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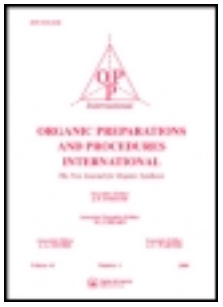

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REDUCTION OF π-DEFICIENT HETEROCYCLIC SECONDARY CARBINOLS WITH SODIUM BOROHYDRIDE/ TRIFLUOROACETIC ACID

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REDUCTION OF π-DEFICIENT HETEROCYCLIC SECONDARY CARBINOLS WITH SODIUM BOROHYDRIDE/TRIFLUOROACETIC ACID

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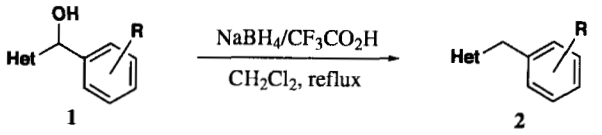
The reduction of diarylcarbinols with sodium borohydride/trifluoroacetic acid (TFA), a reaction developed by Gribble and co-workers in 1977, is a convenient method for the preparation of the corresponding diarylmethanes.[1] In 1991, Nutaitis and co-workers demonstrated that this method was also applicable to the reduction of secondary heterocyclic carbinols substituted with any combination of thiophene, furan, benzothiophene, benzofuran, and phenyl ring systems; the presence of 1,3-azole, 1,3-benzazole, or pyridyl substituents prevented the reduction, leading to recovered starting material.[2] The resistance to reduction of the azole and pyridyl based carbinols was attributed to the inability of the requisite carbocation intermediate to be generated. The postulated mechanism for these reductions involves formation of a benzylic carbocation, which is subsequently trapped by hydride.[1]



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a) Het = 2-thiazolyl, R = 4-OMe; b) Het = 2-benzothiazolyl, R = 4-OMe; c) Het = 2-benzoxazolyl, R = 4-OMe; d) Het = 4-pyridyl, R = 4-OMe; e) Het = 2-pyridyl, R = 4-OMe; f) Het = 2-thiazolyl, R = 4-NMe_2; g) Het = 2-pyridyl, R = 3,4 -OCH_2O-; h) Het = 3-pyridyl, R = 4-OPh; i) Het = 2-benzothiazolyl, R = 2-OMe; j) Het = 2-thiazolyl, R = 2,4-di-OMe; k) Het = 3-pyridyl, R = 4-Br; l) Het = 2-(1-methylimidazolyl), R = 4-Me; m) Het = 2-thiazolyl, R = H

In the strongly acidic medium utilized in this method, the azole or pyridyl nitrogen will be protonated, requiring the formation of a high energy dication if reduction is to occur. Apparently, the one additional aromatic substituent does not provide sufficient resonance stabilization of these very unstable benzylic carbocations since all reduction attempts of these alcohols failed. In 1997, however, we reported that the presence of an additional aromatic substituent on the carbinol carbon atom (phenyl, thienyl, furyl, benzo[b]furyl, benzo[b]thienyl) led to reduction, providing triarylmethanes in 39-73% yields.[3] The successful reduction of these substrates was attributed to increased resonance stabilization of the benzylic carbocation provided by the addi-

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tional aromatic ring. Interestingly, if the additional aromatic ring is another 1,3-azole or 1,3-benzazole, the reduction fails. Finally, in 2002, it was further demonstrated that pyridyl-based carbinols behave similarly to the azoles - that is- secondary alcohols are inert, but tertiary alcohols in which all three substituents are aromatic rings, can be reduced.[4]

To date, only unsubstituted aromatic rings have been explored in this heterocyclic alcohol reduction methodology. It was surmized that incorporation of electron-donating substituents into one of the aromatic rings, especially substituents that donate electron density *via* resonance, could perhaps provide sufficient carbocation stabilization to allow successful reduction of azole and pyridyl based secondary alcohols. To test this hypothesis, α-(2-thiazolyl)-4-methoxybenzyl alcohol (**1a**) was prepared and subjected to the reduction conditions as previously described (sodium borohydride/TFA pre-mix at room temperature).[3,4] This compound was chosen for study as it contains a methoxy substituent present in a remote position from which it can provide additional resonance stabilization of the carbocation intermediate without imposing any steric constraints to its formation. In addition, the chosen substituent does not contain an additional protonation site that could potentially hinder formation of the desired benzylic carbocation. Although analysis of the reaction mixture by both TLC and proton NMR revealed primarily unreacted starting material, both analysis methods also indicated the presence of a small amount of the desired reduction product as evidenced by higher Rf material and a signal for the diaryl methylene unit at δ 4.27. In previous studies, the previously inert diaryl carbinols did not show any sign of reduction products. This result encouraged us to submit the substrate again to reduction by adding it to the sodium borohydride/TFA pre-mix and heating the mixture at reflux. From this reaction, the desired reduction product, 2-(4-methoxybenzyl)thiazole (**2a**) was obtained in 58% yield. As a control experiment to determine whether successful reduction of this alcohol was due to the presence of the substituent or to the fact that the reaction was heated, α-(2-thiazolyl)benzyl alcohol (**1m**), a substrate that was previously reported to be inert to reduction,[2] was refluxed in the sodium borohydride/TFA pre-mix. The alcohol was not reduced and unchanged starting material, which showed no evidence of the reduction product by TLC or proton NMR, was recovered in 92% yield, indicating that successful reduction of the azole-based secondary alcohol was due to the presence of the electron-donating methoxy group and not simply to the reflux conditions.

