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Synthesis of azepino[3,4*b*]indoles via the Plancher rearrangement

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ABSTRACT

The reaction of benzyl 3-formylpiperidine-1-carboxylate and aryl hydrazines under standard Fisher Indole conditions followed by reductive work-up affords azepino[3,4*b*]indoles in moderate to good yields. The products are proposed to be derived via a Plancher rearrangement [(a) Plancher, G. *Gazz. Chim. Ital.* **1898**, *28*, II, 374; (b) Plancher, G. *Atti. Accad. Lincei* **1900**, *9*, 5, 115; (c) Boyd-Barrett, H. S. *J. Chem. Soc.* **1932**, 321].

Indoles have an extremely diverse history in both medicinal and natural product chemistry. Interest has been driven toward it by the vast physiological activity this class of structures exhibits and its broad ranging chemical reactivity.[2] While investigating the preparation of spiroindoles, we isolated an unexpected product in good yields. Here we describe, a novel method for the synthesis of aryl substituted azepino[3,4*b*]indoles (Scheme 1). A mechanism is proposed and examples are presented to better understand the scope, limitations and potential for its broader application.

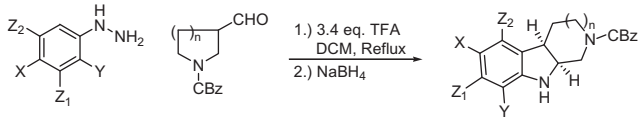
Representative [3,4*b*]-indoles were generated by the treatment of benzyl 3-formylpiperidine-1-carboxylate, aryl hydrazines and trifluoroacetic acid in refluxing dichloromethane. The intermediate indole was directly treated with sodium borohydride to afford the azepino[3,4*b*]indoles in 35–78% isolated yields.[3,4] The reaction is flexible in aryl substitution, as well as cyclic amines. The upper limit appeared to be azepane while the lower limit was pyrrolidine. No products were isolated while investigating the azetidine and azocane ring systems (Table 1).

Much of the previously reported work within this area of indoles has dealt with β-carbolines and the migratory aptitude of pendant substituents.[5] Typically these reactions occur under more forcing conditions, in contrast to the extremely mild conditions employed in this study.

To better understand a possible mechanism of product formation, the reaction was quenched prior to completion. 3,3-Spirocyclic indole (**12**) was isolated in modest yield and found to be quite stable[6] (Scheme 2).

The formation and eventual disappearance of intermediate spiroindolene could be monitored by GC/MS (Table 2). Rearrangement slowly progresses at room temperature (24 h) however; in refluxing DCM the rearrangement is complete after just 1 h (Scheme 3).

With the isolation and characterization of a reaction intermediate, two plausible mechanisms arose for the eventual product for-



Scheme 1. Synthesis of azepino[3,4*b*]indoles.

Table 1
Synthesis of substituted azepino[3,4*b*]indoles

Sl no.	X	Y	Z_1	Z_2	*n*	Yield[a] (%)
1	H	H	H	H	2	34
2	F	H	H	H	2	38
3	Me	H	H	H	2	35
4	Me	Me	H	H	2	69
5	Br	H	H	H	2	78[b]
6	H	H	F	H	2	21[c]
7	H	H	H	F	2	19[c]
8	H	H	H	H	1	59
9	H	H	H	H	3	65
10	H	H	H	H	4	0
11	H	H	H	H	0	0

[a] Reported yields are isolated and unoptimized. Alternative acidic conditions were not investigated[4] while looking at the rearrangements. Compounds are characterized by ^{1}H and MS.
[b] Crude isolated yield, single X-ray determined on derivative.
[c] Isolated from same reaction mixture.

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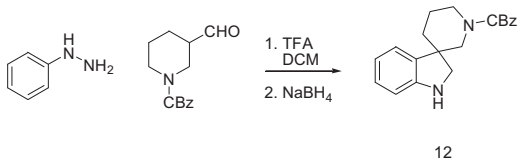


Scheme 2. 3,3-Spirocyclic products.

