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A Mild and Selective C-3 Reductive Alkylation of Indoles

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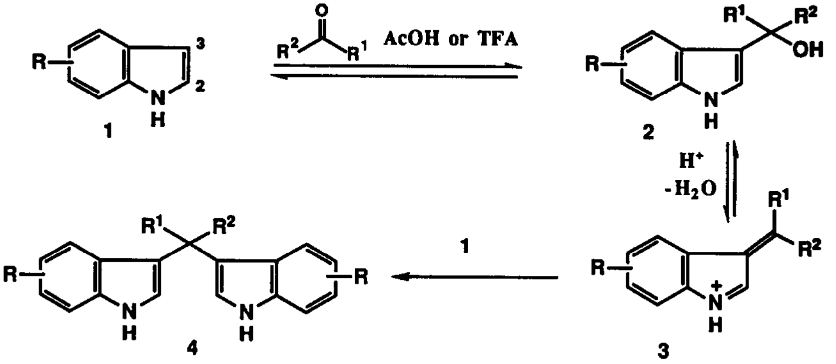
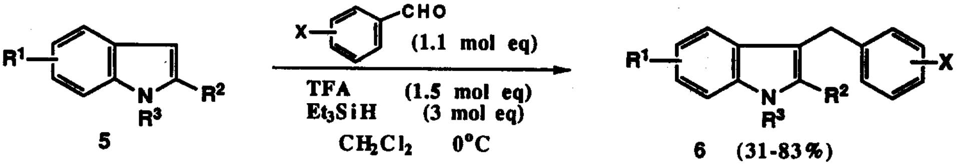
Abstract: *In the presence of triethylsilane and trifluoroacetic acid, the reaction between indoles and aldehydes in dichloromethane at 0°C, results in good yields of C-3 reductively alkylated products. The transformation is most effective for the preparation of 3-(arylmethyl)indoles **6** from aromatic aldehydes.*

The reaction of 3-unsubstituted indoles with aldehydes[1] and ketones[2] is complicated by the high nucleophilicity of the indole component **1** (*Scheme 1*) such that the anticipated carbinol products **2** generally react under acidic conditions with a second equivalent of indole - presumably via **3** - to produce varying yields of *bis*-indolylmethanes **4**.[3]



Scheme 1.

We required a synthetically versatile access to a range of 3-(arylmethyl)indoles **6** and initially pursued the well-established C-3 alkylation of appropriate indolemagnesium bromides with aldehydes[4] or activated alkyl halides.[5] However, neither method is completely regioselective; significant amounts of the N-substituted isomer[5b] are frequently generated and this, in our experience, has become unacceptable. We now disclose that triethylsilane/trifluoroacetic acid smoothly diverts the sequence in Scheme 1, presumably by fast hydride delivery to the species **3**, and facilitates production of C-3 functionalised indoles in moderate to high yields *(Scheme 2)*:

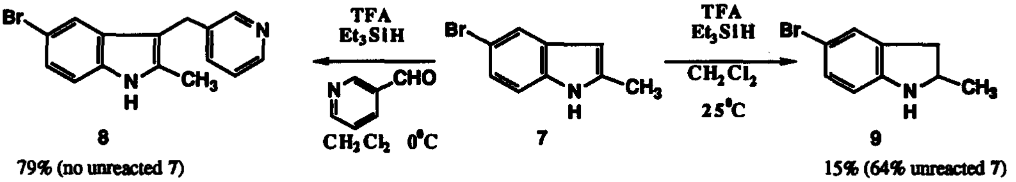


Scheme 2.

Comparable reductive alkylations of pyrroles utilising, *inter alia,* hydriodic acid as the reducing agent have been reported,[6] but these are much less effective on indole substrates. The TFA/Et_3SiH procedure has proven particularly useful for the construction of 3-(arylmethyl)indoles **6** and their 3-(heteroarylmethyl) analogues with no detectable contamination by regioisomeric addition products or *bis*-indolylmethanes. To date only a limited optimisation of conditions has been completed but the following details are clear; (i) a minimum of 3 equivalents of triethylsilane is essential for complete conversion; (ii) an excess of TFA is generally not detrimental, but use of less than one equivalent results in the competitive formation of *bis*-indolylmethane by-products; (iii) In general, a reaction temperature of 0°C is used, although reaction times are still acceptable and yields are unchanged at -70°C.

Table 1 contains a preliminary survey of the reaction scope. Both rate and yield are relatively insensitive to steric and electronic factors associated with the indole **6**, with the exception of the electron-rich 5-methoxy substrate *(entry 10)* which undergoes competing reactions on the indole benzo ring. Although aliphatic aldehydes and ketones readily self condense in the presence of TFA, the ketones permit moderate conversions to alkylated products *(entries 1 and 2)*. The use of larger excesses of the carbonyl substrate does not increase the conversion but results in more complex mixtures of products. N-alkylated indoles are equally reactive under these conditions *(entry 14)* - this potentially offers an advantage over Grignard and other base-catalysed methods of C-3 functionalisation which rely on N-deprotonation.

