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Reduction of N-Acylisatins with [BH_3.THF] Complex

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Abstract: N-acylisatins can be directly converted in high yields to N-alkylindoles by reduction, at room temperature, with freshly prepared BH_3.THF complex. This reduction represents an alternative method for the preparation of N-alkylindoles with long-chain alkyl groups, especially those with halogens within the carbon chain.

The indole nucleus with an alkylated nitrogen atom is common to a large number and a wide variety of biologically active natural compounds [1,2].

The N-alkylation of the indole nucleus can present some difficulties, due to its ambident nucleophilic character. Under normal conditions, the alkylation of this nucleus affords a mixture of the products in the 1(N-alkylation) and 3-positions. The relative amounts of these products depend on the base and on the solvent used [3]. Several methods for the N-alkylation of this nucleus have been reported in the literature, the most successful ones involving the use of phase transfer catalysis [4]. Recently, a new method for indole N-alkylation under Mitsunobu reaction conditions was reported [5]. However, the indole nucleus needs to be activated by two electron withdrawing groups, in order to undergo N-alkylation.

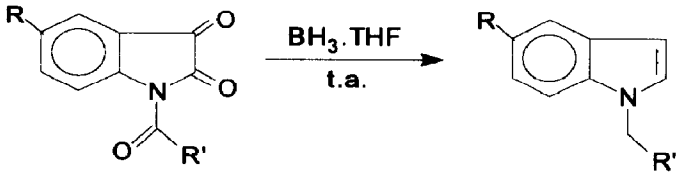
In this paper we describle a rapid and efficient method for the preparation of the N-alkylindoles by reduction of N-acylisatins with freshly prepared BH_3.THF complex (from the reaction of sodium borohydride with boron trifluoride [6]).

The isatins were prepared according to Sandmeyer's method, which consists of the reaction of anilines with chloral hydrate in the presence of sodium sulfate and hydroxylamine hydrochloride, followed by the treatment of the isonitrosoacetanilide intermediate with sulfuric acid [7]. Treatment of the isatins with acyl chlorides or with anhydrides under reflux gave the corresponding N-acylisatins. Their IR spectra showed three strong absorptions, due to carbonyl groups.

Even though the reduction of N-methylisatins [8] and of molecules containing isatins moieties[9] with BH_3.THF complex affords the corresponding indoles in good yields and N-formylindole [10] gives

N-methylindole with the same reducing agent, the reduction of N-acylisatins with BH_3.THF complex had never been investigated. We therefore examined the reduction of N-acylisatins with BH_3.THF complex to the corresponding indoles. Treatment of N-acylisatins with an excess of a BH_3.THF solution in THF at room temperature gave the corresponding indoles in very high yields. If the reaction time is longer than one hour, reduction of the product is observed with formation of the corresponding indoline. Our results are summarized in Table 1; all indoles produced have been previously reported in the literature, with the exception of **13** and **14**.

Table 1 - Reaction of **1** - **7** with BH_3.THF Complex in anhydrous THF, at room temperature



Entry	Substrate	Product	Yield
1	(**1**) R = R' = Me	(**8**) R = R' = Me	85%
2	(**2**) R = H, R' = Et	(**9**) R = H, R' = Et	84%
3	(**3**) R =H, R' = n-Pr	(**10**) R =H, R' = n-Pr	85%
4	(**4**) R = Me, R' = H	(**11**) R = Me, R' = H	84%
5	(**5**) R = H, R' = ϕ	(**12**) R = H, R' = ϕ	80%
6	(**6**) R = H, R' = CH_2Cl	(**13**) R = H, R' = CH_2Cl [11]	86%
7	(**7**) R = H, R' = $(CH_2)_{10}CH_3$	(**14**) R = H, R' = $(CH_2)_{10}CH_3$ [11]	72%

In conclusion, the reductions proceed under mild reaction conditions, with a variety of substrates, in high yield. This reduction is an alternative method for the preparation of N-alkylindoles. This method has a further advantage as it allows the preparation of N-alkylindoles with long-chain alkyl groups. The preparation of N-(2'-chloro)ethylindole in high yields is a potentially useful method for the synthesis of azepindol, a CNS-antidepressive drug. The investigation of similar reduction reactions of more complex substrates is currently under way in our laboratory.

EXPERIMENTAL

General procedure:

To a solution of 1.06 mmoles of N-acylisatins in 8 ml of anhydrous THF at 0°C, 3 ml of BH_3.THF was added dropwise under a N_2 atmosphere. After 1 hour of stirring at room temperature, 1 ml of 6 N aqueous hydrochloric acid was added, followed by saturated aqueous sodium hydroxide to a neutral pH. The solution was extracted with ether (3 x 20 ml) and the ethereal phase collected, washed with water (20 ml), brine (2 x 20 ml), dried over sodium sulfate, and filtered through a silica gel column. The solvent was removed under reduced pressure. The material obtained was dissolved in dichloromethane and filtered again through a silica gel column using dichloromethane as eluent, leading to N-alkylindoles. No further purification was necessary. All the products were characterized by FT-IR, MS and 200 MHz ^1H NMR.

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11. Analytical data for compounds **13** and **14** are given below
13: *^{1}H NMR (200MHz, $CDCl_3$)*: δ = 3.8 (t, 2H), 4.4 (t, 2H), 6.5 (d, 1H), 7.1-7.3 (4H),7.6 (d,1H) ppm. *MS*: m/e = 181 (8%), 179 (22%) and 130 (100%).
14: *^{1}H NMR (200MHz, $CDCl_3$)*: δ = 1.2 (23H), 3.1 (t,2H), 6.7 (d,1H), 7.0-7.4 (4H), 7.5 (d,1H) ppm. *MS*: m/e = 285 (82%), 172 (19%), 158 (18.3%), 130 (100%)

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