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Novel indium-mediated deoxygenative α,α-diallylation of indole- and pyrrole-3-carboxaldehydes

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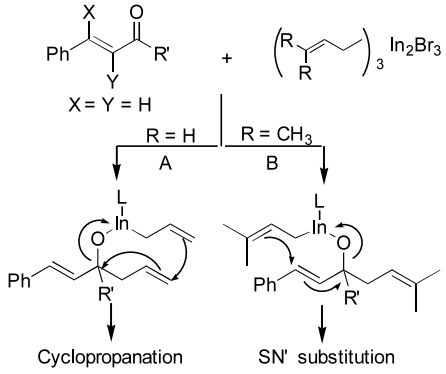
Abstract—1-Alkylindole-3-carboxaldehydes **1** and pyrrole-3-carboxaldehydes **2** on stirring with indium (2 equiv.) and allyl bromide (3 equiv.) in THF–H_2O undergo deoxygenative diallylation at the carbonyl carbon to provide 3-[1,6-diene-4-yl]- indole **3** and pyrrole **4** derivatives. The formation of the normal 1,2-addition product in the case of **1d** (R = COOEt) points towards the contribution of electronic factors due to the enamine double bond in the deoxygenation process. © 2002 Published by Elsevier Science Ltd.

The addition of allylindium reagents to carbonyl groups has emerged as an effective tool for carbon–carbon bond formation.[1] The stereochemical influence of a variety of coordinating substituents (OH, OR, NHR, keto, SR, etc.) at the α-/β-position of the carbonyl group on the diastereoselectivity has been extensively studied[2] but the influence of electronic features on the course of the reaction remains by and large unexplored. Generally in indium-mediated allylations, the homoallylic indium alkoxide intermediate on hydrolysis yields a homoallylic alcohol as the [1,2]-addition product. Only in the case of α,β-unsaturated carbonyl compounds[3] under more elaborate and specific conditions, the homoallylic indium alkoxide intermediates have been made to undergo a second allylation at the terminal carbon–carbon double bond with subsequent deoxygenative rearrangement (path A) to provide vinylcyclopropane derivatives (Scheme 1). In the case of sterically hindered allyl halides ($R = CH_3$), alternative attack on the allylic β-carbon displaces the oxygen (path B) a parallel of SN′ substitution.[4] Interestingly, in these reactions the second allylic carbanion attacks at a relatively electron rich carbon–carbon double bond to effect 1,4- (path A) or 1,3- (path B) diallylation, whereas the more electrophilic C–OIn centre is not attacked by the allylic carbanion. The necessity of the allylic position of the C–OIn bond for these rearrangements is noteworthy.

We envisioned that the presence of an electron donating/withdrawing group(s) at the α/β position of an α,β-unsaturated carbonyl compound would enhance/restrict the contribution of the double bond and as a result deoxygenative rearrangements will be affected. These systematic investigations on the role of substituents in α,β-unsaturated carbonyl compounds in allylation reactions are expected to provide new chemical strategies/entities.

For such investigations, indole-3-carboxaldehydes **1** and pyrrole-3-carboxaldehydes **2** with an inbuilt β-amino-α,β-unsaturated carbonyl unit are an obvious substrate choice. Herein, the nitrogen lone pair, through resonance, enhances the electron density at the C2–C3 double bond, which can be effectively controlled by changing the nature of the substituent on the N-1 nitrogen. Moreover, the indole nucleus is the core of various biologically important alkaloids, and studies may lead to new biologically potent indole derivatives.



Scheme 1.

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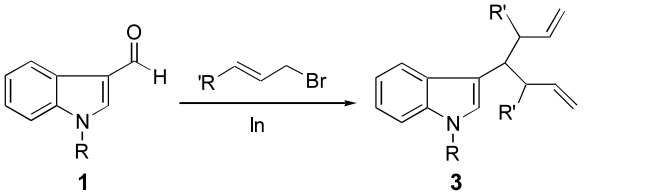
Here, we report the first examples of indium-mediated deoxygenative α,α-diallylation of the carbonyl group in 1-alkylindole-3-carboxaldehydes **1** and 1-alkylpyrrole-3-carboxaldehydes **2** to give 3-[1,6-diene-4-yl]-indoles **3** and pyrroles **4**. In these reactions, the electronic contribution of the N-1 substituent remarkably affects the α,α-diallylation reaction.

