)/cm^{-1} 3140, 1634, 1609, 1548, 1443, 1318, 1272, 1180, 1120, 880, 810, 760; δ_H (300 MHz; DMSO-d_6; Me_4Si) 9.53 (1H, d, *J* 8.5 Hz, 10–H), 7.50–7.80 (5H, m); δ_C (75 MHz; DMSO-d_6; Me_4Si) 159.0 (C1), 104.4 (C2), 156.3 (C3), 101.3 (C4), 119.0 (C5), 132.0 (C6), 124.8 (C6a), 126.5 (C7), 128.2, 128.8 (C8, C9), 121.4 (C10), 135.0, 136.0 (C10a, 4a); *m*/*z* (EI) 281 (M^+ + 2, 68%), 279 (M^+, 100) (Found: C, 55.69; H, 3.28; N, 5.04. $C_{13}H_7Cl_2NO_2$ requires C, 55.74; H, 3.23; N, 5.00%).
Compound 5. Mp 249–250 °C; yield 68%; λ_{max}(MeOH)/nm 400 (ε/dm^3 mol^{-1} cm^{-1} 27952); ν_{max}(KBr)/cm^{-1} 3150, 1630, 1608, 1555, 1455, 1323, 1231, 1145, 1105, 1042, 860, 820, 800, 762; δ_H (300 MHz; DMSO-d_6; Me_4Si) 9.44 (1H, d, *J* 9 Hz, 10-H), 7.65 (1H, d, *J* 9.6 Hz), 7.60 (1H, d, *J* 9.6 Hz) (6-H, 5-H), 7.54 (1H, d, *J* 1.8 Hz, 7-H), 7.39 (1H, dd, *J* 1.8, 9 Hz, 9-H), 2.41 (3H, s, 8-Me); δ_C (75 MHz; DMSO-d_6; Me_4Si) 158.8 (C1), 104.3 (C2), 156.1 (C3), 101.0 (C4), 118.8 (C5), 132.0 (C6), 124.7 (C6a), 127.8 (C7), 133.0 (C8), 121.2 (C9), 129.8 (C10), 135.9, 136.0 (C10a, C4a), 20.1 (Me); *m*/*z* (EI) 295 (M^+ + 2, 67%), 293 (M^+, 100) (Found: C, 57.20; H, 3.03; N, 4.74. $C_{14}H_9Cl_2NO_2$ requires C, 57.16; H, 3.08; N, 4.76%).
Compound 6. Mp 218–219 °C; yield 67%; λ_{max}(MeOH)/nm 402 (ε/dm^3 mol^{-1} cm^{-1} 27022); ν_{max}(KBr)/cm^{-1} 3592, 3440, 2948, 1645, 1520, 1470, 1049, 861, 795; δ_H (300 MHz; DMSO-d_6; Me_4Si) 9.57 (1H, d, *J* 9.6 Hz, 10-H), 7.74 (1H, d, *J* 9.6 Hz), 7.68 (1H, d, *J* 9.6 Hz) (6-H, 5-H), 7.35 (1H, d, *J* 3 Hz, 7-H), 7.19 (1H, dd, *J* 3, 9.6 Hz, 9-H), 3.88 (3H, s, 8-OMe); δ_C (75 MHz; DMSO-d_6; Me_4Si) 158.6 (C1), 104.3 (C2), 155.8 (C3), 100.9 (C4), 116.2 (C5), 132.0 (C6), 126.4 (C6a), 110.1 (C7), 156.7 (C8), 119.3 (C9), 123.0 (C10), 129.0, 135.6 (C10a, C4a); *m*/*z* (EI) 311 (M^+ + 2, 67%), 309 (M^+, 100) (Found: C, 54.38; H, 2.90; N, 4.47. $C_{14}H_9Cl_2NO_3$ requires C, 54.34; H, 2.94; N, 4.51%).
17 **Crystal data of 5.** $C_{14}H_9Cl_2NO_2$, M_r = 294.12, space group monoclinic $P2_1/a$. Crystals were obtained from solution in MeOH. The specimen used for X-ray experiments had dimensions of

0.72 × 0.42 × 0.20 mm. Lattice constants (Å, degrees) a = 22.123 (3), b = 7.040 (1), c = 15.937(3), β = 92.8 (1), cell volume V = 2479.2 Å^3, formula units/cell Z = 8, X-ray density ρ_x = 1.576 g cm^{-3}, number of independent reflections 4608, unobserved ($F_o < 4\sigma(F_o)$) 174, linear absorption coefficient μ(Cu-Kα) = 46.87 cm^{-1}, R_1 = 0.041, wR_2 = 0.138. CCDC reference number 207/458. See http://www.rsc.org/suppdata/p1/b0/b004444j for crystallographic files in .cif format.

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22 **Compound 11.** Mp 249–250 °C, yield 66%; λ_{max}(MeOH)/nm 390 (ε/dm^3 mol^{-1} cm^{-1} 27016); ν_{max}(KBr)/cm^{-1} 3420, 1615, 1560, 1470, 1400, 1265, 800; δ_H (300 MHz; DMSO-d$_6$; Me$_4$Si) 9.35 (1H, d, *J* 8.5 Hz, 11-H), 8.63 (1H, d, *J* 7.6 Hz, 6-H), 7.25 (1H, d, *J* 7.6, 7-H), 7.62–7.83 (3H, m); δ_C (75 MHz; DMSO-d$_6$; Me$_4$Si) 101.7 (C1), 154.8 (C2), 102.4 (C3), 157.8 (C4), 131.2 (C6), 113.8 (C7), 124.3 (C7a), 126.8 (C8), 127.2, 128.3 (C9, C10), 122.9 (C11), 135.5 (C11a), 132.5 (C11b); *m*/*z* (EI) 281 (M$^+$ + 2, 67%), 279 (M$^+$, 100) (Found: C, 55.70; H, 3.26; N, 4.96. $C_{13}H_7Cl_2NO_2$ requires C, 55.74; H, 3.23; N, 5.00%).

23 **Crystal data of 11.** $C_{13}H_7Cl_2NO_2$, M_r = 280.10, space group monoclinic $P2_1/c$. Crystals were obtained from solution in MeOH. The specimen used for X-ray experiments had dimensions of 0.38 × 0.18 × 0.04 mm. Lattice constants (Å, degrees) a = 5.539 (5), b = 16.57 (1), c = 12.285 (9), β = 96.54 (7), cell volume V = 1120.2 Å^3, formula units/cell Z = 4, X-ray density ρ_x = 1.661 g cm^{-3}, number of independent reflections 1668, unobserved ($F_o < 4\sigma(F_o)$) 187, linear absorption coefficient μ(Cu-Kα) = 51.54 cm^{-1}, R_1 = 0.096, wR_2 = 0.243. CCDC reference number 207/458. See http://www.rsc.org/suppdata/p1/b0/b004444j/ for crystallographic files in .cif format.

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