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MILD REDUCTION OF INDOLES TO INDOLINES WITH ZINC BOROHYDRIDE

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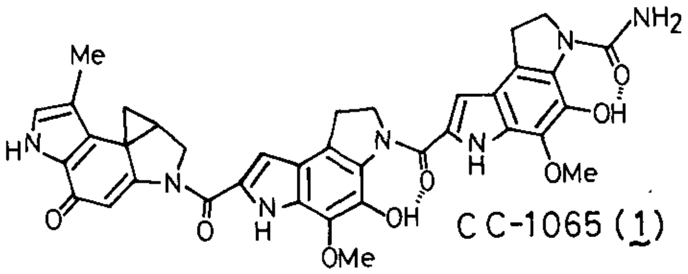
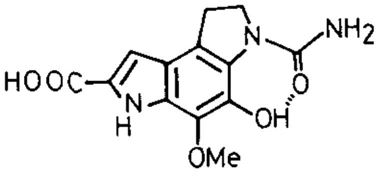
Abstract —— Mild reduction of indoles to indolines was achieved by using zinc borohydride as a neutral reducing agent.

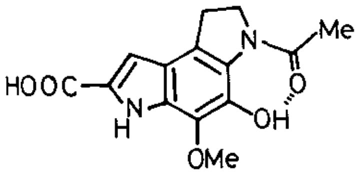
In the course of our studies on the use of zinc borohydride for the selective reduction of various functional groups, we have reported that the reagent is very useful for the reduction of benzenethiol esters,[1] acyl chlorides,[2] acetals and ketals.[3] In this paper we wish to describe a mild reduction of indoles to indolines. There has been known a variety of methods for the reduction of indoles to indolines[4] including the reagents such as borane,[5] amine-borane complexes,[6] borohydrides,[7] NaCNBH$_3$,[8] silicon hydrides,[9] dissolving metals,[10] H$_2$ over catalysts,[11] and others.[12] The utility of this transformation has become increasingly important in connection with the synthetic interest of an antitumor agent CC-1065 (1) or phosphodiesterase inhibitors PDE-I (2) and PDE-II (3).[13, 14] Generally, for this purpose borane or



CC-1065 (1)

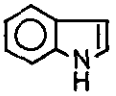
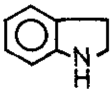
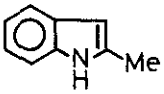
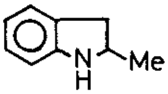
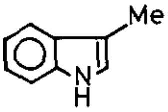
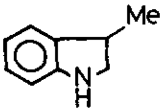
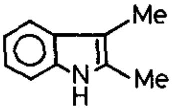
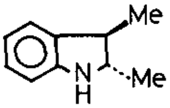
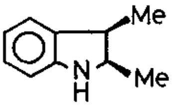
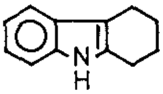
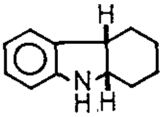
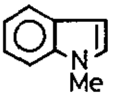
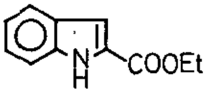


PDE-I (2)



PDE-II (3)

Table 1. Reduction of Indoles to Indolines with Zinc Borohydride[a]

Substrate	Indoline	Yield/%[b]
		92, 96[c]
		94
		38(62)
	 	39(61)[d] 61[c,e]
		30(64)
	——	NR
	——	NR

[a] Reactions were carried out for 2 days at room temperature unless otherwise noted. All the products gave satisfactory ir, nmr, and high resolution ms data.

[b] All yields refer to isolated materials, values in parentheses are recovery.

[c] At 40 °C. [d] Trans : cis = 16 : 1. [e] Trans : cis = 4.5 : 1.

$NaCNBH_3$ has been employed under strongly acidic conditions (*e.g.*, in CH_3COOH or CF_3COOH).[13, 15]

We found that indoles can be reduced to the corresponding indolines with zinc borohydride at room temperature under neutral conditions, although there is a remarkable difference in reactivity depending on their structure (Table 1). Thus, indole and 2-methylindole gave indoline and 2-methylindoline in 92 and 94 % yields respectively.

Reduction of 3-methylindole, 2,3-dimethylindole, and tetrahydrocarbazole was rather slow and a considerable amount of starting material was recovered in every case. However, it would be worth to note the high stereoselectivity of the reduction of 2,3-dimethylindole providing a 16 : 1 mixture of trans- and cis-products,[16] whereas the use of bis(trifluoroacetoxy)borane or borane itself gives a 2 : 1 or 53 : 47 mixture of each isomer.[5, 17] In the case of tetrahydrocarbazole only cis-product was obtained.[18]

1-Methylindole and ethyl indole-2-carboxylate were recovered unchanged.

Since zinc borohydride is readily available from $ZnCl_2$ and $NaBH_4$,[19] the above procedure is a useful addition to the present methodology for the mild and selective reduction of indoles to indolines.[20] The advantage of this reaction is the use of ether as a solvent which precludes the contamination by alkylation on nitrogen or the destruction of the reducing agent.

The general procedure is as follows. To a solution of indoles(1 mmol) in 1.3 ml of dry ether at 0 °C under N_2 was added 6.7 ml of zinc borohydride (*ca.* 0.15 M ether solution, 1 mmol) and the mixture was stirred at room temperature for 2 days. During the reaction a white insoluble substance was gradually formed. After quenching by addition of dil HCl followed by basification with 2N NaOH, the mixture was extracted with AcOEt. Conventional treatment and purification by preparative TLC (silica gel) gave the desired indolines in pure form.[21]

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20. As pointed out by referee, borane and amine-borane complexes are also mild reducing agents and in some cases rather reactive under slightly acidic conditions. See Ref. 5 and 6.
21. All the products gave satisfactory ir, nmr, and high resolution ms data.

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