Table 2
Synthesis of substituted azepino[3,4*b*]indoles

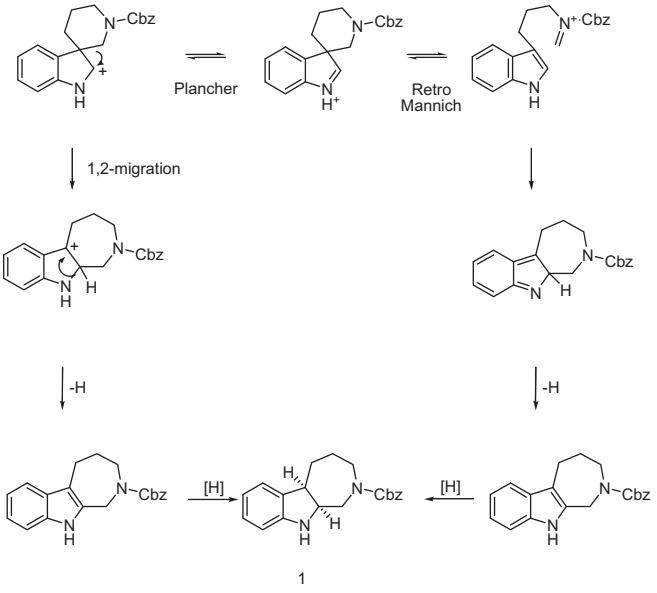
Time (h)	% Hydrazone (**13**)	% Spiroindole (**14**)	% Fused indole (**15**)
0	100	0	0
1	42	43	15
4	0	49	57
6.5	0	32	68
8.5	0	29	71
22.5	0	9	91
24	0	0	100

mation: a retro-Mannich pathway or a Plancher rearrangement (Scheme 4).[1]

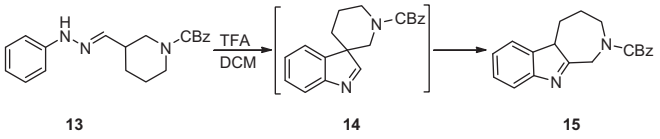
To distinguish the possible mechanistic pathways, the electron-deficient *N*-methanesulfonyl aldehyde (**16**) was submitted to typical reaction conditions (Scheme 5). The electron-withdrawing nature of the mesylate would be expected to disfavor retro-Mannich chemistry from occurring. Although the reaction did require extended reaction times, the major product isolated was once again the ring expanded indole (**17**)[7] which provides supportive evidence for a Plancher rearrangement pathway.

Based on these results, the proposed mechanism is depicted in Scheme 6.

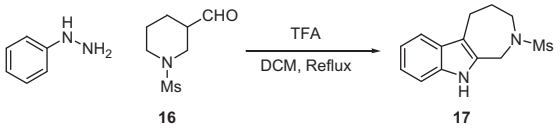
With a clearer understanding of product formation, work is continuing in an effort to improve yields as well as to expand upon the scope. The preparation of a variety of chiral piperidines, furans and thiophenes are currently the areas of active research. Future reports will detail these findings.



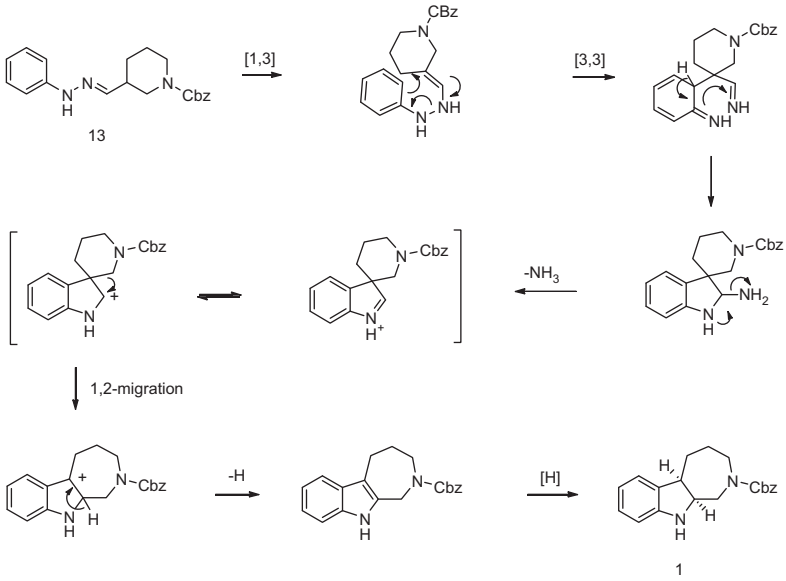
Scheme 4. Possible mechanism for product formation.