In order to test the generality of this reaction, a number of additional substrates were prepared and subjected to the same reduction conditions; yields of 34-74% for those substrates that underwent reduction were obtained. The results are summarized in the Table. As can be seen, a variety of π-deficient heterocyclic alcohols were successfully reduced and several substituents, including alkoxy, aryloxy, and dialkylamino, are capable of providing enough additional resonance stabilization to allow the cation to be generated. Substituents *ortho* to the required benzylic carbocation are not tolerated, presumably due to steric constraints; two substituents, bromo and alkyl, do not appear to provide sufficient stablilization for carbocation

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formation and thus subsequent reduction. Surprisingly, the *meta* alkoxy substituent present in substrate **1g**, which is not capable of resonance interaction with the benzylic carbocation and therefore inductively acts as an electron-withdrawing substituent, did not prevent reduction.

Table. Reduction of Secondary Alcohols with $NaBH_4/CF_3CO_2H$

Product	Yield (%)[a]	^1H NMR of benzylic H (δ)
2a	58	4.27
2b	40[b]	4.37
2c	65[b]	4.21
2d	41[b]	3.88
2e	48[b]	4.09
2f	74	4.24
2g	39[b]	4.05
2h	45	3.95
2i	0	----
2j	0	----
2k	0	----
2l	0	----
2m	0	----

a) Yields after flash chromatography. b) Previously reported products exhibited satisfactory physical and/or spectral properties.[5]

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EXPERIMENTAL SECTION

All reactions were performed in oven-dried glassware (120°C), and all lithiation reactions were performed under nitrogen. Tetrahydrofuran (THF) was distilled from sodium/benzophenone. Thin layer chromatography was performed on pre-coated (0.25 mm) silica gel 60 F_{254} plastic sheets and was visualized with 254 nm ultraviolet light. Flash chromatography was performed with silica gel 60 (200-400 mesh).[6] Proton and carbon NMR spectra were recorded on a Jeol Eclipse400 FT-NMR spectrometer; chemical shifts are reported in parts per million relative to internal-TMS (proton) or the solvent $CDCl_3$ (carbon). Melting points were determined in open capillary tubes with a Mel-Temp Laboratory Devices apparatus and are uncorrected. All of the alcohols except for the ones described below have been previously reported[7] and were prepared by standard literature procedures.

Preparation of α-(2-Benzothiazolyl)-4-methoxybenzyl Alcohol (1b). Typical Procedure- To a magnetically stirred solution of benzothiazole (1.98 g, 14.7 mmol) in dry THF (50 mL), at –78°C under nitrogen, was added by means of a syringe *n*-butyllithium (6.50 mL, 2.25 M, 14.6 mmol) over a period of 4 min. The reaction mixture was stirred at –78°C for 30 min then 4-methoxybenzaldehyde (1.80 mL, 14.8 mL) was added by means of a syringe. The reaction

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mixture was allowed to warm to room temperature and stirred for 24 hrs. It was diluted with water (100 mL) and extracted with ether (3 x 50 mL). The combined extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* with direct adsorption onto silica gel. Flash chromatography (2:1 hexanes/ether) gave α-(2-benzothiazolyl)-4-methoxybenzyl alcohol (**1b**) as a pale yellow oil (2.60 g, 66%). ^{1}H NMR($CDCl_3$): δ 7.99 (d, 1H), 7.84 (d, 1H), 7.48-7.41 (m, 3H), 7.36 (br t, 1H), 6.91 (d, 2H), 6.09 (d, 1H), 3.81 (s, 3H), 3.49 (d, 1H); ^{13}C NMR ($CDCl_3$): δ 175.3, 160.0, 152.8, 135.4, 133.3, 128.3, 126.2, 125.2, 123.2, 121.9, 114.3, 74.2, 55.4; IR (neat): 3186 cm^{-1}.