Indole itself afforded no identifiable products, possibly due to preferential ionic hydrogenation of the C2-C3 bond.[7] In all other cases, no evidence for conversion to 2,3-dihydroindole products was observed under the reaction conditions, although a control experiment using 5-bromo-2-methylindole **7** in the absence of aldehyde indicated partial conversion to dihydroindole **9** after 24 hours at 25°C. In contrast, the same substrate was converted to a representative alkylated product **8** in 15 minutes at 0°C (*Scheme 3*).



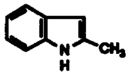
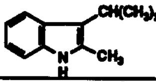
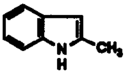
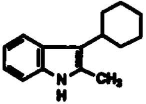
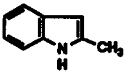
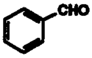
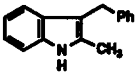
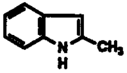
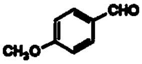
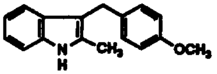
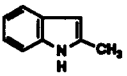
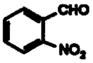
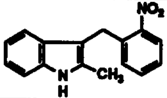
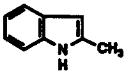
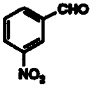
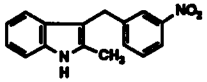
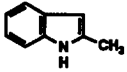
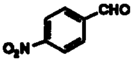
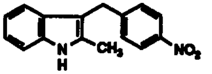
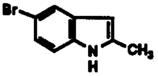
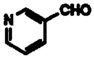
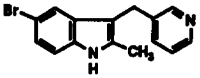
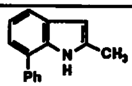
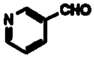
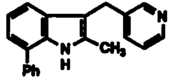
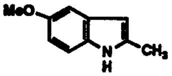
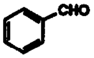
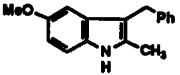
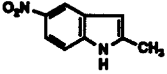
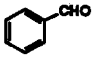
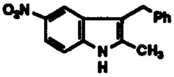
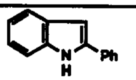
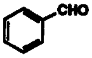
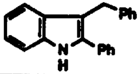
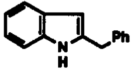
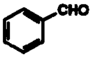
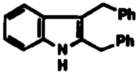
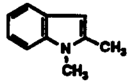
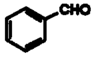
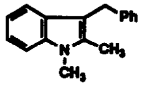
Scheme 3.

General Procedure. *The following protocol has been used for 1-50 mmol scale reactions:*

> A solution of indole **5** (1mmol) and the aldehyde/ketone (1.1mmol) in CH_2Cl_2 (5ml) is added in drops to a stirred, ice-cold solution of TFA (1.5mmol) and Et_3SiH (3mmol) in CH_2Cl_2 (2ml). The reaction is monitored by TLC until judged complete (10-60 minutes) then basified to pH 8-9 with 2*M* NaOH and partitioned between CH_2Cl_2 and brine. Evaporation of the dried ($MgSO_4$) organic phase affords the crude alkylated indole **6** which may be further purified by crystallization or flash chromatography on silica gel.

In summary, a mild and general route to 3-substituted indoles has been established. This method overcomes the over-reactivity of indole systems toward aromatic aldehydes and should complement the existing methods used to synthesise these systems. Yields are lower for reactions involving ketones, although relatively few examples have yet been explored. We are currently investigating the reactivity of other π-excessive aromatic substrates with carbonyl compounds under these conditions.

Table 1: TFA-Triethylsilane Promoted Reductive Alkylation of Indoles

Entry	Substrate	Aldehyde/Ketone	Product [a]	Yield %[b]	Mp/°C
1				31[c]	oil
2				36	69-70
3				83	122-3
4				58	120-1
5				74	109-11
6				58	145-7
7				52	124-5
8				79	188-90
9				71	187-9
10				31	111-3
11				77	169-70
12				69	77-9
13				81	124-6
14				50	145-7

Notes: [a] All products were characterised by satisfactory combustion analysis (CHN), 300MHz ^1H NMR, MS and IR spectroscopy. [b] Yields are unoptimised and are calculated after isolation and recrystallization. [c] Purified by flash chromatography on SiO_2.

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4. Bader, H.; Oroshnik, W. *J. Am. Chem. Soc.*, **1959**, *81*, 163-167.

5. (a) For example Dolman, D.; Sainsbury, M. *Tetrahedron Lett.*, **1981**, *22*, 2119-2120.

   (b) For a discussion of factors affecting regioselectivity see Nunomoto, S.; Kawakami, Y.; Yamashita, Y.; Takeuchi, H; Eguchi, S. *J. Chem. Soc. Perkin Trans. I*, **1990**, 111-114.

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7. For example:
   (a) Carter, P.; Fitzjohn, S.; Halazy, S.; Magnus, P. *J. Am. Chem. Soc.*, **1987**, *109*, 2711-2717.

   (b) Lanzilotti, A.E.; Littell, R.; Fanshawe, W.J.;McKenzie, T.C.; Lovell, F.M. *J. Org. Chem.*, **1979**, *44*, 4809-4813.

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