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A New Synthetic Entry to the Indolo[2,3-*a*]quinolizidine System. Electrophilic Cyclizations on the Indole Ring from 2-(2-Piperidyl)indoles

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Abstract: A new synthetic route to the indolo[2,3-*a*]quinolizidine system, involving the Pd(0)-catalyzed cross-coupling of a 2-indolylzinc derivative with a 2-halopyridine, stereoselective hydrogenation of the pyridine ring, and electrophilic cyclization upon the indole 3-position from the resulting 2-(2-piperidyl)indole, is reported.

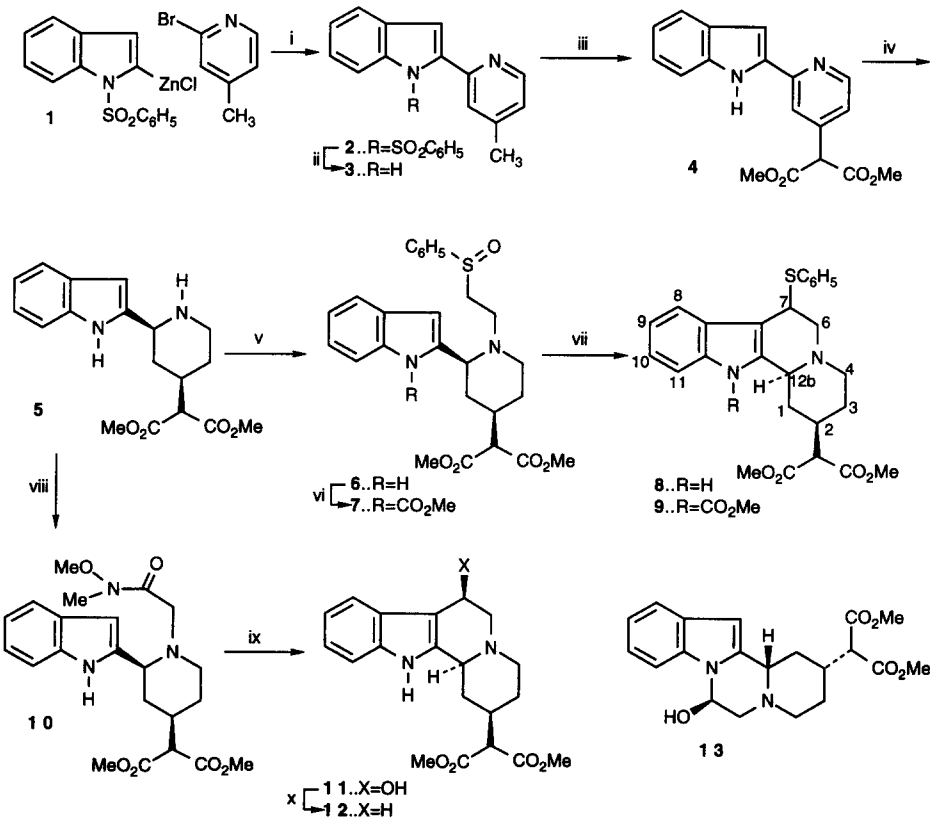
The indolo[2,3-*a*]quinolizidine ring system is present in a large number of indole alkaloids belonging to several structural types, such as Corynanthean, Vallesiachotaman, and Eburnan.[1] This has stimulated the development of a number of synthetic approaches, most of them involving either the closure of ring C by formation of C_{12a}-C_{12b} bond or the construction of the piperidine ring in the key step.[2] However, the strategy based on the elaboration of ring C by cyclization upon the indole 3-position (bond formed C_7-C_{7a}) from 2-(2-piperidyl)indoles bearing an appropriately functionalized two-carbon substituent on the piperidine nitrogen has been little explored. Some years ago we reported the first construction of the indolo[2,3-*a*]quinolizidine system by the foregoing strategy: treatment of a 2-[1-(benzenesulfonyl)-2-indolyl]-1-(2-hydroxyethyl)-4-piperidone derivative with potassium *tert*-butoxide brought about the desired cyclization.[3]

We present here a new synthetic entry to the indolo[2,3-*a*]quinolizidine system. The synthesis takes advantage of our simple and general method for the preparation of 2-(2-pyridyl)indoles based on the palladium(0)-catalyzed cross-coupling of 1-(benzenesulfonyl)-2-indolylzinc chloride (**1**) with 2-halopyridines[4] and involves an electrophilic cyclization upon the indole 3-position in the key synthetic step.

