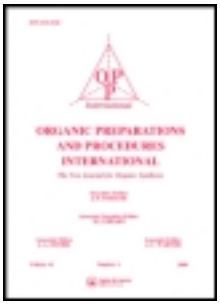

Organic Preparations and Procedures International: The New Journal for Organic Synthesis

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/uopp20

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Version of record first published: 18 Feb 2009.

To cite this article: Charles F. Nutaitis , Thomas J. Greshock , Stephen R. Houghton , Lynn N. Moran & Melissa A. Walter (2002): REDUCTION OF PYRIDYL CARBINOLS WITH SODIUM BOROHYDRIDE/ TRIFLUOROACETIC ACID, Organic Preparations and Procedures International: The New Journal for Organic Synthesis, 34:3, 332-335

To link to this article: http://dx.doi.org/10.1080/00304940209356774

REDUCTION OF PYRIDYL CARBINOLS WITH SODIUM BOROHYDRIDE/TRIFLUOROACETIC ACID

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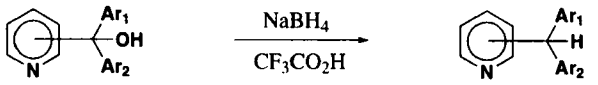
In 1977 Gribble and coworkers[1] reported that di- and triarylcarbinols could be efficiently reduced with sodium borohydride/trifluoroacetic acid to afford the corresponding di- and triarylmethanes. In 1991, Nutaitis and coworkers[2] extended this methodology to the synthesis of di- and triheteroarylmethanes from carbinols possessing thiophene, furan, benzothiophene, benzofuran, or phenyl substituents, and in 1997 to the reduction of 1,3-azole and 1,3-benzazole carbinols provided there was an additional aryl or pi-excessive heteroaryl (thienyl, benzo[*b*]thienyl, furyl, or benzo[*b*]furyl) substituent.[3] Carbinols possessing a 1,3-azole or 1,3-benzazole ligand and only one additional aryl or heteroaryl substituent were inert to reduction. By analogy, it was anticipated that compounds possessing a pyridyl substituent in place of the 1,3-azole/1,3-benzazole ligand would behave similarly. This transformation would prove useful as the corresponding α-substituted pyridylmethanes have been shown to be valuable as fungicides,[4] inducers of hepatic microsomal heme oxygenase and cyctochrome P450,[5] extraction agents for a variety of metals including chromium,[6a] gold,[6b] zinc,[6c] cobalt,[6d] mercury,[6e,f] palladium,[6g] arsenic,[6h] and silver,[6i] and as precursors of image enhancing agents for magnetic resonance imaging.[7] We now report that pyridylcarbinols possessing two additional aromatic or heteroaromatic ligands for sufficient stabilization of the carbocation intermediate can be effectively reduced with sodium borohydride/trifluoroacetic acid to afford the corresponding pyridylmethanes in 57-93% yields (*Table*).



1 2

a) 4-Pyridyl, $Ar_1 = Ar_2 = Ph$ b) 3-Pyridyl, $Ar_1 = Ar_2 = Ph$
c) 4-Pyridyl, $Ar_1 = Ph$, Ar_2 = 2-Thienyl d) 2-Pyridyl, $Ar_1 = Ph$, Ar_2 = 2-Benzo[*b*]furyl
e) 3-Pyridyl, $Ar_1 = Ar_2$ = 2-Thienyl f) α-(3-Pyridyl)benzyl alcohol

Table. Reduction of Pyridylcarbinols with $NaBH_4/CF_3CO_2H$

Compound	Yield(%)[a,b,c]	mp(°C)	*lit.* mp.(°C)
2a[b]	93%	123-125	124-125[9]
2b[b]	77%	74-76	78-79[9]
2c[b]	91%	82-84	----
2d	70%	52-54	----
2e	57%	oil	----
2f[c]	0%	----	----

a) Isolated yields after flash chromatography. b) Products 2a, 2b, and 2c exhibited satisfactory spectral data consistent with those previously reported[7,8] c) Recovered starting material 2f unchanged.