1-Ethylindole-3-carboxaldehyde **1a** on stirring with indium metal and allyl bromide (1:1.5) in THF:H_2O (1:1) after aqueous workup gave **3a** (40%).[5] Here instead of providing the normal homoallylic alcohol as the 1,2-addition product, **1a** has undergone deoxygenative α,α-diallylation at the carbonyl carbon. On increasing the amount of indium metal and allyl bromide (2:3 molar ratio w.r.t. **1a**) the yield of **3a** increased up to 81% (Scheme 2).

The deoxygenative diallylation may proceed through an indium alkoxide intermediate or through a discrete carbocation, which might have arisen due to the acidic reaction conditions associated with aqueous indium-mediated allylations. To rule out the possibility of formation of a discrete carbocation, reactions of **1a** were performed under anhydrous Grignard and Barbier type conditions. Aldehyde **1a** with $allyl_3In_3Br_3$ (2 equiv.) pregenerated in dry THF (Grignard conditions), and on stirring with indium metal and allyl bromide in dry THF (Barbier conditions), gave deoxygenated diallylated product **3a** (70–80%) as the only product (Table 1, entries 2 and 3). Also, on performing the reaction in absolute ethanol (entry 4) only **3a** was isolated. Therefore, it is the inherent property of the 1-ethylindole-3-carboxaldehyde molecule to undergo deoxygenative diallylation where acidic aqueous reaction conditions appear to play no role in the attack of the second allylic carbanion.

Similarly **1a** with crotyl and cinnamyl bromide undergoes deoxygenative diallylation to provide **3b** and **3c**, respectively. In each case the reaction proceeds smoothly with complete regioselectivity providing only the γ-addition product, however, only moderate diasteroselectivities were observed.

In order to evaluate the projected role of the electron resonance of the amine N on the deoxygenative diallylation process, various indole-3-carboxyaldehydes (**1b** R = CH_2Ph, **1c** R = CH_2CO_2Et, **1d** R = CO_2Et), with increasing orders of the electron withdrawing nature of the R substituent, were synthesised and their allylation reactions were investigated. The electronic influence of the N-1 substituents is evident from the downfield shift of C-2 H from δ 7.60 in the case of **1a** to δ 7.68, 7.76 and 8.82, respectively, in **1b**, **1c** and **1d**.



1 **3**

1a R = C_2H_5
1b R = CH_2Ph
1c R = CH_2CO_2Et
1d R = CO_2Et

3a R = C_2H_5, R' = H
3b R = C_2H_5, R' = CH_3
3c R = C_2H_5, R' = Ph
3d R = CH_2Ph, R' = H
3e R = CH_2Ph, R' = CH_3
3f R = CH_2CO_2Et, R' = H
3g R = CH_2CO_2Et, R' = CH_3

Scheme 2.

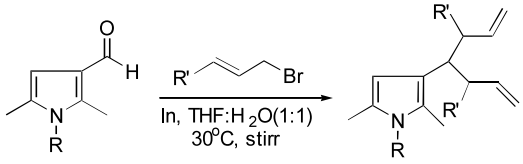
Table 1. Indium-mediated diallylations of **1a–c**

Entry	Indole	Conditions[a]	**3** (%)[b]	d.r.[c]
1	**1a**	A	**3a** (81)	–
2	**1a**	B	**3a** (72)	–
3	**1a**	C	**3a** (81)	–
4	**1a**	D	**3a** (75)	–
5	**1a**	A	**3b** (77)	8:2
6	**1a**	A	**3c** (80)	7:3
7	**1b**	A	**3d** (82)	–
8	**1b**	A	**3e** (77)	3:2
9	**1c**	A	**3f** (85)	–
10	**1c**	A	**3g** (89)	3:2

[a] A = THF:H_2O (1:1), 30°C; B = $allyl_3In_2Br_3$, dry THF, 30°C; C = dry THF, 30°C; D = absolute ethanol.
[b] Isolated yields.
[c] Calculated from ^1H NMR.