Thus, pyridylindole **2**,[5] prepared in 92% yield from the indolylzinc derivative **1** and 2-bromo-4-methylpyridine,[4] was efficiently converted to the *cis* piperidylindole **5**[6] by deprotection of the indole ring followed by bis(methoxycarboxylation) and catalytic hydrogenation, as outlined in Scheme 1. It is worth mentioning that hydrogenation of the pyridine ring took place stereoselectively to give a *cis*-2,4-disubstituted piperidine.

Closure of the C ring was first investigated by using the Pummerer reaction.[7] The interest of this approach lies in the fact that, in contrast with Pummerer cyclizations either upon the indole 2-position[8] or the indole 3-position in 3-substituted indoles,[9] which have received considerable synthetic attention, to our

knowledge, there are no precedents of synthetically useful Pummerer cyclizations upon the indole 3-position in 3-unsubstituted indoles.[7,8]



Scheme 1. *Reagents and conditions*: i) $PdCl_2(Ph_3P)_2$, DIBAH, THF, reflux, 92%; ii) NaOH, EtOH-H_2O, reflux, 96%; iii) LDA, THF, then $ClCO_2CH_3$, 25°C, 64%; iv) H_2, PtO_2, EtOH, 60%; v) CH_2=CHS(O)C_6H_5, MeOH, reflux, 60%; vi) NaH, TMEDA, $NCCO_2CH_3$, 25°C, 75%; vii) TFAA, CH_2Cl_2, 25°C, 28% (from **6**); TFAA, TFA, CH_2Cl_2, reflux, 45% (from **7**); viii) $ClCH_2CON(OMe)Me$, NaI, K_2CO_3, MeCN, 45°C, 92%; ix) Red-Al®, toluene, -25°C, 30%; x) Et_3SiH, TFA, CH_2Cl_2, reflux, 70%.

The required β-amino sulfoxide **6** (epimeric mixture at the sulfur atom) was prepared by alkylation of the piperidine nitrogen of **5** with phenyl vinyl sulfoxide. Treatment of **6** with TFAA (2 equiv) at room temperature led to a complex mixture from which the expected tetracyclic compound **8** (the 7H-β epimer was predominant) was isolated in 28% yield. The *N*-unsubstituted piperidine **5**, resulting from hydrolysis of the exocyclic iminium ion formed through the equilibrium thionium ion-vinyl sulfide (an enamine)-iminium ion, was also isolated to a considerable extent (15-20% yield).[10] Probably, under the reaction conditions the indole ring is partially protonated and the above equilibrium leading to the exocyclic iminium ion competes with cyclization of the initially formed thionium ion.

The above modest result was improved by carrying out the TFAA-induced Pummerer reaction in the presence of trifluoroacetic acid, once the indole ring was protected as a *N*-methoxycarbonyl derivative. Thus,

treatment of sulfoxide **7** with TFAA (4 equiv) and TFA (4 equiv) in refluxing CH_2Cl_2 afforded indoloquinolizidine **9** (nearly equimolecular mixture of epimers at C-7)[11] as the only isolable product (45% yield). Under these conditions, the piperidine nitrogen is protonated, thus preventing the formation of the exocyclic iminium ion and avoiding the undesirable competing *N*-dealkylation.

