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Preparation of RCM substrates for azepinoindole synthesis: reductive amination versus tetrahydro-γ-carboline formation

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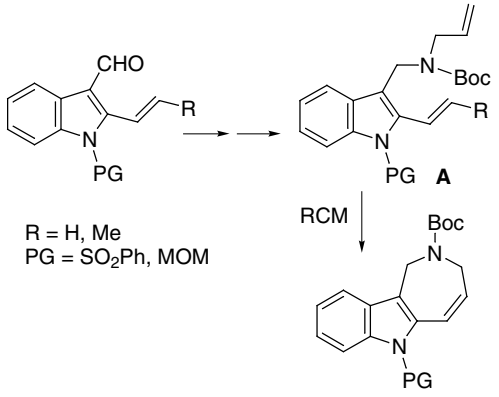
Dedicated to Professor Joaquín Plumet on the occasion of his 60th Birthday

Abstract—Treatment of *N*-(phenylsulfonyl)-2-vinyl-3-indolecarbaldehydes with primary aliphatic amines under mild reductive amination conditions leads to tetrahydro-γ-carbolines in high yield. The process can be suppressed by changing the protecting group at the indole nitrogen for a methoxymethyl group, thus allowing the preparation of RCM substrates for azepinoindole synthesis.

Ruthenium-catalysed ring-closing metathesis (RCM) reactions[1] are well-established processes for the construction of a great variety of nitrogen heterocycles.[2] In this context, cyclisations of indole-containing dienes[3] are particularly interesting as the resulting heterocyclic systems constitute structural arrangements present in many natural and medicinal compounds.[4] Our interest in the synthesis of azacycles fused to the 2,3-position of the indole ring[5] led us to study RCM reactions of 2-vinyl-3-(allylaminomethyl)indoles (for instance **A**, Scheme 1) as a synthetic entry to azepino[4,3-*b*]indoles. We planned to prepare the required RCM substrates from the corresponding *N*-protected (phenylsulfonyl or methoxymethyl) 3-indolecarbaldehydes, using simple reductive amination techniques followed by acylation of the aliphatic nitrogen.

Our attention was first focused on the indole *N*-phenylsulfonyl series as this strong electron-withdrawing substituent would guarantee the stability of the proposed gramine-type intermediates. Rather surprisingly, when 3-indolecarbaldehyde **1**[6] was treated with allylamine and $NaBH(OAc)_3$ in the presence of acetic acid in dichloromethane at room temperature, tetrahydro-γ-carboline **4a**[7] was isolated in high yield (90%, Scheme 2). No trace of the expected secondary amine **6a** was detected in the reaction mixture.



Scheme 1. Synthetic plan to azepino[4,3-*b*]indoles.

Initially, this unexpected result was rationalised considering that the imine **B** (Scheme 3), coming from the reaction of the primary amine with the aldehyde carbonyl group, would not be reduced by the hydride. Instead it would undergo cyclisation upon the alkene moiety, most probably through an electrocyclic reaction involving the indole 2,3-bond. Subsequent reduction of the resulting tetracycle **C** (for instance, through iminium cation **E**) would account for the formation of the tetrahydro-γ-carboline nucleus. In fact, we were aware that thermal

