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Aminocatalytic preparation of bisindolylalkanes

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An aminocatalytic method for the formation of bisindolylalkanes is described; the reaction proceeds effectively at ambient temperature in the presence of moisture and air for both aldehyde and ketone substrates and has been applied to the one-step preparation of a series of naturally-occurring bis- and tris-indolylalkanes.

The use of aminocatalysis as an effective platform for carrying out synthetic transformations and has recently caught the imagination of the chemical community.[1] Ease of operation, tolerance of functional groups and readily accessible catalysts has led to an exponential growth in the reaction portfolio available to the synthetic chemist. We have become interested in the structure–activity relationship of the catalyst architecture, in particular how the α-effect can be used as an effective platform for iminium ion catalysis.[2] Herein we report the first aminocatalytic method for the preparation of bisindolylalkanes and its application to the preparation of a series of naturally-occurring systems representing this structurally important class of bioactive metabolites.[3]

It has been shown previously that bisindolylalkanes can be prepared using both Brønsted[4] and Lewis acids[5] by treatment of the appropriate aldehyde with a two-fold excess of the indole to generate the corresponding adduct (Fig. 1). These reactions generally require strongly acidic conditions and elevated temperatures in order to generate the product in reasonable yield.[6] Recently, it was reported that *N*-*tert*-butanesulfinyl aldimines could be used as effective substrates for this transformation using a stoichiometric amount of a Brønsted acid for the transformation, and this approach was used to prepare the addition product of a series of these aldimines.[7] We reasoned that this process could be rendered catalytic by the use of a secondary amine and an equivalent of aldehyde, generating an aldimine intermediate *in situ*, and also sought to discover if the process could also be applied to more challenging ketone substrates, to provide an efficient route through to a diverse range of representatives of this class of compound.

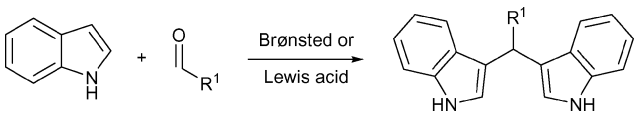
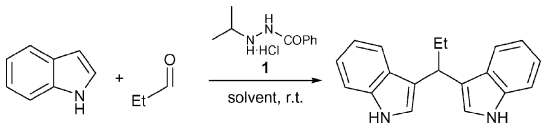


Fig. 1 Acid-catalysed formation of bisindolylalkanes.

We chose as our initial catalyst the benzoic hydrazide derived catalyst **1** which has been shown previously to be an effective catalyst in iminium ion-catalysed transformations.[2] Our investigations started with the reaction between propionaldehyde and indole (Table 1). In less polar solvents such as acetonitrile the product was formed in negligible amounts (Table 1, entry 1); however, increasing the polarity of the solvent gave an indication that the reaction was indeed feasible (entries 2 and 3). Changing to a protic solvent such as methanol led to a remarkable change in the reaction profile, with the desired bisindolylalkane being isolated in 84% yield (entry 4). Although water was also effective as the reaction solvent (entry 5), we generally found the reactions to be operationally simpler in methanol and adopted it as our solvent of choice. In the absence of any catalyst none of the desired product was detected (entry 6). Indication that this reaction proceeds *via* an iminium ion intermediate, rather than being accelerated by the HCl present in the reaction medium, came from the fact that no product was detectable when 10 mol% triethylamine hydrochloride was used as the catalyst (entry 7). Acetic acid was also ineffective at accelerating this reaction at room temperature (entry 8).[8]

Table 1 Amino-catalysed reaction of indole and propionaldehyde[a]



Entry	Catalyst (mol%)	Solvent	Yield (%)
1	**1** (5)	MeCN	0
2	**1** (5)	DMF	62
3	**1** (5)	DMSO	55
4	**1** (10)	MeOH	84
5	**1** (5)	H_2O	62
6	None	MeOH	0
7	NEt_3·HCl (10)	MeOH	0
8	AcOH (10)	MeOH	0

[a] All reactions were performed at room temperature for 24 h.