The second procedure we planned to investigate was the cyclization of the *N*-(2-oxoethyl) derivative of the piperidylindole **5**.[12] The preparation of this aldehyde was attempted by Red-Al® reduction of *N*-methoxy-*N*-methylamide **10**, which was easily accessible (92% yield) by alkylation of piperidylindole **5** with *N*-methoxy-*N*-methylchloroacetamide. However, rather unexpectedly, treatment of **10** with Red-Al® led directly to a mixture of indoloquinolizidine **11**[13] (35% yield) and tetracycle **13** (30% yield). The initially formed aldehyde undergoes smooth cyclization, presumably promoted by the alane generated during the process. Finally, both Raney Ni desulfurization of sulfide **8** and reduction of alcohol **11** with Et_3SiH-TFA gave the known[14] indoloquinolizidine **12**.

The strategy developed here, combined with the flexible method previously reported[4] for the preparation of the starting 2-(2-pyridyl)indoles, provides a short and valuable synthetic entry to the indolo[2,3-*a*]quinolizidine system that may be applicable to the synthesis of *Corynanthe* alkaloids.

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3. (a) Rubiralta, M.; Diez, A.; Bosch, J.; Solans, X. *J. Org. Chem.* **1989**, *54*, 5591. (b) For further examples of this type of cyclization, see: Rubiralta, M.; Diez, A.; Vila, C. *Tetrahedron* **1990**, *46*, 4443. (c) For a related approach involving the use of 3-(2-piperidyl)indole derivatives followed by rearrangement of the intermediate spiroindolenine, see: Diez, A.; Vila, C.; Sinibaldi, M.-E.; Troin, Y.; Rubiralta, M. *Tetrahedron Lett.* **1993**, *34*, 733.
4. Amat, M.; Hadida, S.; Bosch, J. *Tetrahedron Lett.* **1993**, *34*, 5005.
5. All yields are from material purified by column chromatography. Satisfactory analytical and/or spectral data were obtained for all new compounds.
6. **5**: ^{1}H-NMR ($CDCl_3$) δ 1.32 (m, 1H); 1.42 (q, *J*= 11.7 Hz, 1H); 1.75 (dm, *J*= 12.7 Hz, 1H); 2.02 (dm, *J*= 11.7 Hz, 1H); 2.35 (m, 1H); 2.84 (td, *J*= 12.2, 2.6 Hz, 1H); 3.20 (dm, *J*= 12.2 Hz, 1H); 3.25 (d, *J*= 9.0 Hz, 1H); 3.72 (s, 3H); 3.75 (s, 3H); 3.93 (dd, *J*= 11.3, 2.6 Hz, 1H); 6.34 (s, 1H); 7.00-7.20 (m, 2H); 7.32 (d, *J*= 7.8 Hz, 1H); 7.54 (d, *J*= 7.3 Hz, 1H); 8.73 (s, 1H).^{13}C-NMR ($CDCl_3$) δ 29.8 (C-5); 36.3 (C-4);

36.8 (C-3); 45.9 (C-6); 52.4 (2 CH_3O); 54.6 (CH); 57.2 (C-2); 98.6 (C-3'); 110.9 (C-7'); 119.7 (C-4'); 120.4 (C-5'); 121.6 (C-6'); 128.0 (C-3'a); 136.0 (C-7'a); 141.0 (C-2'); 168.8 (2 C=O). Picrate: m.p. 156-158°C (EtOH).