1-Benzyl/1-ethoxycarbonyl methyl indole-3-carboxaldehydes **1b** and **1c** under similar reaction conditions gave diallylated products **3d–g** (Table 1, entries 7–10). Similarly, pyrrole-3-carboxaldehydes **2** undergo allylation with allyl, crotyl and cinnamyl bromides to provide deoxygenated diallylated products **4a–d** (Scheme 3, Table 2).

Indole **1d**, bearing an electron withdrawing COOEt group at N-1, with indium and allyl bromide provided only the usual 1,2-addition product **5a** and even on



2 **4**

2a R = CH_2Ph
2b R = C_6H_4-*p* CH_3

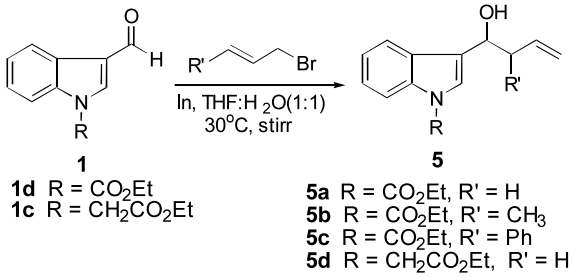
4a R = CH_2Ph, R' = H
4b R = CH_2Ph, R' = CH_3
4c R = CH_2Ph, R' = Ph
4d R = C_6H_4-*p* CH_3, R' = H

Scheme 3.

Table 2. Indium-mediated diallylations of **2**

Entry	Pyrrole	**4** (%)[a]	d.r.[b]
1	**2a**	**4a** (67)	–
2	**2a**	**4b** (69)	1:1
3	**2a**	**4c** (63)	2:1
4	**2b**	**4d** (72)	–

[a] Isolated yields.
[b] Calculated from ^1H NMR.



Scheme 4.

Table 3. Indium-mediated monoallylation of **1c–d**

Entry	Aldehyde	R′	Product (%)[a]	d.r.[b]
1	**1d**	H	**5a** (91)	–
2	**1d**	CH_3	**5b** (87)	1:1
3	**1d**	Ph	**5c** (90)	99:1
4	**1c**	H	**5a** (91)	–

[a] Isolated yields.
[b] Calculated from ^{1}H NMR.

using an excess of indium and allyl bromide, the deoxygenated diallylated product could not be isolated (Scheme 4).

Similarly, **1d** with crotyl and cinnamyl bromides gave **5b** and **5c**, respectively. In each case the reaction proceeded with complete regioselectivity providing only the γ-addition product. The addition of cinnamyl bromide proceeded in a highly diasteroselective manner (Table 3, entry 3). However, **1c** using indium and allyl bromide in 0.75:1 mol ratios in THF–H_2O (1:1) at 0°C gave only **5d** as the 1,2-addition product (Table 3, entry 4).

In conclusion, 1-alkylindole/pyrrole 3-carboxaldehydes **1**, **2** undergo facile indium-mediated deoxygenative diallylation to provide 3-[1,6-diene-4-yl]indole/pyrrole derivatives. These findings clearly indicate the role of the electron density of the enamine nitrogen in the deoxygenation process, where the nature of the N-1 alkyl group plays an important role in dictating the reaction course and can be easily tailored to synthesize the target molecules.

Acknowledgements

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5. Representative procedure: A suspension of the aldehyde (1 mmol), allyl bromide (3 mmol) and indium metal (2 mmol) in THF:H_2O (1:1, 5 ml) was stirred at 30°C until completion (4–6 h) of the reaction (TLC). The reaction mixture was diluted with water and extracted with dichloromethane. Evaporation of the solvent followed by purification of the crude product by silica gel column chromatography provided the pure product.