Tetrahedron Letters,Vol.30,No.49,pp 6833-6836,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

# THE REDUCTION OF N-(PHENYLSULFONYL)INDOLES WITH SODIUM CYANOBOROHYDRIDE IN TRIFLUOROACETIC ACID

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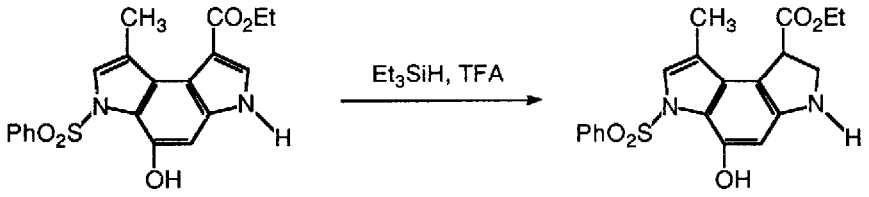
***Summary:*** *The reduction of N-(phenylsulfonyl)indoles to the corresponding N-(phenylsulfonyl)indolines can be accomplished with good to excellent yields using sodium cyanoborohydride ($NaCNBH_3$) in trifluoroacetic acid (TFA).*

The reduction of indoles to indolines (2,3-dihydroindoles) is a frequently encountered synthetic manipulation and is most commonly effected under acidic conditions via initial protonation at the C-3 position followed by reduction of the resultant indolenium species.[1] In recent years, however, we have found that 2- and 3-acyl-1-(phenylsulfonyl) indoles undergo reductive deoxygenation without concomitant reduction of the indole double bond using either sodium borohydride ($NaBH_4$) in TFA,[2] or borane-*tert* -butylamine complex in the presence of aluminum chloride.[2,3] Although these results contradict the well known tendency of N-unprotected or N-alkylindoles to be reduced to indolines by a variety of hydride sources in the presence of acids (e.g., $NaBH_4$ in carboxylic acids[4,5] or $ZnCl_2$,[6] $NaCNBH_3$ in acetic acid[4,7] or TFA,[8] $BH_3$[8a,9] or $BH_3$-pyridine in HCl,[10] $BH_3$·THF[8c,d,11] or $Et_3SiH$ in TFA[8b,12]), the exceptional behavior of the N-phenylsulfonyl derivatives seemed to reinforce a common assumption that indoles bearing a strong electron-withdrawing group were resistant to C-3 protonation and thus effectively inert to reduction.[13] This resistance to reduction is typified by a recent example from the Magnus group involving the pyrroloindole below, in which only the apparently more basic indole-3-carboxylate fused pyrrole ring suffers protonation and subsequent reduction.[12b]



A consideration of the accepted mechanism for reduction of indoles under acidic conditions indicates that some factors capable of influencing or limiting the effectiveness of this process are: a) the basicity of the indole substrate, or conversely the strength of the acid employed, and b) the nature, strength and survivability of the actual reducing species existing in this acidic milieu. Our recent observation that TFA is capable of inducing a slow (24 hr) dimerization of N-(phenylsulfonyl)indole,[14] and thus capable of protonating (at least to some extent) a highly deactivated indole, suggested that a hydride source with greater acid-stability than $NaBH_4$ or $Et_3SiH$ would be required if one were to effect the successful reduction of such indoles.

We now wish to report that when $NaCNBH_3$[15] is substituted for $NaBH_4$ in the TFA mediated reduction of 2- and 3-acyl-1-(phenylsulfonyl)indoles (**1a-e**), tandem reduction of both the carbonyl group and the indole double bond occurs to afford 2- and/or 3-alkyl-1-(phenylsulfonyl)indolines (**2a-e**) in very good yields and without rearrangement of substituents, or reductive loss of bromine from the C-5 position.[2b,16] As can be seen in Table 1, the presence of an oxygen function on the 2- or 3-substituent is not a necessary requirement for reduction, since N-(phenylsulfonyl)indole (**1f**) as well as a variety of alkyl-substituted derivatives (**1g-j**) are also reduced to the corresponding N-(phenylsulfonyl)indolines in very high yields.

