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Unexpected synthesis of azepino[4,3,2-*cd*]indoles from 4-aminoindoles

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Abstract

Unexpected regioselectivity for the Skraup-Doebner-Von Miller reaction was observed during the synthesis of quinolines from 4-aminoindoles and acetone in the presence of hydrochloric acid as a catalyst. The products were unambiguously assigned as 1-alkyl-3,5,5-trimethyl-5,6-dihydro-1*H*-azepino[4,3,2-*cd*]indoles instead of 2,2,4-trimethyl-2,7-dihydro-1*H*-pyrrolo[2,3-*h*]quinolones based on NMR spectroscopy and X-ray crystallographic analysis.

Keywords: indoles, 4-aminoindoles, azepino[4,3,2-*cd*]indoles, Skraup-Doebner-Von Miller synthesis

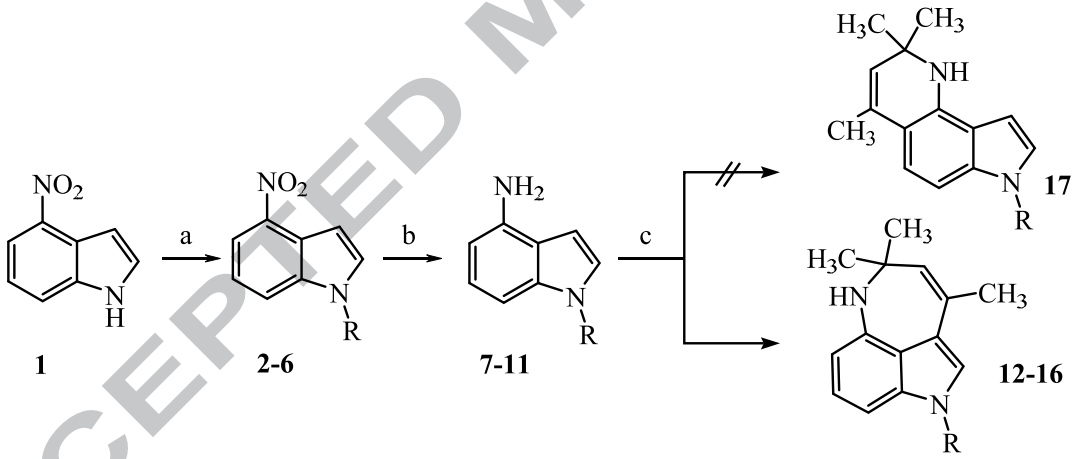
Introduction

The indole motif is arguably one of the most significant heterocycles since they are found in numerous natural products and bioactive molecules.[1,2] Among naturally occurring indole alkaloids, 3,4-fused indoles (in which position 3 of the indole is bridged to position 4) have been considered as attractive synthetic targets due to their biological activities[3] and challenging synthesis. Various strategies have been developed for the construction of 3,4-fused tricyclic indoles. For example, 3,4,5,6-tetrahydro-1*H*-azepino[4,3,2-*cd*]indole was synthesized in seven steps from 4-nitroindole.[4-6] Substituted azepino[4,3,2-*cd*]indoles have also been obtained *via* an intramolecular Larock indolization reaction,[7] substitution of cyclic Baylis–Hillman adducts with indoles,[8,9] and the three-component condensation reaction of isatins, indol-4-amines, and Meldrum's acid.[10] Notably, a series of novel 3,4,5,6-tetrahydro-1*H*-azepino[4,3,2-*cd*]indoles have been identified as selective V2 receptor antagonists.[11]

Herein, we report an efficient synthetic approach to novel 1-alkyl-3,5,5-trimethyl-5,6-dihydro-1*H*-azepino[4,3,2-*cd*]indoles using the Skraup-Doebner-Von Miller reaction conditions.

Results and discussion

Starting 4-nitroindole **1** was alkylated to give 1-substituted 4-nitroindoles **2**–**6**[12-14] using the corresponding alkyl halides and NaH in DMF at room temperature.[15-17] Treatment of compounds **2**–**6** under Bechamp reduction conditions resulted in the formation of 4-aminoindoles **7**–**11** in excellent yields. 4-Aminoindoles have been widely used for the synthesis of polycyclic systems including 2-phenylpyrroloquinolin-4-ones,[17,18] pyrrolo[3,2-*a*]phenazines[19] and pyroloquinolines.[20] However, in these cases intramolecular cyclization was performed *via* the indole C-5 position. The Skraup-Doebner-Von Miller quinoline synthesis reaction[21] of 4-aminoindoles **7**–**11** with acetone in the presence of conc. hydrochloric acid as a catalyst was examined by heating at reflux for 4 h. To our surprise, 3,5,5-trimethyl-5,6-dihydro-1*H*-azepino[4,3,2-*cd*]indoles **12**–**16** were obtained instead of the expected 2,2,4-trimethyl-2,7-dihydro-1*H*-pyrrolo[2,3-*h*]quinolines **17**.[22]