Scheme 3. Synthesis of azepino[3,4*b*]indoles.



Scheme 5. Synthesis of electronically biased system.



Scheme 6. Proposed mechanism of product formation.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.06.029.

References and notes

1. (a) Plancher, G. *Gazz. Chim. Ital.* **1898**, *28, II*, 374; (b) Plancher, G. *Atti. Accad. Lincei* **1900**, *9, 5*, 115; (c) Boyd-Barrett, H. S. *J. Chem. Soc.* **1932**, 321.
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3. Intermediate indoles could be isolated in fair to good yields prior to reduction.
4. *General experimental procedure for synthesis of azepino[3,4b]indoles:* A three neck round bottomed flask equipped with an overhead stirrer, an addition funnel and a reflux condenser was charged with DCM (1 L per 0.25 mol), phenyl hydrazine (1.0 equiv) and benzyl 3-formylpiperidine-1-carboxylate (1.0 equiv). Trifluoroacetic acid (3.4 equiv) was slowly added to the reaction mixture producing a slight exotherm. After complete addition the mixture was warmed to 40 °C overnight. The resultant darkened reaction mixture of (**1**) was carefully treated with $NaBH_4$ (1.5 equiv) followed by an additional 4 h of stirring at room temperature. The reaction mixture became orange in color. The reaction was checked for completion by GC/MS, and then carefully poured over a satd aq $NaHCO_3$ (1 L per 0.25 mol) and stirred till evolution of gas ceased. The layers are separated followed by extraction of the aqueous layer with an additional Et_2O (2×1 L per 0.25 mol). The combined organic layers were dried over $MgSO_4$ and concentrated to a thick dark oil which was purified by silica gel chromatography using 25% EtOAc/Hex as eluent. The clean fractions were combined, concentrated and crystallized from hexanes to afford the title compound (**1**). Alternatively the dark oil could be dissolved in Et_2O (1 L per 0.25 mol) followed by cooling to 0 °C. HCl gas was bubbled through the ether solution resulting in a thick slurry. The slurry was filtered to afford the title compound (**1**) as HCl salt.
   3,4,5,5a,10,10a-Octahydro-1H-azepino[3,4-b]indole-2-carboxylic acid phenyl ester (**1**): Yield 34%: mp (hexanes) 84–87 °C; ^{1}H NMR (300 MHz, CD_3OD) 7.36 (m, 4H), 6.92 (m, 2H), 6.45 (dd, 1H), 5.11 (dd, 2H), 4.16 (m, 1H), 4.00–3.75 (m, 3H), 3.42–3.09 (m, 4H), 3.05–2.98 (m, 1H), 2.00–1.54 (m, 5H). HRMS calcd for $C_{20}H_{22}N_2O_2$ $[M+H]^+$ 322.1681, found 322.1614.
   7-Fluoro-3,4,5,5a,10,10a-octahydro-1H-azepino[3,4-b]indole-2-carboxylic acid benzyl ester (**2**): Yield 38%; mixture of rotomers: mp (hexanes) 103–105 °C; ^{1}H (CD_3OD) 7.38 (m, 5H), 6.78 (dd, 1H), 6.62 (m, 1H), 6.42 (m, 1H), 5.11 (m, 2H), 4.19 (m, 1H), 4.0–3.75 (m, 2H), 3.45–3.02 (m, 3H), 2.05–1.56 (m, 5H). HRMS calcd for $C_{20}H_{21}FN_2O_2$ $[M+H]^+$ 340.1587, found 340.1649.
