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An efficient synthesis of 9*H*-pyrrolo[1,2-*a*]indoles

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ABSTRACT

A novel and effective method has been developed for the synthesis of 9*H*-pyrrolo[1,2-*a*]indoles by treatment of 3-substituted-4,6-dimethoxyindoles with chalcones in the presence of hydrochloric acid.

Indoles are widely distributed in Nature, and possess a variety of significant biological activities.[1] They also serve as useful intermediates for the synthesis of a wide range of more complex heterocyclic compounds. Consequently, the synthesis and reactions of indoles are continuing areas of interest.[2]

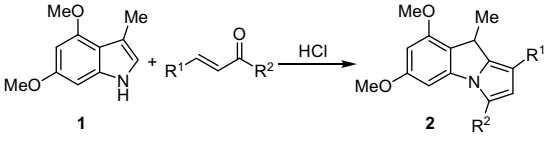
We have previously reported that 4,6-dimethoxy-3-methylindole **1** undergoes acid-catalyzed reactions with aryl aldehydes to give 2,2′-di-indolylmethanes and macrocyclic calixindoles.[3] Similar treatment of indole **1** with ketones such as acetone and acetophenones in methanolic hydrochloric acid gave reduced pyrroloindoles of the isoborreverine type.[4]

As part of our continuing interest in the development of new synthetic methods for the preparation of indole alkaloids and to extend our earlier work on α,β-unsaturated ketones, the dimethoxy indole **1** was treated with a range of chalcones in the presence of hydrochloric acid. Surprisingly, we observed the formation of a new series of 9*H*-pyrrolo[1,2-*a*]indoles **2** (Scheme 1).

9*H*-Pyrroloindole is an important precursor for the synthesis of mitomycin antibiotics.[5] In addition, the parent 9*H*-pyrrolo[1,2-*a*]indole (fluorazine) is known for its anticholinergic activity,[6] and for inhibition of GABA transport and Na^+/K^+-ATPase.[7]

Synthetic routes to 9*H*-pyrrolo[1,2-*a*]indoles have been reported in the literature;[8] however, most of them have been directed towards the synthesis of mitomycin antibiotics. 9*H*-Pyrroloindole can be obtained from the Wolff–Kishner reduction of corresponding 9-keto-9*H*-pyrroloindole.[5] Hirata et al.[9] and Cotterill et al.[10] prepared 9*H*-pyrroloindole by treating indole-2-carbaldehyde with sodium hydride and vinyltriphenylphosphonium bromide. A tandem Wittig-metathesis reaction uses *N*-allylindole-2-carbaldehyde to generate the target compound.[11] Caddick et al. developed a radical cyclization procedure to synthesize 9*H*-pyrroloindole from *N*-(3-bromopropyl)-2-(4-methylbenzenesulfonyl)indole.[12] However, these preparations of 9*H*-pyrroloindoles involve multiple steps and the yields are often poor. Despite the numerous advances made, the synthesis of functionalized indoles still represents a significant synthetic challenge.

The structures of 9*H*-pyrrolo[1,2-*a*]indoles **2** were determined through 1D and 2D NMR spectroscopy. The ^{1}H NMR spectrum



Entry	Product	R^1	R^2	Yield %
1	**2a**	Cl	OMe	59
2	**2b**	Cl	Me	36
3	**2c**	OMe	Cl	31
4	**2d**	Cl	Cl	79

Scheme 1. Reagents and conditions: HCl, *i*-PrOH, reflux, 2 h.

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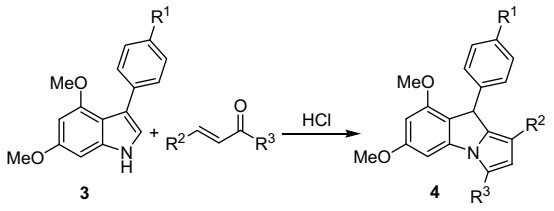
showed the disappearance of the H2 and NH signals of the starting material, while the *meta*-coupled H5 and H7 signals remained intact. It was deduced that the aromaticity of the indole had been disrupted as the 9-methyl group appeared as a doublet, coupling to a new signal at 4.4 ppm assigned to H9.[13] Finally, a new singlet at 6.4 ppm was assigned to the pyrrole H2. The chalcone aromatic rings were assigned through NOE correlations to H5 and H9, and in all cases the substituent adjacent to the ketone in the chalcone was found closer to the nitrogen in the product.