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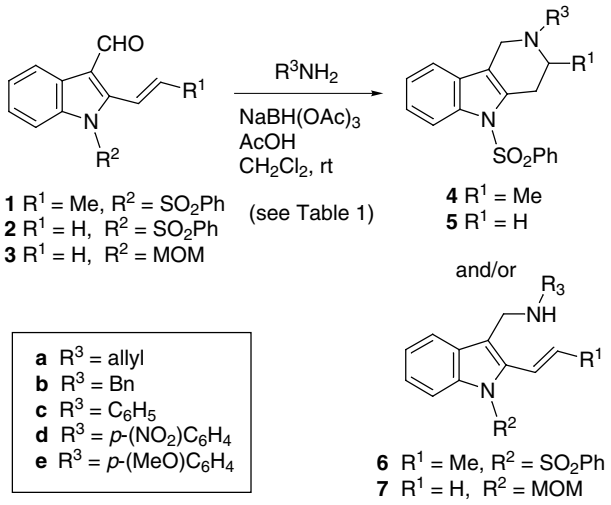
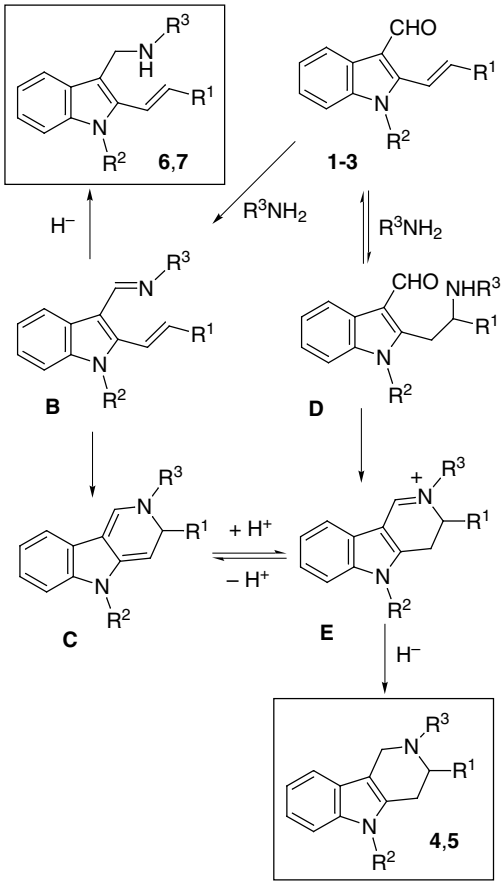


Scheme 2.



Scheme 3.

electrocyclic ring closures from the related indole-containing 1,3,5-hexatriene systems are common in the literature.[8–11] However, these substrates can be generally isolated and so the required temperatures for their cyclisation are usually high (>100 °C). From 2,3-divinylindoles, fully aromatic carbazoles are obtained after the in situ oxidation of the initially formed dihydro derivatives.[8] Closely related to our work, Hibino has exploited the cyclisation of vinyl oximes for the construction of β-[9] as well as γ-carbolines,[10] the aromaticity being achieved after dehydration. Cyclisations of vinyl imines, although less common, are also known.[11,12] To the best of our knowledge, no examples of electrocyclisations leading to tetrahydrocarbazoles or tetrahydrocarbolines after reduction have been reported.

Taking into account the mildness of our reaction conditions and the fact that the proposed imine intermediate was not present in the crude reaction mixture when the above experimental protocol was reproduced *without* $NaBH(OAc)_3$,[13] we envisaged an alternative mechanistic interpretation in which the tetrahydrocarboline ring would be produced by the initial conjugate addition of the primary amine to the γ,δ-unsaturated aldehyde.[14] This reversible step would be followed by the intramolecular reductive amination of the resulting secondary amine (**D**, Scheme 3), which would drive the reaction to completion.

With the aim of gaining more insight into the above annulation process, we examined the behaviour of other primary amines towards aldehyde **1** or the simpler derivative **2**[15] under the same set of conditions.[16] As can be observed in Table 1, the reaction with benzylamine proceeded along the same lines as described previously with allylamine, either from **1** or **2**, to give tetrahydro-γ-carbolines **4b**[17] or **5b**[18] as the only products (entries 2 and 3). Nevertheless, aniline exhibited a different reactivity profile towards aldehyde **1**, probably reflecting a lower tendency to undergo the aforementioned conjugate addition. Thus, the *normal* reductive amination pathway competed with the γ-carboline annulation and gave a nearly equimolecular mixture of the γ-carboline **4c** and the secondary amine **6c** (entry 4). Significantly, the substitution by an electron-withdrawing nitro group at the amine phenyl ring led to the secondary amine **6d** as the major product (entry 5), whereas the substitution by an electron-releasing methoxy group led to the γ-carboline **4e** as the main product (entry 6).