2. R = CH_3, 95%
3. R = $CH(CH_3)_2$, 92%
4. R = $CH_2CH(CH_3)_2$, 84%
5. R = $(CH_2)_2CH(CH_3)_2$, 86%
6. R = CH_2Ph, 93%

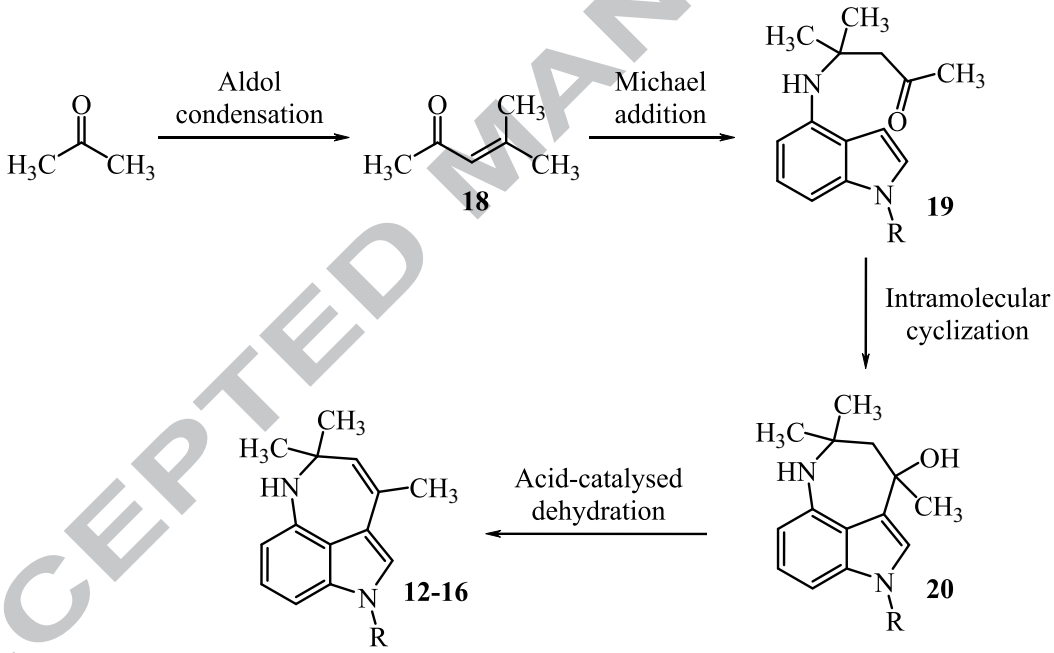
7. R = CH_3, 85%
8. R = $CH(CH_3)_2$, 89%
9. R = $CH_2CH(CH_3)_2$, 92%
10. R = $(CH_2)_2CH(CH_3)_2$, 81%
11. R = CH_2Ph, 93%

12. R = CH_3, 86%
13. R = $CH(CH_3)_2$, 89%
14. R = $CH_2CH(CH_3)_2$, 82%
15. R = $(CH_2)_2CH(CH_3)_2$, 76%
16. R = CH_2Ph, 91%

Scheme 1. Synthesis of azepino[4,3,2-*cd*]indoles **12**-**16**. Reagents and conditions: (a) **1** (50 mmol), NaH (50 mmol), R-Hal (55 mmol), DMF (50 mL), 4 h, r.t., 84–95%; (b) **2**–**6** (40 mmol), Fe (60 mmol), conc. HCl (5 mL), EtOH (100 mL), reflux, 1 h, 81–93%; (c) **7**–**11** (4 mmol), acetone (5 mL), conc. HCl (1 mL), reflux, 4 h, 76–91%.

The structures of azepino[4,3,2-*cd*]indoles **12–16** were confirmed by NMR spectral data and single crystal X-ray analysis. The ^{1}H NMR spectra showed the characteristic sequence of four aromatic 3,4-fused indole protons (H-2, H-5, H-6 and H-7), while the ^{1}H NMR and ^{13}C NMR spectra also showed typical signals for an annulated 2,2,4-trimethyl-1,2-dihydropyridine type ring (ESI).

In our opinion, the reaction pathway initially proceeds *via* the acid catalysed self aldol condensation of acetone to give α,β-unsaturated ketone **18**, followed by Michael addition of 4-aminoindole to yield aryl amino ketone **19**. Subsequent intramolecular cyclization leads to compound **20**, which after acid catalysed dehydration yields the target 3,5,5-trimethyl-5,6-dihydro-1*H*-azepino[4,3,2-*cd*]indole derivatives **12–16** (Scheme 2).



Scheme 2. Plausible pathway for the formation of 5,6-dihydro-1*H*-azepino[4,3,2-*cd*]indoles **12–16** .

The structure of compound **13** was confirmed by single crystal X-ray crystallography (Fig. 1, ESI, Fig. S1 and Tables S1–S3).[23] Two symmetry-independent molecules form the asymmetric part of the unit cell. The C10–C11 bond lengths (1.333(2) Å and 1.344(3)/1.332(8) Å) in the two independent molecules confirms the presence of a double bond between these atoms (ESI, Fig. S1).