Encouraged by these initial results we went on to investigate the generality of this procedure (Table 2).† The reaction was effective for a variety of aldehydes including propionaldehyde (Table 2, entry 1) and cyclopropanecarboxaldehyde (entry 2). It was possible to lower the catalytic loading to just 1 mol% **1**, with the adduct between benzaldehyde and indole being isolated in an excellent 84% yield after 32 h (entry 3). The reaction was tolerant of unprotected phenols (entry 4) with the adduct of 4-hydroxybenzaldehyde being isolated in 89% yield. We were also able to obtain the bisindolylalkane upon reaction of ketone substrates with indole, for example, both cyclohexanone (entry 5) and methyl cyclopropyl ketone (entry 6) gave the expected products in acceptable yields. Acid-sensitive functional groups such as ethylene ketal (entry 7) could also tolerate the reaction conditions, exemplifying the mildness under which these reactions proceed. The reaction was not limited to indole as the substrate with *N*-methylindole reacted with both aldehydes (entry 8) and ketones (entry 9). Electron-rich (entry 10) and electron-deficient (entry 11) indoles also gave the expected products.[9]

Having established that we had a general, mild and efficient aminocatalytic method of accessing the bisindolylalkane framework, we then sought to apply the methodology to preparing a variety of naturally-occurring compounds (Scheme 1 and 2). We first targeted vibrindole A **2**,[10] which was obtained in 80% yield from the reaction of acetaldehyde and indole. The trisindolylalkane **3**, isolated from the bacterium *Vibrio parahaemolyticus*,[11] was prepared by the reaction of indole-3-carboxaldehyde and indole in 77% yield. We were also able to obtain the compound **4**, isolated from the same natural source

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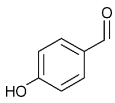
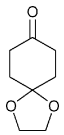
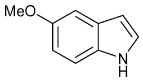
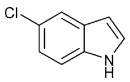
Table 2 Scope of bisindolylalkane formation[a]

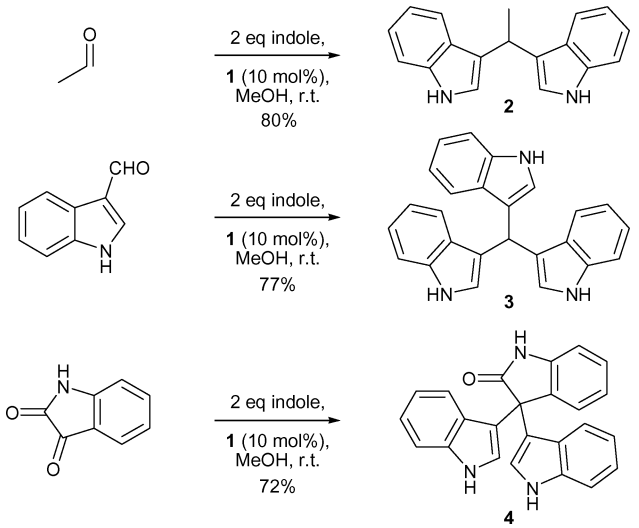
Entry	Indole	Carbonyl	Yield (%)
1			84
2			74
3[b]			84
4			89
5			58
6			69
7			50
8			81
9			69
10			55
11			42

[a] All reactions were carried out with 1 equiv. of carbonyl compound and 2 equiv. of indole in MeOH at room temperature for 16–24 h in the presence of 10 mol% **1** except where noted. [b] Reaction was carried out in the presence of 1 mol% **1** for 32 h.

