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A general method for C_3 reductive alkylation of indoles

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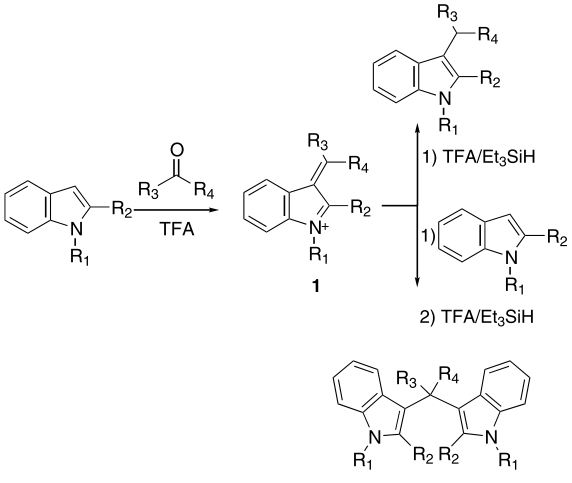
Abstract—General indole C_3 reductive alkylation conditions have been developed. The scope of this reaction includes C_2 unsubstituted indoles, aryl and alkyl aldehydes, as well as N–H and *N*-alkyl indole substrates. © 2003 Published by Elsevier Science Ltd.

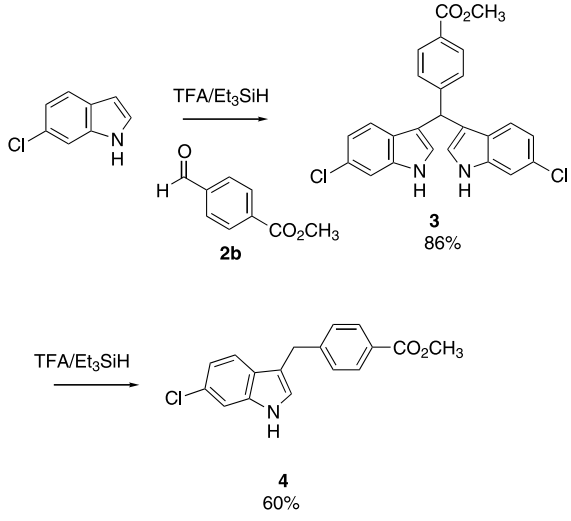
In the context of a medicinal chemistry project the convergent synthesis of C_3 functionalized indoles became a priority. One of the requirements for this transformation was that it could be performed with the indole nitrogen substituted or unsubstituted. There are many methods to functionalize the C_3 position of the indole nucleus,[1] but very few of them allow the use of both *N*-alkylated and N–H indole skeletons. A reaction reported by Steele[2] allows the delivery of C_3 alkylated products with the desired flexibility at N_1 (Scheme 1). In this reaction it is crucial that the indolium ion **1** undergoes reduction before a second indole nucleus adds to this electrophilic species to give the bis-indolylmethane. There are many examples of the formation of bis-indolylmethanes[3] and no other examples of the intermolecular reaction where reduction occurs before addition of a second indole moiety.[4]

There are two limitations stated in the published work: indole and other C_2 unsubstituted substrates do not react cleanly, and alkyl aldehydes self-condense under the reaction conditions before reacting in the desired fashion. In this communication it is demonstrated that both of these problems can be overcome by varying the reaction conditions.

The first substrate that was investigated was 6-chloroindole. Treatment of this indole with TFA/Et_3SiH and aryl aldehyde **2b** afforded the bis-indolylmethane **3** in 86% yield (Scheme 2). Since the isolated bis-indolyl-



Scheme 1.



Scheme 2.

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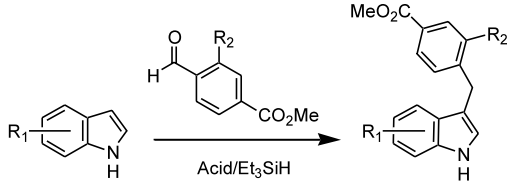
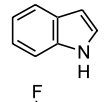
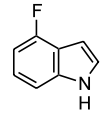
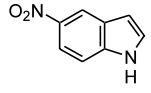
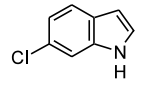
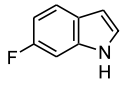
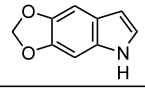
methane intermediate could be reduced to the desired product **4**, in 60% yield *under the same reaction conditions*, it became clear that this could constitute a one-pot transformation. This observation indicates that the bis-indolylmethane acts as a product sink and that reduction of intermediate **1** before further reaction is not as important as initially reported. The reaction conditions were adjusted so that an excess of indole was used (1.6 equiv.), and these conditions proved to be quite general for a variety of indoles.[5] The excess indole could be recovered after column chromatography but was not routinely recycled.