In light of the successful cyclization reactions of 3-methylindole **1**, the methodology was extended to 3-arylindoles **3**. The reaction proved to be highly versatile, accommodating 3-aryl indoles **3** with a variety of substituents (Scheme 2). Reaction yields of 9*H*-pyrroloindoles **4** were improved by reducing the solvent volume and cooling prior to collection in order to maximize the precipitation of product. A similar reaction of the parent 3-methylindole with chalcone was very sluggish, and gave only a low yield of the reduced pyrroloindole related to structure **4**. This is consistent with an earlier report that the reaction of 3-methylindole with methyl vinyl ketone gave a complex mixture of products that included a very low yield of a reduced pyrroloindole (of uncertain structure) resulting from the addition of 2 equiv of methyl vinyl ketone.[14] The structure of compound **4i** was confirmed by X-ray crystallography (Figure 1).



Entry	Product	R^1	R^2	R^3	Yield %
1	**4a**	OMe	4-Cl	4-Me	87
2	**4b**	OMe	4-OMe	4-Cl	62
3	**4c**	OMe	4-Cl	4-Cl	59
4	**4d**	OMe	4-Cl	Me	74
5	**4e**	Cl	4-OMe	4-Cl	63
6	**4f**	Cl	4-Cl	4-Cl	65
7	**4g**	Cl	4-Cl	Me	58
8	**4h**	Br	4-Cl	4-OMe	95
9	**4i**	Br	H	H	83
10	**4j**	Br	4-OMe	4-Cl	58
11	**4k**	Br	4-Cl	Me	73
12	**4l**	Me	4-Cl	4-Me	63
13	**4m**	Me	4-OMe	4-Cl	81
14	**4n**	Me	4-Cl	4-Cl	88

Scheme 2. Reagents and conditions: HCl, *i*-PrOH, reflux 3 h.

Formation of these 9*H*-pyrroloindoles proceeds through the Michael addition of the indole to the chalcone double bond and subsequent ring closure to the nitrogen with concurrent loss of water. This was confirmed as the reaction of 1-methylindole **5** with chalcone **6** gave the simple Michael addition product **7** (Scheme 3). Conversely, no reaction occurred when 2,3-dimethyl-4,6-dimethoxyindole was reacted with chalcone. This reaction sequence determines the nature of the pyrrole ring substituents R^2 and R^3, and is consistent with the observed NOE data.

The ratio of indole to chalcone was varied in order to examine whether the reduced pyrroloindole structure could be obtained comparable to those found when reacting 3-substituted indoles with ketones under the same conditions. However, only the monomeric pyrroloindoles **4** were obtained even at a 2:1 ratio of indole to chalcone and in much lower yields.

In an attempt to extend this work to non-aryl α,β-unsaturated ketones, mesityl oxide was reacted with indole **1** in the presence of hydrochloric acid. The precipitated product was found to be the reduced pyrroloindole **8** in 70% yield. This compound is the product of the reaction of indole **1** with acetone under acidic conditions.[4] No product could be isolated from the reaction with 3-penten-2-one. 1,3-Dimethylindole has been shown to react with