As can be seen in the Table, carbinols at all three positions of the pyridine ring are susceptible to reduction. Furthermore, the reduction pattern parallels that of the previously reported 1,3-azoles – that is, two additional aromatic or heteroaromatic rings are required for stabilization of the intermediate carbocation and hence reduction of the carbinol to the corresponding methane. The last entry in the Table, which possesses only one additional carbocation-stabilizing substituent, was not reduced.

EXPERIMENTAL SECTION

All reactions were performed in oven-dried glassware (120°), and all lithiation reactions were performed under nitrogen. Alkyllithium reagents were purchased from Aldrich and standardized with 2,5-dimethoxybenzyl alcohol.[10] Tetrahydrofuran was distilled from sodium/benzophenone. Thin layer chromatography was performed on precoated (0.25 mm) silica gel 60 F_{254} plastic sheets and was visualized with 254 nm ultraviolet light. Flash chromatography[11] was performed with silica gel 60 (200-400 mesh). 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 chloroform-d (carbon). Infrared spectra were recorded on a Mattson Satellite FTIR spectrometer. Melting points were determined in open capillary tubes with a Mel-Temp Laboratory Devices apparatus and are uncorrected. The starting materials α-(4-pyridyl)benzhydrol, α-(3-pyridylbenzhydrol), and α-(2-thienyl)-α-(4-pyridyl)benzyl alcohol were prepared according to literature methods.[7,12]

Preparation of α-(2-Benzo[*b*]furyl)-α-(2-pyridyl)benzyl alcohol.- To a magnetically stirred solution of benzo[*b*]furan (0.754 g, 6.38 mmol) in dry THF (25 mL), at –78° under nitrogen, was added *n*-butyllithium (3.90 mL, 1.66 M, 6.47 mmol) by means of a syringe over a period of 2 min. The cooling bath was removed and the reaction mixture was allowed to warm to room temperature over 30 min, then re-cooled to –78°. A solution of 2-benzoylpyridine (1.167 g, 6.37 mmol) in dry THF (5 mL) was added by means of a syringe and the resulting mixture was allowed to warm to room temperature and stirred for 20 hrs. The mixture was poured into water (50 mL) and extracted with ether (3 x 50 mL). The combined extracts were dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo* with adsorption onto silica gel. Flash chromatography (7:1 hexanes/ether) gave α-(2-benzo[*b*]furyl)-α-(2-pyridyl)benzyl alcohol a white solid (1.025 g, 53%), mp. 151-152°. ^{1}H NMR($CDCl_3$): δ 8.60 (d, 1H), 7.69 (td, 1H), 7.52 (d, 1H), 7.45-7.17 (m, 11H), 6.61 (s, OH; exchangeable with D_2O), 6.59 (s, 1H); ^{13}C NMR($CDCl_3$): δ 160.1, 159.8, 155.4, 147.4, 143.6, 136.9, 128.2, 127.93, 127.89, 127.4, 124.2, 123.0, 122.8, 122.7, 121.2, 111.5, 106.1, 77.2; IR (nujol): 3389 cm^{-1}.

Anal. Calcd for $C_{20}H_{15}NO_2$: C, 79.72; H, 5.02; N, 4.65. Found: C, 79.57; H, 5.18; N, 4.53