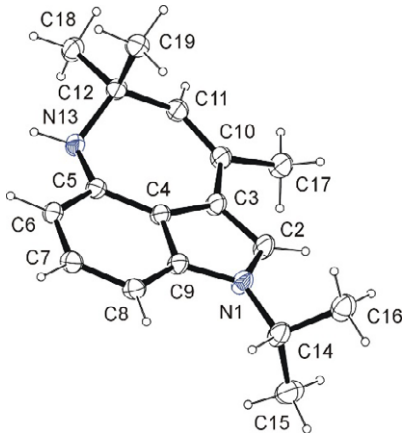


Figure 1. ORTEP view of one of the two symmetry independent molecules of **13** showing the atomic labeling scheme.

Conclusion

In summary, we have developed an efficient procedure for the synthesis of 5,6-dihydro-1*H*-azepino[4,3,2-*cd*]indole derivatives *via* the Skraup-Doebner-Von Miller quinoline synthesis reaction conditions.

Supplementary data

Analytical and spectral data for the synthesized compounds as well as single crystal X-ray data for compound **13**.

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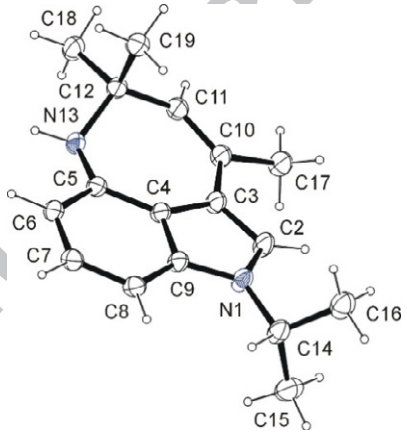
22. *General procedure for the synthesis of 1-alkyl-3,5,5-trimethyl-5,6-dihydro-1H-azepino[4,3,2-cd]indoles* **12-16**. Conc. HCl (1 mL) was added to a solution of 4-aminoindole **7-11** (5 mmol) in acetone (5 mL) and heated at reflux for 4 h. Upon reaction completion (TLC), the solvent was removed under vacuum and the reaction mixture neutralized by the addition of 3N KOH then diluted with CH_2Cl_2 (10 mL). The organic phase was washed with brine (10 mL) and water (2×10 mL), dried over magnesium sulfate and the solvent evaporated. The crude product was purified by silica gel column chromatography using a

petroleum ether and EtOAc (9:1) as eluent. *1,3,5,5-Tetramethyl-5,6-dihydro-1H-azepino[4,3,2-cd]indole* (**12**). Grey solid, mp 108–109 ºC, yield 86%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02 (t, 1H, J = 7.8 Hz, H-8), 6.85 (s, 1H, H-2), 6.72 (d, 1H, J = 8.1 Hz, H-7), 6.28 (d, 1H, J = 7.5 Hz, H-9), 5.43 (s, 1H, H-4), 3.68 (s, 3H, CH_3-1), 2.06 (s, 3H, CH_3-3), 1.37 (s, 6H, CH_3-5). ^{13}C NMR (100 MHz, DMSO-d_6) δ 143.26, 137.94, 129.93, 127.82, 124.23, 122.80, 115.49, 115.44, 104.87, 99.09, 53.09, 32.49, 30.35, 21.74. LC-MS calculated for $C_{15}H_{18}N_2$ $[M + H]^+$ 227.32, found 227.1 (100%). Calcd. for $C_{15}H_{18}N_2$: C, 79.61; H, 8.02; N, 12.38; Found: C, 79.90; H, 8.20; N, 12.50%.

23. Crystallographic data for **13**: Empirical formula: $C_{17}H_{22}N_2$, formula weight: 508.73, colourless block crystals, crystal system: monoclinic, space group: $P2_1/n$, a = 8.98861(10), b = 7.86603(8), c = 19.4785(2) Å, β = 99.1695(10)°, V = 2902.47(4) Å^3, Z = 8 (Z' = 2), D_{calc} = 1.580 g/cm^3. A colourless crystal (CH_3OH) (0.20 x 0.12 x 0.06 mm) was used to record 36589 (CuKα radiation, θ_{max} = 76.5°) intensities on a SuperNova Dual A diffractometer. The supplementary crystallographic data of **13** have been deposited at the Cambridge Crystallography Data Centre (CCDC) as supplementary publication CCDC 1523501. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

Graphical abstract



Highlights for "Unexpected synthesis of azepino[4,3,2-*cd*]indoles from 4-aminoindoles"

by Olexandr Halaiev, Myroslav Garazd, Andrzej Gzella, Roman Lesyk

- 4-Aminoindoles were utilized for the synthesis of azepino[4,3,2-*cd*]indoles.
- Regioselective Skraup-Doebner-Von Miller reaction conditions were used.
- 5 examples in up to 76% yield.