   7-Methyl-3,4,5,5a,10,10a-octahydro-1H-azepino[3,4-b]indole-2-carboxylic acid benzyl ester (**3**): Yield 78% crude: mixture of rotomers: mp (hexanes) 89–92 °C; ^{1}H (CD_3OD) 7.38–7.27 (m, 5H), 6.80 (m, 2H), 6.45 (dd, 1H) 5.20–4.99 (m, 2H), 4.22 (m, 1H), 4.02–3.02 (m, 6H), 2.27 (s, 3H), 2.05–1.56 (m, 4H). HRMS calcd for $C_{21}H_{24}N_2O_2$ $[M+H]^+$ 336.1838, found 336.1897.
   7,9-Dimethyl-3,4,5,5a,10,10a-octahydro-1H-azepino[3,4-b]indole-2-carboxylic acid benzyl ester (**4**): Yield 69%: mixture of rotomers: mp (hexanes) 143–145 °C; ^{1}H (CD3OD) 7.40 (m, 5H), 6.68 (s, 1H), 6.62 (ms 1H), 5.11 (m, 2H), 4.19–3.85 (m, 2H), 3.75 (m, 2H), 3.45–3.02 (m, 3H), 2.19 (d, 3H), 2.05 (d, 3H), 2.04–1.56 (m, 5H). HRMS calcd for C22H26N2O2 $[M+H]^+$ 350.1994, found 336.2085.
   7-Bromo-3,4,5,5a,10,10a-octahydro-1H-azepino[3,4-b]indole-2-carboxylic acid benzyl ester (**5**): Mp (hexanes) 128–133 °C; ^{1}H ($CDCl_3$) 7.31 (m, 4H), 7.21 (m, 2H), 7.05 (m, 1H), 6.38 (dd, 1H), 5.11 (m, 2H), 4.23 (m, 1H), 3.92–3.11 (m, 5H), 2.11–1.57 (m, 5H). HRMS calcd for C20H21BrN2O2 $[M+H]^+$ 400.0786, found 400.0773.
   (6/8)-Fluoro-3,4,5,5a,10,10a-hexahydro-1H-azepino[3,4-b]indole-2-carboxylic acid benzyl ester (**6** + **7**): Yield 40%; mixture of isomers: mp (hexanes) 95–100 °C; ^{1}H ($CDCl_3$) 7.37 (m, 5H), 6.94–6.82 (m, 1H), 6.38 (m, 1H), 6.24–6.08 (m, 1H), 5.06 (m, 2H), 4.60 (dd, 1H), 4.39–4.18 (m, 1H), 3.91–3.05 (m, 5H), 2.05–1.56 (m, 5H). HRMS calcd for $C_{20}H_{21}FN_2O_2$ $[M+H]^+$ 340.1587, found 340.1611.
   2,3,4,4a,9,9a-Hexahydro-1H-β-carboline-2-carboxylic acid phenyl ester (**8**): Yield 59%. ^{1}H NMR (300 MHz, CD_3OD) 7.30 (m, 4H), 6.95 (m, 2H), 6.60 (m, 2H), 5.02 (bd, 2H), 3.77 (m, 1H), 3.48 (m, 1H), 3.24 (m, 3H), 1.97 (m, 2H), 1.68 (m, 1H). HRMS calcd for $C_{19}H_{20}N_2O_2$ $[M+H]^+$ 308.1525, found 308.1565.
   2,3,4,5,6a,11,11a-Octahydro-1H-azepino[3,4-b]indole-2-carboxylic acid phenyl ester (**9**): Mixture of rotomers: Yield 65%. ^{1}H NMR (300 MHz, CD_3OD) 7.26 (m, 5H), 7.00 (m, 2H), 6.65 (m, 2H), 5.11 (m, 2H), 4.05–3.82 (m, 2H), 3.47–2.92 (m, 4H), 1.98–1.44 (m, 4H). HRMS calcd for $C_{21}H_{24}N_2O_2$ $[M+H]^+$ 336.1838, found 336.1894.
   3,3-(2,3-Dihydro-1H-indol-3yl)-piperidine-1-carboxylic acid phenyl ester (**12**): Mixture of rotomers: Yield 25%. ^{1}H NMR (300 MHz, CD_3OD) 7.42–6.84 (m, 9H), 5.11 (m, 2H), 3.98–3.65 (m, 3H), 3.47–2.92 (m, 3H), 2.11–1.44 (m, 7H). HRMS calcd for $C_{20}H_{22}N_2O_2$ $[M+H]^+$ 322.1681, found 322.1622.
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7. X-ray data provided.