In order to assess the stereoselectivity of this reduction, 2,3-dimethyl-1-(phenylsulfonyl)indole[17] was prepared and subjected to treatment with $NaCNBH_3$/TFA at ice bath temperature. The product mixture was found to consist of an approximately 70:30 mixture (NMR)[18] of stereoisomers, in which the more stable trans-isomer of 2,3-dimethyl-1-(phenylsulfonyl)indoline predominates.

As might be expected, the $NaCNBH_3$/TFA system fails to reduce 3-cyano-1-(phenylsulfonyl)indole and ethyl 1-(phenylsulfonyl)indole-3-carboxylate, which are recovered unchanged after 24 hours under these conditions. Apparently the combined deactivating effects of an N-phenylsulfonyl group in addition to a cyano or ester function at the C-3 position render these species inert to C-3 protonation and subsequent reduction.

**Representative Procedure:** To magnetically stirred TFA (10 mL) at 0 °C under a nitrogen atmosphere was added slowly and in portions $NaCNBH_3$ (0.30 g).* The resulting mixture was stirred for an additional 15 min at ice bath temperature and 3-ethyl-1-(phenylsulfonyl)indole (0.30 g, 1.1 mmol) was added slowly. The mixture was allowed to warm to ambient temperature and, after one hour, additional $NaCNBH_3$ (0.30 g) was added in portions. After thin layer chromatography indicated complete disappearance of starting indole, water (30 mL) was added slowly and the mixture stirred overnight (with slow evolution of gas). The resulting white crystals were then vacuum filtered, washed thoroughly with distilled water, and dried in vacuo to afford 0.25 g of analytically pure 3-ethyl-1-(phenylsulfonyl)indoline, mp 94-95 °C. Extraction of the aqueous filtrate with methylene chloride afforded an additional 0.02 g of product (89% combined).

*NOTE: Sodium cyanoborohydride reacts with trifluoroacetic acid with vigorous evolution of hydrogen. Minor explosions were sometimes observed in the absence of a blanket of nitrogen.

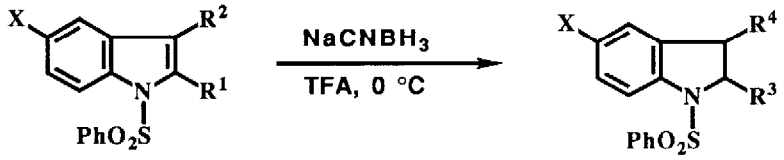



**TABLE 1.** Reductions with $NaCNBH_3$ in TFA at 0 °C.

| | Substrate (1) X | $R^1$ | $R^2$ | Product (2) $R^3$ | $R^4$ | mp, °C | Yield, % [a,b] |
|---|---|---|---|---|---|---|---|
| **1a** | -H | -H | -COMe | -H | -Et | 99-101 (Lit.[19] 97-97.5) | 83 |
| **1b** | -H | -H | -COEt | -H | -Pr | 93-94 | 93 |
| **1c** | -H | -COMe | -H | -Et | -H | 101-103 | 94 |
| **1d** | -H | -COEt | -H | -Pr | -H | 103-105 | 91 |
| **1e** | -Br | -COMe | -H | -Et | -H | 90.5-91.5 | 75 |
| **1f** | -H | -H | -H | -H | -H | 129.5-131 (Lit.[19] 132-132.5) | 98 |
| **1g** | -H | -H | -Me | -H | -Me | 85-88 | 84 |
| **1h** | -H | -H | -Et | -H | Et | 94-95 | 89 |
| **1i** | -H | -Me | -H | -Me | -H | 84.5-86.5 (Lit.[19] 88-89) | 92 |
| **1j** | -H | -Me | -Me | -Me | -Me | 72-76[c] | 85 |

a Yield after filtration and drying.
b All compounds were fully characterized by IR, $^1H$ NMR and combustion analysis.
c Recrystallization of this 70:30 mixture from methanol afforded the pure *trans*-isomer, mp 111-113 °C (Lit.[7a] 100-102). This sample was identical (mp, IR, NMR) to the a recrystallized sample of the *trans*-isomer prepared from 2,3-dimethylindoline (Aldrich) and benzenesulfonyl chloride.

**Acknowledgements.** We thank the Donors of the Petroleum Research Fund, administered by the American Chemical Society, and the Wright State University Research Council for support of this research.

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(Received in USA 6 September 1989)