Table 1. Reaction of vinyl aldehydes **1**–**3** with primary amines[a]

Entry	Aldehyde	Primary amine	Product	Yield[b] (%)
1	**1**	Allylamine	**4a**	90
2	**1**	Benzylamine	**4b**	85
3	**2**	Benzylamine	**5b**	80
4	**1**	Aniline	**4c** + **6c** (1:1)	70
5	**1**	*p*-Nitroaniline	**4d** + **6d** (1:15)	90
6	**1**	*p*-Methoxyaniline	**4e** + **6e** (9:1)	70
7	**3**	Allylamine	**7a**	65
8	**3**	Benzylamine	**7b**	65

[a] Experimental conditions: see Ref. 16.
[b] Isolated yield.

The reaction of aldehyde **2** with a secondary amine such as *N*-methylbenzylamine was also investigated. As could have been expected from the above mechanistic considerations, the reductive amination through iminium cation **F** was the only productive pathway, giving the tertiary amine **8** in 90% yield (Fig. 1).

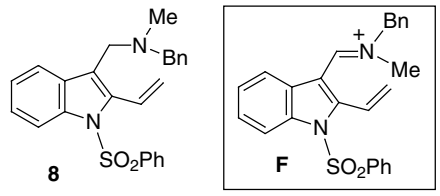
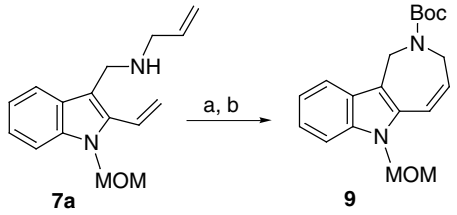


Figure 1.



Scheme 4. Reagents and conditions: (a) $(t\text{-BuOCO})_2O$, 4:1 MeOH–Et_3N, reflux, 4 h; (b) 5 mol % $(PCy_3)_2(Cl)_2Ru{=}CHPh$, CH_2Cl_2, reflux, overnight, 70%.

At this point, we reasoned that the indole *N*-phenylsulfonyl group could benefit the γ-carboline annulation, enhancing the ability of 2-vinylindole to act as a Michael acceptor. Thus, in order to make the reductive amination of 2-vinyl-3-indolecarbaldehydes with primary aliphatic amines feasible, it would be better to place a less electron-withdrawing group, such as methoxymethyl, at the indole nitrogen. Our reasoning proved to be correct as secondary amines **7a** or **7b** were obtained as the only products by treatment of the *N*-MOM protected aldehyde **3**[15] with allylamine or benzylamine under mild reductive amination conditions (Table 1, entries 7 and 8). As expected, reaction of **7a** with di-*tert*-butyl dicarbonate followed by RCM reaction of the resulting carbamate with the first generation Grubbs catalyst gave the azepino[4,3-*b*]indole **9**[19] in good yield (Scheme 4).

In conclusion, the reaction of 2-vinyl-3-indolecarbaldehydes with primary amines under mild reductive amination conditions follows a different course depending on the substituent located at the indole nitrogen. Whereas tetrahydro-γ-carbolines are formed from *N*-(phenylsulfonyl)indoles **1** and **2** and aliphatic amines (and also the highly nucleophilic *p*-methoxyaniline), the initially expected secondary amines are formed from *N*-MOM indole **3**. Further work is currently underway to more fully establish the scope of this smooth γ-carboline annulation.