Preparation of 3-Pyridyl-*bis*-2-thienylmethanol.- To a magnetically stirred solution of thiophene (1.0 mL, 13 mmol) in dry THF (50 mL), at –78° under nitrogen, was added by means of a syringe n-butyllithium (5.70 mL, 2.21 M, 12.6 mmol) over a period of 2 min. The cooling bath was removed and the reaction mixture was allowed to warm to room temperature over 30 min, then re-cooled to –78°. A solution of methyl nicotinate (0.87 g, 6.3 mmol) in dry THF (10 mL) was added by means of a syringe and the resulting mixture was allowed to warm to room temperature and stirred for 20 hrs. The mixture was poured into water (150 mL) and extracted with ethyl acetate (2 x 100 mL). The

combined extracts were dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo* with adsorption onto silica gel. Flash chromatography (1:1 hexanes/ether) gave 3-pyridyl-*bis*-2-thienylmethanol as a white solid (1.00 g, 59%), mp. 166-168°. ^{1}H NMR($CDCl_3$): δ 8.52 (d, 1H), 8.31 (dd, 1H), 7.82 (dt, 1H), 7.25 (dd, 2H), 7.19 (dd, 1H), 6.91 (dd, 2H), 6.80 (dd, 2H), 5.71 (s, OH; exchangeable with D_2O); ^{13}C NMR($CDCl_3$): δ 151.4, 148.3, 148.0, 142.3, 134.6, 126.74, 126.67, 126.1, 122.9, 76.4; IR(thin film): 3469-2987 (broad) cm^{-1}.

Anal. Calcd for $C_{12}H_{11}NOS_2$: C, 61.51; H, 4.06; N, 5.12; S, 23.46.
Found: C, 61.74; H, 4.14; N, 5.15; S, 23.58

General Reduction Procedure. Preparation of α-(2-Benzo[*b*]furyl)-α-(2-pyridyl)toluene.- To magnetically stirred trifluoroacetic acid (30 mL) at room temperature, was added sodium borohydride (4 pellets, 1.6 g, 42 mmol) over a period of 25 min; the resulting mixture was stirred at room temperature for 1.5 hrs. A solution of α-(2-benzo[*b*]furyl)-α-(2-pyridyl)benzyl alcohol (0.292 g, 0.970 mmol) in methylene chloride (10 mL) was added in portions over a period of 25 min. The resulting mixture was magnetically stirred at room temperature for 45 min, then poured into 25% aqueous sodium hydroxide/ice (50 mL) to basify to pH 11 and extracted with ether (2 x 75 mL). The extracts were dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo* with adsorption onto silica gel. Flash chromatography (4:1 hexanes/ether) gave α-(2-benzo[*b*]furyl)-α-(2-pyridyl)toluene as a beige solid (0.194 g, 70%), mp. 52-54°. ^{1}H NMR($CDCl_3$): δ 8.63 (d, 1H), 7.64 (td, 1H), 7.50 (d, 1H), 7.43 (d, 1H), 7.38-7.17 (m, 9H), 6.41 (s, 1H), 5.79 (s, 1H); ^{13}C NMR($CDCl_3$): δ 160.6, 158.8, 155.2, 149.8, 140.0, 136.9, 129.0, 128.8, 128.6, 127.3, 123.9, 123.4, 122.8, 122.2, 120.9, 111.2, 105.8, 54.1.

Anal. Calcd for $C_{20}H_{15}NO$: C, 84.19; H, 5.30; N, 4.91. Found: C, 83.91; H, 5.46; N, 4.84

3-Pyridyl-*bis*-2-thienylmethane was prepared analogously from 3-pyridyl-*bis*-2-thienylmethanol (57%) as a colorless oil: ^{1}H NMR($CDCl_3$): δ 8.58 (br d, 1H), 8.51 (d, 1H), 7.60 (d, 1H), 7.24 (d, 1H), 7.22 (d, 2H), 6.94 (t, 2H), 6.82 (d, 2H), 5.88 (s, 1H); ^{13}C NMR($CDCl_3$): δ 149.9, 148.7, 146.4, 139.3, 135.8, 126.9, 126.4, 125.2, 123.5, 45.1.

Anal. Calcd for $C_{14}H_{11}NS_2$: C, 65.33; H, 4.31; N, 5.44; S, 24.92.
Found: C, 65.20; H, 4.40; N, 5.48; S, 24.82

Acknowledgements.- We wish to thank Lafayette College for support of this research.

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