A potential side product of this reaction would be reduction of the indole to the indoline. This transformation has been reported[6] using TFA/Et_3SiH at 25°C, but under the reaction conditions described no reduction was observed.

Table 1. Reductive alkylation of indole N–H substrates with methyl 4-formyl-3-methoxybenzoate and methyl 4-formylbenzoate



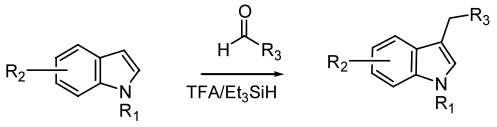
Entry	Indole	Aldehyde	Acid	Yield[a]
1		**2b**	TFA	55%
2		**2b**	TFA	90%
		2b	$BF_3{\cdot}OEt_2$	71%
3		**2a**	$BF_3{\cdot}OEt_2$	52%
4		**2a**	TFA	61%
		2a	$BF_3{\cdot}OEt_2$	43%
5		**2b**	TFA	64%
		2a	$BF_3{\cdot}OEt_2$	47%
6		**2a**	TFA	20%

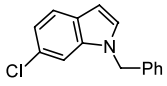
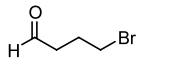
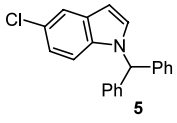
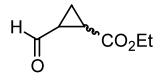
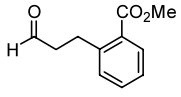
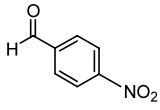
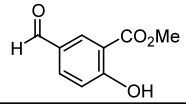
[a]Isolated yields of purified products, all compounds characterized by ^1H NMR and acid derivatives were also characterized by CHN or HRMS.

Table 1 lists several other examples of this reaction that have been performed on indole N–H substrates. Electron withdrawing groups at either the 5 or 6 position of the indole gave higher yields than electron donating groups, cf. entries 3–5 and entry 6. Higher yields were generally obtained with TFA as the acid source. The low yield seen with 5,6-methylenedioxyindole, entry 6, was due to difficulty in reducing the bis-indolylmethane intermediate which required refluxing in dichloroethane. The products resulting from these reductive alkylations were then alkylated,[5b] using benzhydryl bromide and sodium hydride, and subsequently hydrolyzed using lithium hydroxide to yield the desired acids.

N-Substituted indoles were then examined. The benzoylcarbamate of 6-methoxyindole gave no reaction with TFA. When the reaction was performed with $BF_3{\cdot}OEt_2$ or $SnCl_4$, the aldehyde was reduced and the bis-indolylmethane was formed very slowly. The carbamate protecting group was deemed too deactivating for this reaction. The SEM protecting group cleaved in the presence of TFA in CH_2Cl_2. *N*-Alkylated indole substrates proved to be quite reactive under these conditions (Table 2).[5,7] The benzyl derivative of 6-chloroindole gave the desired product under the standard reaction conditions, entry 1. 6-Chloro-*N*-benzhydrylindole, **5**, turned out to be a very effective substrate for the reductive alkylation reaction. A variety of aldehydes were examined with this substrate; alkyl aldehydes, hindered and non-hindered, react in moderate to good yield (entries 2–3).

Table 2. Reductive alkylation of *N*-substituted indoles



Entry	Indole	Aldehyde	Yield[a]
1			48%
2	 **5**		79%
3	**5**		55%
4	**5**		42%
5	**5**		78%

[a] Isolated yields of purified products, all compounds characterized by ^1H NMR and acids derived from these products were further characterized by CHN and/or HRMS.

No competing reduction or self-condensation of these aldehydes is seen. This is attributed to the speed at which the initial reaction to generate the intermediate **1** occurs. The *N*-alkylated substrates were quite reactive towards aryl aldehydes, examples 4–5, with the yield decreasing as electron withdrawing groups were substituted on the ring. The use of this reaction to explore further derivatives is under investigation.

