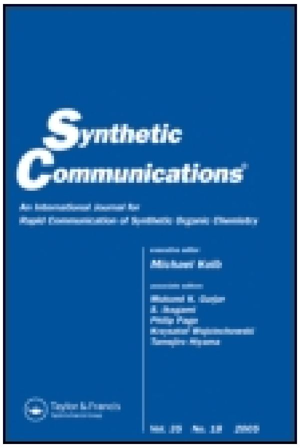

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Reduction of 3-Acyl Derivatives of Oxindoles, Benzo[b]furan-2-ones, and Benzo[b]thiophen-2-ones to the Corresponding Alkyl Derivatives by Sodium Borohydride-Acetic Acid

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Reduction of 3-Acyl Derivatives of Oxindoles, Benzo[b]furan-2-ones, and Benzo[b]thiophen-2-ones to the Corresponding Alkyl Derivatives by Sodium Borohydride–Acetic Acid

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Abstract: It was found that 3-acyl derivatives of oxindoles, benzo[b]furan-2-ones, and benzo[b]thiophen-2-ones could be efficiently and conveniently reduced to the corresponding alkyl derivatives by pelletized sodium borohydride in acetic acid. A typical procedure involves heating the acylated substrates for approximately 90 min in a slurry of glacial acetic acid and sodium borohydride to provide the 3-alkyl product in yields ranging from 62% to 96%. This synthetic methodology represents a convenient approach to the synthesis of the alkyl derivatives.

Keywords: Benzofuran-2-one, benzothiophen-2-one, borohydride, oxindole, reduction

Several years ago, we reported that acylated derivatives of barbituric acid, 4-hydroxycoumarin, and Meldrum's acid were easily reduced to the corresponding alkyl derivatives by treatment with sodium cyanoborohydride–acetic acid.[1] We now report that this transformation can be made to occur with 3-acyl derivatives of oxindoles, benzo[b]furan-2-ones, and benzo[b]thiophen-2-ones,

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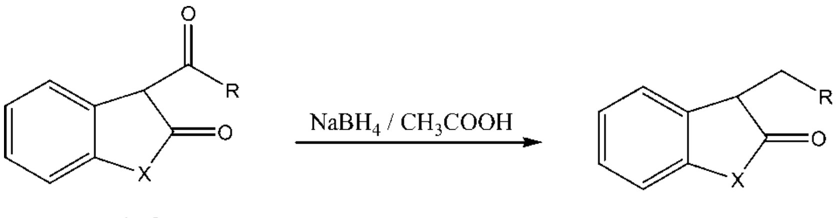
and that pelletized sodium borohydride in acetic acid is quite effective as a reducing agent. Efforts to synthesize alkylated oxindoles directly from oxindole often result in mixtures because of multiple alkylations and *N*-alkylations.[2] Multiple alkylations can be avoided by an acylation reaction followed by reduction. However, these reductions are typically carried out using a metal catalyst and hydrogen gas under high pressures. This method is inconvenient, and side products resulting from reduction of the oxindole carbonyl have been reported.[3] The synthetic strategy under investigation avoids the problem of multiple alkylations by replacing the direct alkylation with an acylation. The inconvenience of reduction under high pressure along with potential loss of the oxindole is eliminated by a convenient reduction procedure involving acetic acid and pelletized sodium borohydride at low temperatures and atmospheric pressures. Success with this endeavor has led to an expansion of the methodology to include the reduction of 3-acyl-benzo[b]furan-2-ones and 3-acyl-benzo[b]thiphen-2-ones to the corresponding alkyl derivatives.

The general synthetic procedure that was developed is unique in its simplicity (Figure 1). Briefly, a specific substrate is added to a magnetically stirred slurry of glacial acetic acid and sodium borohydride. The reaction mixture is subsequently heated at mild temperatures under atmospheric pressure for about 90 min. After gradually cooling to room temperature, the reaction mixture is diluted with distilled water, and the products are extracted with diethyl ether. Table 1 lists the specific results for a variety of the reductive transformations that were performed.

Removal of the extraction solvent under vacuum provided products **2a** and **2c–h** with a high degree of purity as determined by GC/MS and melting or boiling points. However, the extraction procedure consistently yielded the product **2b** as an oil, although it is known to exist as a crystalline solid. It was found that **2b** could be purified by column chromatography with 20% ethyl acetate (EtOAc/hexane) as the eluting solvent or by recrystallization from ether/hexane, which provided the product as a yellow crystalline solid with the appropriate melting point.



1a-h

2a-h

Figure 1. General reaction scheme for the reduction of the 3-acyl derivatives. Refer to Table 1 for the empirical results pertaining to the reduction of specific substrates.