Acknowledgements

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7. Tetrahydro-γ-carboline **4a**: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.12 (d, $J = 6$ Hz, 3H, Me), 2.90 (dm, $J = 11$ Hz, 1H, 4-H), 3.23 (m, 4H, 3-H, 4-H and CH_2), 3.65 (s, 2H, 1-H), 5.16 (m, 2H, $=CH_2$), 5.92 (m, 1H, CH=), 7.10–7.60 (m, 6H), 7.75 (d, $J = 7.5$ Hz, 2H), 8.15 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 14.7 (Me), 31.1 (C-4), 44.4 (C-1), 51.8 (C-3), 55.8 (CH_2), 114.5 (C-6), 115.6 (C-9b), 117.7 (C-9), 117.8 ($=CH_2$), 123.2 (C-8), 123.8 (C-7), 126.0, 128.9, 132.4, 133.3 (Ph), 128.3 (C-9a), 134.8 (CH=), 136.6 (C-4a), 138.5 (C-5a).
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13. Unfortunately, we were not able to isolate any definite compound under these conditions. However the subsequent reduction of the complex reaction mixture gave **4a**, although in a low yield (25%).
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16. General procedure: To a 0.1 M solution of the appropriate aldehyde in CH_2Cl_2 the primary amine (2 equiv), acetic acid (1 equiv) and $NaBH(OAc)_3$ (2 equiv) were added, and the resulting mixture was stirred at rt overnight. The reaction mixture was diluted with CH_2Cl_2, washed with 10% aqueous Na_2CO_3, dried and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (SiO_2, 1:1 hexanes–AcOEt).
17. Tetrahydro-γ-carboline **4b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.14 (d, $J = 6$ Hz, 3H, Me), 2.90 (dm, $J = 11$ Hz, 1H, 4-H), 3.25 (m, 2H, 3-H and 4-H), 3.61 (m, 2H, 1-H), 3.65 and 3.72 (2d, $J = 13$ Hz, 2H, CH_2), 7.17–7.52 (m, 11H), 7.78 (d, $J = 8$ Hz, 2H), 8.14 (d, $J = 8.4$ Hz, 1H, 6-H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 15.0 (Me), 31.3 (C-4), 44.9 (C-1), 52.3 (C-3), 57.2 (CH_2), 114.8 (C-6), 116.2 (C-9b), 118.3 (C-9), 123.7 (C-8), 124.4 (C-7), 127.4 (C-9a), 126.6, 128.7, 133.2, 133.9 (Ph), 136.7 (C-4a), 139.3 (C-5a).
18. Tetrahydro-γ-carboline **5b**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.85 (m, 2H, 3-H), 3.13 (m, 2H, 4-H), 3.57 (s, 2H, 1-H), 3.73 (s, 2H, CH_2), 7.15–745 (m, 10H), 7.50 (t, $J = 7.5$ Hz, 1H), 7.79 (d, $J = 8$ Hz, 2H), 8.13 (d, $J = 8.4$ Hz, 1H, 6-H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 25.8 (C-4), 49.5 (C-1), 50.5 (C-3), 62.5 (CH_2), 114.6 (C-6), 118.2 (C-9), 123.6 (C-8), 124.4 (C-7), 126.7, 127.6, 128.7, 129.3, 129.6, 133.8 and 133.9 (Ph), 136.5 (C-4a), 138.4 (C-5a).
19. Azepino[4,3-*b*]indole **9**: ^{1}H NMR ($CDCl_3$, 400 MHz, mixture of rotamers) δ 1.29 and 1.45 (2s, 9H, Me), 3.22 (s, 3H, OMe), 4.12 and 4.31 (2s, 2H, 3-H), 4.74 and 4.92 (2s, 2H, 1-H), 5.46 (s, 2H, OCH_2), 6.06 (m, 1H, 4-H), 6.65 (d, $J = 10$ Hz, 1H, 5-H), 7.15 (t, $J = 7.8$ Hz, 1H, 9-H), 7.22 (t, $J = 8$ Hz, 1H, 8-H), 7.40 (d, $J = 8.4$ Hz, 1H, 7-H), 7.53 (d, $J = 7.8$ Hz, 1H, 10-H); ^{13}C NMR ($CDCl_3$, 75.4 MHz, major rotamer) δ 28.6 (Me), 44.7 (C-1), 48.9 (C-3), 56.0 (OMe), 73.8 (OCH_2), 80.1 (C), 109.7 (C-7), 116.4 (C-10b), 118.5 (C-10), 118.6 (C-5), 120.6 (C-9), 123.0 (C-8), 126.1 (C-10a), 131.4 (C-4), 133.5 (C-5a), 137.4 (C-6a), 155.8 (CO).