References

1. (a) See for example: Sundberg, R. J. *Indoles*; Academic Press: San Diego, CA, 1996; pp. 105–118; (b) Comins, D. L.; Stroud, E. D. *Tetrahedron Lett*. **1986**, *27*, 1869–1872; (c) Matassa, V. G.; Maduskuie, T. P.; Shapiro, H. S.; Hesp, B.; Snyder, D. W.; Aharony, D.; Krell, R. D.; Keith, R. A. *J. Med. Chem*. **1990**, *33*, 1781–1790; (d) Katritzky, A. R.; Lan, X.; Lam, J. N. *J. Org. Chem*. **1991**, *56*, 4397–4403.
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4. For an intramolecular version, see: Martin, T.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 241–246.
5. (a) Table 1, entry 4 ($BF_3{\cdot}Et_2O$ procedure): To a solution of methyl 4-formyl-3-methoxy-benzoate (**2a**, 4.52 g, 23 mmol) in CH_2Cl_2 (212 mL) at −30°C was added $BF_3{\cdot}Et_2O$ (2.9 mL, 23 mmol) followed by dropwise addition of a solution of 6-chloro indole (3.21 g, 21 mmol) in CH_2Cl_2. After a few minutes triethylsilane (10.1 mL, 64 mmol) was added, the cooling bath was removed after 15 min and the reaction was stirred until the disappearance of the initially formed spot (bis-indolylmethane intermediate) was observed by TLC analysis. The reaction was worked up by addition of 1N NaOH, diluted with CH_2Cl_2 and washed with 1N NaOH, water, and brine, dried over sodium sulfate and concentrated under reduced pressure. The crude mixture was then purified by column chromatography using 10–20% EtOAc/hexanes as eluent to give 3 g (43% yield) of the product as a white solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.96 (br s, 1H), 7.53 (br s, 1H), 7.52 (dd, J=1.7, 7.7 Hz, 1H), 7.41 (d, J=8.5 Hz, 1H), 7.35 (d, J=1.7 Hz, 1H), 7.10 (d, J=7.7 Hz, 1H), 7.04 (dd, J=1.7, 8.5 Hz, 1H), 6.94 (d, J=2.5 Hz, 1H), 4.09 (s, 2H), 3.92 (s, 3H), 3.89 (s, 3H). Anal. calcd for $C_{18}H_{16}ClNO_3$: C, 65.56; H, 4.89; N, 4.25; Cl, 10.75. Found: C, 65.36; H, 4.91; N, 4.38; Cl, 10.86.
   (b) Alkylation with benzhydryl bromide (general procedure): To a solution of indole (1.0 equiv.) in DMF (0.2 M) was added NaH (1.2 equiv.). After 15 min benzhydryl bromide (1.1 equiv.) was added and the reaction mixture was stirred for 18 h at ambient temperature. The reaction was diluted with EtOAc and washed with water, brine, dried over sodium sulfate and concentrated under reduced pressure and purified by column chromatography using EtOAc/hexanes as eluent to give the product.
   (c) Table 2, entry 1 (TFA) procedure: To a solution of 1-benzyl-6-chloro indole (4.0 g, 16.6 mmol) and 4-bromobutyraldehyde (2.5g, 16.6 mmol) in CH_2Cl_2 (165 mL) at 0°C was added triethylsilane (5.79 g, 47 mmol) followed by trifluoroacetic acid (2.6 mL, 33 mmol). After 10 min at 0°C the ice bath was removed and the reaction was stirred until the disappearance of the initially formed spot (bis-indolylmethane intermediate) was observed by TLC analysis. The reaction was worked up by addition of saturated $NaHCO_3$, diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$, water, and brine, dried over sodium sulfate and concentrated under reduced pressure. The crude mixture was then purified by column chromatography using 1–5% EtOAc/hexanes as eluent to give 3.78 g (48% yield) of the product as a white solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.48 (d, J=8.2 Hz, 1H), 7.29 (m, 3H), 7.23 (d, J=1.9 Hz, 1H), 7.07 (m, 2H), 7.06 (dd, J=1.7, 6.6 Hz, 1H), 6.89 (br s, 1H), 5.22 (s, 2H), 3.43 (t, J=6.6 Hz, 2H), 2.75 (t, J=6.8 Hz, 2H), 1.91 (m, 4H). Anal. calcd for $C_{19}H_{19}BrClN$: C, 60.58; H, 5.08; N, 3.72. Found: C, 60.71; H, 5.08; N, 3.62.
6. (a) Ward, J. S.; Fuller, R. W.; Merritt, L.; Snoddy, H. D.; Paschal, J. W.; Mason, N. R.; Horng, J. S. *J. Med. Chem*. **1988**, *31*, 1512–1519; (b) Lanzilotti, A. E.; Littel, R.; Fanshawe, W. J.; McKenzie, T. C.; Lovell, F. M. *J. Org. Chem*. **1979**, *44*, 4809–4813.
7. When the indole was *N*-alkylated under NaH/benzyl/benzhydryl bromide conditions approximately 15% of the N_1C_3 dialkylated indole was formed. The desired product was difficult to separate from the dialkylated product and the resulting mixture was used in the reductive alkylation reaction. The yield on these reactions is thus based upon the amount of aldehyde used.