Table 1. Results for a variety of reductive transformations

Substrate	Product	X	R	Yield (%)
1a	**2a**	N—H	H	72
1b	**2b**	N—H	CH_3	74
1c	**2c**	N—H	CH_2Ph	84
1d	**2d**	N—H	CH_2OPh	82
1e	**2e**	O	CH_3	96
1f	**2f**	O	CH_2CH_3	72
1g	**2g**	S	H	62
1h	**2h**	S	CH_3	74

Representative compounds from three classes (oxindoles, benzo[b]furan-2-ones, and bezo[b]thiophen-2-ones) have been subjected to the general reduction procedure with good to excellent yields (62–96%), and consequently, it is envisioned that the procedure could be applied to a large variety of acylated compounds of these types.

EXPERIMENTAL

All commercially available reagents were used without further purification. Each substrate was prepared according to literature procedures; the starting materials used for the preparation of the substrates were reacted under a nitrogen atmosphere in a round-bottomed flask of the appropriate size equipped with a reflux condenser. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian EM360L CW 60-MHz spectrometer upgraded with an Anasazi Instruments, Inc. EFT FT NMR upgrade with carbon-13 accessory. Carbon-type assignments were made from ^{13}C NMR DEPT data. Quantitative Technologies, Inc. (Whitehouse, NJ) and Atlantic Microlab, Inc. (Norcross, GA) performed analyses. For the general reduction procedure, the appropriate mass of pelletized sodium borohydride was achieved by shaving the pellets with a razor blade. It should be noted that although less hazardous than the powder form, pelletized sodium borohydride creates a possible ignition hazard.

General Reduction Procedure

In a 100-mL round-bottomed flask equipped with a water-cooled reflux condenser, 3.32 mmol of the acylated substrate were magnetically stirred in 6.5 mL of glacial acetic acid. To the resulting suspension was added 10.2 mmol of sodium borohydride in the form of a pellet. Gas evolved upon the addition. The reaction mixture was gradually warmed to 75°C over a

30-min period. Another 10.2 mmol of pelletized sodium borohydride was added to the transparent reaction mixture that resulted. The temperature was maintained at ca. 75°C for an additional 60 min. After a total reaction time of 90 min, the reaction mixture was gradually cooled to room temperature, diluted with 50 mL of distilled water, and extracted with three 20-mL portions of diethyl ether. The combined organic layers were washed with three 45-mL portions of 5% sodium bicarbonate, thoroughly dried over anhydrous magnesium sulfate, filtered by gravity, and concentrated in vacuo.

The following 3-acyl and 3-alkyl derivatives of oxindoles, benzo[b]furan-2-ones, and benzo[b]thiophen-2-ones are known compounds that have spectral data in accord with the literature data: **1a**,[4] **2a**,[2] **1b**,[5] **2b**,[6] **1c**,[5] **2c**,[5] **1d**,[6] **2d**,[6] **1e**,[7] **2e**,[8] **1f**,[9] **1g**,[10] **2g**,[11] and **1h**.[10] Purity was verified by melting point and/or elemental analysis as follows:

2a: Mp 120–121°C (heptane), lit. mp 123–124°C. **2b:** Mp 97–99°C (ether/hexane), lit. mp 104°C. **2c:** Anal. calcd. for $C_{16}H_{15}NO$: C, 80.98; H, 6.37: N, 5.90. Found: C, 80.93; H, 6.40; N, 5.89. **2d:** Mp 106–107°C (ether/hexane), lit. mp 108°C **2e:** Anal. calcd. for $C_{10}H_{10}O_2$: C, 74.09; H, 6.17. Found: C, 74.18; H, 6.24. **2g:** Anal. calcd. for C_9H_8OS: C, 65.84; H, 4.92; S, 19.49. Found: C, 65.71; H, 4.98; S, 19.38. Products **2f** and **2h** are new compounds with the following characterization data.

3-Propyl-2(3H)-benzofuranone (**2f**): The colorless oil boiled at 165–166°C (33 mm). 72% yield. ^{1}H NMR (60 MHz, $CDCl_3$) δ 7.2 (m, 4H), 3.7 (t, 1H), 1.9 (m, 2H), 1.5 (m, 2H), 0.95 (t, 3H). Anal. calcd. for $C_{11}H_{12}O_2$: C, 74.97; H, 6.86. Found: C, 75.00; H, 6.87. 3-Ethyl-benzo[b]thiophen-2(3H)-one (**2h**): The colorless oil boiled at 143–144°C (14 mm). 74% yield. ^{1}H NMR (60 MHz, $CDCl_3$) δ 7.4 (m, 4H), 3.85 (t, 1H), 2.1 (m, 2H), 0.85 (t, 3H). Anal. calcd. for $C_{10}H_{10}OS$: C, 67.43; H, 5.61; S, 17.97. Found: C, 67.27; H, 5.68; S, 17.85.

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