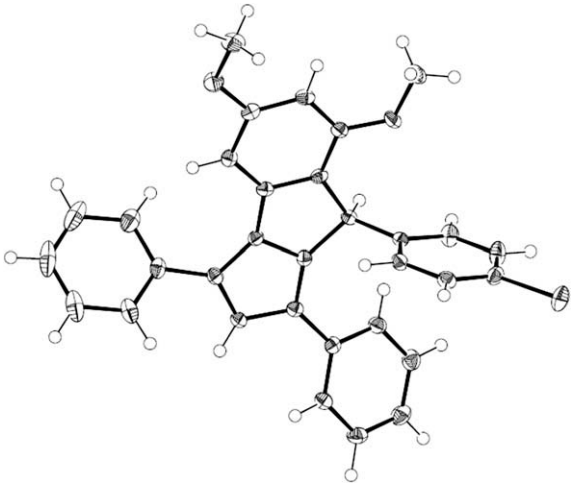
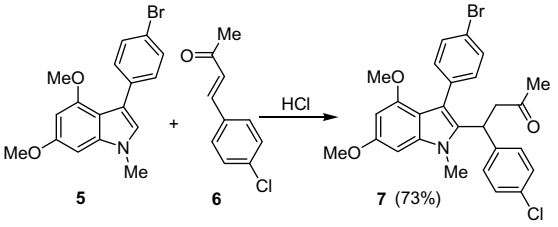
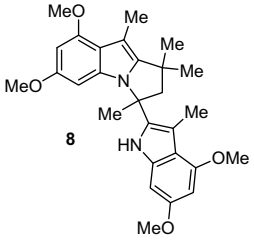


Figure 1. ORTEP diagram of compound **4i**.[15]



Scheme 3. Reaction of 1-methylindole **5** with chalcone **6**.

mesityl oxide to give a reduced carbazole.[14,16] The presence of the two activating methoxy groups clearly has a major influence both on the regioselectivity and the product yields.



8

In conclusion, 3-substituted indoles have been converted effectively, in a single step, to the corresponding 9*H*-pyrrolo[1,2-*a*]indoles. This newly developed method offers quick access to building blocks for various molecular constructions.

Acknowledgements

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13. *Representative procedure for compound* **2d**: Indole **1** (1.0 mmol) and 3-(4-chlorophenyl)-1-(4-chlorophenyl)prop-2-en-1-one (1.5 mmol) were dissolved together in isopropanol (10 ml), and concentrated hydrochloric acid (1 ml) was added. The reaction was refluxed for 2 h before cooling. The precipitate was collected and recrystallized from acetonitrile to give **2d** as a white solid. Mp 192–193 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.49 (3H, d, *J* 6.75 Hz, CH_3), 3.67 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 4.40 (1H, q, *J* 6.78 Hz, H9), 6.23 (1H, d, *J* 1.89 Hz, H7), 6.28 (1H, d, *J* 1.89 Hz, H5), 6.49 (1H, s, H2), 7.34 (2H, d, *J* 8.67 Hz, H_{aryl}), 7.42 (2H, d, *J* 8.28 Hz, H_{aryl}), 7.52 (2H, d, *J* 8.28 Hz, H_{aryl}), 7.53 (2H, d, *J* 8.67 Hz, H_{aryl}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.4, 34.3, 55.3, 55.4, 91.4, 93.6, 112.6, 116.7, 119.2, 126.9, 127.1, 128.4, 128.7, 130.2, 130.8, 130.9, 133.5, 133.6, 140.4, 141.5, 156.9, 160.8 ppm; IR (KBr): ν_{max} 2968, 2931, 1624, 1599, 1577, 1559, 1488, 1468, 1430, 1303, 1202, 1169, 1149, 1090, 1058, 1012, 836, 786 cm^{-1}; UV–vis (MeOH): λ_{max} 204 nm (ε 53,600 cm^{-1} M^{-1}), 211 (46,700), 234 (35,800), 293 (33,000); Anal. Calcd for $C_{26}H_{21}Cl_2NO_2$: C, 69.34; H, 4.70; N, 3.11. Found C, 69.23; H, 4.82; N, 3.10.
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15. Crystallographic data for the structure in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 703105 (**4i**). X-ray crystal structures were obtained by Don Craig and Mohan Bhadbhade, Crystallography Laboratory, UNSW Analytical Centre, Sydney, Australia.
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