Anal. Calcd for $C_{15}H_{13}NO_2S$: C, 66.40; H, 4.83; N, 5.16; S, 11.82
Found: C, 66.30; H, 4.87; N, 5.17: S, 11.69

α-(2-Benzoxazolyl)-4-methoxybenzyl Alcohol (1c) was analogously prepared from benzoxazole and 4-methoxybenzaldehyde as a beige solid (39%), mp. 92-94°C. ^{1}H NMR($CDCl_3$): δ 7.73-7.69 (m, 1H), 7.48-7.46 (m, 1H), 7.44 (d, 2H), 7.33-7.31 (m, 2H), 6.91 (d, 2H), 5.97 (br s, 1H), 3.79 (s, 3H), 3.52 (br s, 1H); ^{13}C NMR($CDCl_3$): δ 166.8, 160.1, 151.1, 140.5, 131.1, 128.3, 125.3, 124.6, 120.2, 114.3, 111.0, 70.3, 55.4; IR (nujol): 3236 cm^{-1}.

Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49
Found: C, 70.62; H, 5.16; N, 5.50

α-(2-Thiazolyl)-2,4-dimethoxybenzyl Alcohol (1j) was analogously prepared from thiazole and 2,4-dimethoxybenzaldehyde as an orange-brown solid (53%), mp. 81-83°C. ^{1}H NMR($CDCl_3$): δ 7.70 (d, 1H), 7.27-7.24 (m, 2H), 6.50-6.47 (m, 2H), 6.18 (s, 1H), 3.81 (s, 6H); ^{13}C NMR($CDCl_3$): δ 175.0, 161.1, 157.8, 142.2, 128.9, 122.5, 119.2, 104.6, 99.0, 70.1, 55.54, 55.47; IR (nujol): 3213 cm^{-1}.

Anal. Calcd for $C_{12}H_{13}NO_3S$: C, 57.35; H, 5.21; N, 5.57; S, 12.76
Found: C, 57.41; H, 5.22; N, 5.56; S, 12.72

Preparation of 2-(4-Methoxybenzyl)thiazole (2a). Typical Procedure.- To magnetically stirred trifluoroacetic acid (25 mL) at room temperature, was added sodium borohydride (4 pellets, 1.6 g, 42 mmol) over a period of 10 min; the resulting mixture was stirred at room temperature for 10 min. A solution of α-(2-thiazolyl)-4-methoxybenzyl alcohol (0.252 g, 1.14 mmol) in methylene chloride (10 mL) was added and the mixture was refluxed for 3 hrs. The reaction mixture was allowed to cool to room temperature, carefully poured into 25% aqueous sodium hydroxide/ice (50 mL) to basify to pH 11, and extracted with ether (2 x 50 mL). The ethereal extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* with direct adsorption onto silica gel. Flash chromatography (3:1 hexanes/ether) gave 2-(4-methoxybenzyl)thiazole (**2a**) as an orange oil (0.132 g, 56%); ^{1}H NMR($CDCl_3$): δ 7.68 (d, 1H), 7.23 (d, 2H), 7.17 (d, 1H), 6.86 (d, 2H), 4.27 (s, 2H), 3.78 (s, 3H); ^{13}C NMR($CDCl_3$): δ 171.3, 158.8, 142.5, 130.2, 119.0, 114.3, 91.9, 55.3, 38.8.

Anal. Calcd for $C_{11}H_{11}NOS$: C, 64.36; H, 5.40; N, 6.82; S, 15.62
Found: C, 64.28; H, 5.35; N, 6.84; S, 15.32

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3-(4-Phenoxybenzyl)pyridine (2h) was prepared analogously from α-(3-pyridyl)-4-phenoxybenzyl alcohol (45%) as a colorless oil. ^{1}H NMR($CDCl_3$): δ 8.50 (s, 1H), 8.46 (d, 1H), 7.48 (d, 1H), 7.32 (t, 2H), 7.22 (dd, 1H), 7.13 (d, 2H), 7.08 (t, 1H), 6.98 (d, 2H), 6.94 (d, 2H), 3.95 (s, 2H); ^{13}C NMR($CDCl_3$): δ 157.4, 155.9, 150.2, 147.7, 136.7, 136.4, 134.7, 130.2, 129.8, 123.6, 123.3, 119.2, 118.8, 38.4.

Anal. Calcd for $C_{18}H_{15}NO$: C, 82.73; H, 5.79; N, 5.36
Found: C, 82.34; H, 5.78; N, 5.40

2-(4-Dimethylaminobenzyl)thiazole (2f) was prepared analogously from α-(2-thiazolyl)-4-dimethylaminobenzyl alcohol (74%) as an orange oil. ^{1}H NMR($CDCl_3$): δ 7.67 (d, 1H), 7.18 (d, 2H), 7.16 (d, 1H), 6.71 (d, 2H), 4.24 (s, 2H), 2.93 (s, 6H); ^{13}C NMR($CDCl_3$): δ 172.3, 149.8, 142.4, 129.8, 125.9, 118.8, 112.9, 40.7, 38.7.

Anal. Calcd for $C_{12}H_{14}N_2S$: C, 66.02; H, 6.46; N, 12.83: S, 14.69
Found: C, 65.78; H, 6.37; N, 12.68; S, 14.51

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