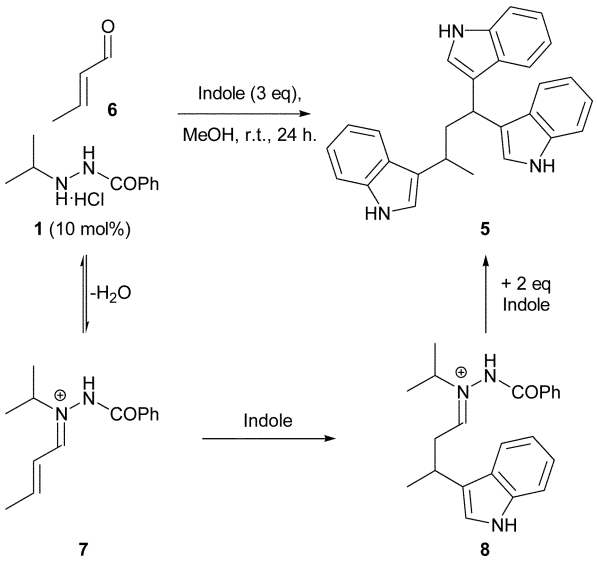
from the coupling of isatin and two equivalents of indole, thus reinforcing the generality of the reaction to both aldehydes and ketones.

Finally, we targeted the naturally-occurring tris-indole **5** which was isolated as a racemate from the bacterium *Vibrio parahaemolyticus*.[11] This was prepared by the reaction of crotonaldehyde and three equivalents of indole (Scheme 2). We believe this reaction proceeds *via* initial iminium ion formation by reaction of the catalyst **1** with crotonaldehyde **6** to give **7**, followed by conjugate addition of indole.[12] Protonation of the resulting enamine to restore the iminium ion **8**, followed by the 1,2-addition of indole, elimination and regeneration of the catalyst and addition of a third molecule of indole then furnishes the observed product **5**, which was isolated in a respectable 51% yield after three C–C bond-forming reactions.

In summary, we have described the first aminocatalytic method for the preparation of the bisindolylalkane framework



Scheme 1 Synthesis of naturally-occurring bisindolylalkanes.



Scheme 2 Tandem conjugate addition–condensation reaction.

that takes place at room temperature in the presence of both moisture and air. The reaction is effective for both aldehydes and ketones and is also tolerant of substitution on the indole ring. The methodology can also be applied to a tandem iminium ion-catalysed conjugate addition–condensation reaction for the introduction of three indole units to give the tris-indole **5** in one step, expanding the organocatalytic reaction portfolio and providing further evidence of the potential and significance that aminocatalysis can play in the construction of complex organic molecules.

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Notes and references

† Typical experimental procedure: a solution of 5-methoxyindole (200 mg, 1.35 mmol, 2.0 equiv.) and benzoic acid *N′*-isopropylhydrazide **1** (14.5 mg, 0.0675 mmol, 0.1 equiv.) in methanol (2.5 mL) was treated with propionaldehyde (39 mg, 0.675 mmol, 0.049 mL, 1.0 equiv.) and the resulting reaction mixture was stirred at 25 °C for 24 h. The solvent was removed *in vacuo* and the resulting mixture was purified by flash column chromatography eluting with 25% ethyl acetate–light petroleum to give 1,1-bis-3-(5-methoxyindolyl)propane (124 mg, 55%) as an off-white solid; Mp 70–72 °C; IR (nujol) 3403, 2360, 1622, 1579, 1483, 1435, 1288, 1208, 1171, 1096 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (bs, 2H, N*H*), 7.24 (d, 2H, *J* 8.8 Hz, Ar*H*), 7.04 (d, 2H, *J* 2.4 Hz, Ar*H*),

7.01 (d, 2H, *J* 2.3 Hz, Ar*H*), 6.83 (dd, 2H, *J* 8.8 and 2.4 Hz, Ar*H*), 4.28 (t, 1H, *J* 7.4 Hz, C*H*), 3.78 (s, 6H, OCH_3), 2.23 (pent, 2H, *J* 7.4 Hz, CH_2), 1.01 (t, 3H, *J* 7.4 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.5, 131.8, 127.7, 122.3, 120.0, 111.7, 111.6, 101.9, 55.9, 35.9, 28.4, 13.1; *m*/*z* (APcI) 335 (M + H); HRMS (ES) (found 335.1752 $[M + H]^+$; $C_{21}H_{22}N_2O_2$ requires 335.1754).

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