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11. **9** (7H-α epimer): ^{1}H-NMR ($CDCl_3$) δ 1.36 (ddd, *J*= 12.4, 11.3, 10.7 Hz, 1H); 1.40-1.56 (m, 2H); 1.97 (dm, *J*= 12.4 Hz, 1H); 2.46 (m, 1H); 2.85 (dd, *J*= 12.3, 3.0 Hz, 1H); 3.15 (m, 1H); 3.20 (d, *J*= 8.3 Hz, 1H); 3.21 (m, 1H); 3.45 (dd, *J*= 12.3, 3.5 Hz, 1H); 3.71 (s, 3H); 3.72 (s, 3H); 4.06 (s, 3H); 4.43 (dd, *J*= 10.7, 1.6 Hz, 1H); 4.58 (t, *J*= 3.2 Hz, 1H); 7.20 (m, 5H); 7.53 (m, 2H); 7.63 (dm, *J*= 7.2 Hz, 1H); 8.13 (dm, *J*= 7.3 Hz, 1H). ^{13}C-NMR ($CDCl_3$) δ 25.1 (C-3); 30.1 (C-1); 36.9 (C-2); 42.5 (C-7); 51.0 (C-4); 52.4 (MeO); 53.7 (MeO); 54.3 (C-6); 57.1 (CH); 57.2 (C-12b); 111.4 (C-7a); 115.6 (C-11); 119.3 (C-8); 123.1 (C-9); 124.5 (C-10); 125.6 (C-7b); 135.8 (C-12a); 136.4 (C-11a); 127.1 (C-*p*); 128.6 (C-*ipso*); 129.0 (C-*o*); 132.0 (C-*m*); 151.7 (C=O); 168,5 (C=O). **9** (7H-β epimer): 1.05 (td, *J*= 12.5, 11.0 Hz, 1H); 1.45-1.65 (m, 2H); 2.08 (dm, *J*= 12.5 Hz, 1H); 2.38 (m, 1H); 2.77 (td, *J*= 12.5, 3.5 Hz, 1H); 3.05 (dm, *J*= 12.5 Hz, 1H); 3.14 (d, *J*= 8.5 Hz, 1H); 3.12-3.25 (m, 2H); 3.73 (s, 3H); 3.74 (s, 3H); 3.85 (dm, *J*= 11.0 Hz, 1H); 4.03 (s, 3H); 4.43 (m, 1H); 7.20-7.35 (m, 5H); 7.42 (m, 2H); 7.75 (dm, *J*= 7.2 Hz, 1H); 8.10 (dm, *J*= 7.3 Hz, 1H). ^{13}C-NMR ($CDCl_3$) δ 27.8 (C-3); 33.6 (C-1); 36.9 (C-2); 42.7 (C-7); 52.4 (MeO); 53.8 (MeO); 54.5 (C-6); 55.7 (C-4); 57.4 (CH); 59.1 (C-12b); 115.3 (C-11); 119.7 (C-8); 123.1 (C-9); 124.5 (C-10);127.3 (C-*p*); 128.8 (C-*o*); 132.9 (C-*m*); 151.9 (C=O); 168.7 (C=O).
12. For the use of this strategy in the construction of the seven-membered C ring of *Iboga* alkaloids, see: (a) Sundberg, R. J.; Amat, M.; Fernando, A. *J. Org. Chem.* **1987**, *52*, 3151. (b) Sundberg, R. J.; Gadamasetti, K. G. *Tetrahedron* **1991**, *47*, 5673.
13. **11**: ^{1}H-NMR ($CDCl_3$) δ 1.35 (q, *J*= 12.0 Hz, 1H); 1.56 (qd, *J*= 12.0, 4.1 Hz, 1H); 1.73 (dm, *J*= 11.5 Hz, 1H); 2.22 (dm, *J*= 12.0 Hz, 1H); 2.37 (m, 1H); 2.48 (td, *J*= 11.5, 2.8 Hz, 1H); 2.73 (dd, *J*= 12.0, 2.6 Hz, 1H); 3.00 (dm, *J*= 11.5 Hz, 1H); 3.10 (dd, *J*= 12.0, 1.8 Hz, 1H); 3.20 (dd, *J*= 11.5, 2.2 Hz, 1H); 3.25 (d, *J*= 8.5 Hz, 1H); 3.77 (s, 3H); 3.78 (s, 3H); 4.88 (br s, 1H); 7.15 (m, 2H); 7.30 (m, 1H); 7.68 (m, 1H); 8.0 (br s, 1H). ^{13}C-NMR ($CDCl_3$) δ 29.4 (C-3); 33.1 (C-1); 35.8 (C-2); 52.5 (OCH_3); 54.5 (C-4); 56.7 (CH); 59.3 (C-12b); 61.5 (C-6); 62.0 (C-7); 110.8 (C-7a); 111.1 (C-11); 118.4 (C-8); 120.0 (C-9); 121.8 (C-10); 126.2 (C-7b); 136.0 (C-12a); 136.5 (C-11a); 168.7 (C=O).
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