Preparation of aryl benzyl ketones by [1,2]-Wittig rearrangement

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Dedicated to Professor S. V. Kessar on the occasion of his 70th birthday
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Abstract
α-(Benzotriazol-1-yl)benzyl ethers **4a–f** were readily prepared by condensation of benzotriazole, aryl aldehydes and benzyl alcohols. A one-pot reaction involving deprotonation of **4** followed by [1,2]-Wittig rearrangement and departure of the benzotriazolyl group resulted in aryl benzyl ketones **6a–f** in good yields.

Keywords: α-(Benzotriazol-1-yl)benzyl ethers, [1,2]-Wittig rearrangement, aryl benzyl ketones

Introduction

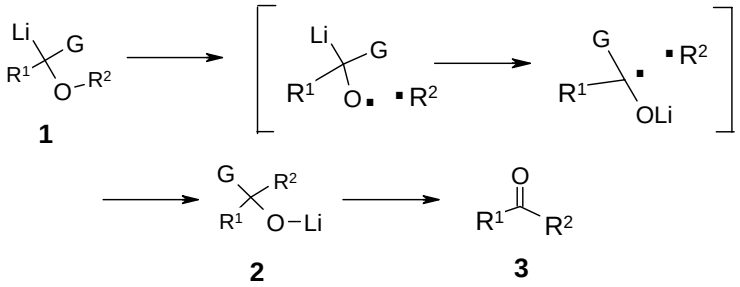
The [1,2]-Wittig rearrangement[1] has been reviewed extensively.[2] It is now widely accepted that the rearrangement proceeds *via* a radical dissociation-recombination mechanism,[3,4] with configuration retention at the migrating carbon and inversion at the Li-bearing terminus.[5]

Substituted ethers **1**, in which G can function as a leaving group as well as an electron-withdrawing group, eliminate group G after [1,2]-Wittig rearrangement to form the carbonyl compounds **3** (Scheme 1). Such reactions have been reported for G = cyano,[6] imidazolium and benzimidazolium[7] groups. α-(Benzotriazol-1-yl)alkyl allyl ethers have been successfully utilized in the synthesis of homoallylic ketones and alcohols *via* [2,3]-Wittig rearrangements.[8] We now report an extension of this methodology: [1,2]-Wittig rearrangements of α-(benzotriazol-1-yl)arylmethyl ethers to give aromatic ketones.

Results and Discussion

Condensation of an aromatic aldehyde, an aliphatic alcohol and benzotriazole in the presence of a catalytic amount of *p*-TsOH and 4Å molecular sieves in methylene chloride at room temperature as expected,[8,9] gave the α-(benzotriazol-1-yl)alkyl ethers **4a–f** in 60–78% yield.

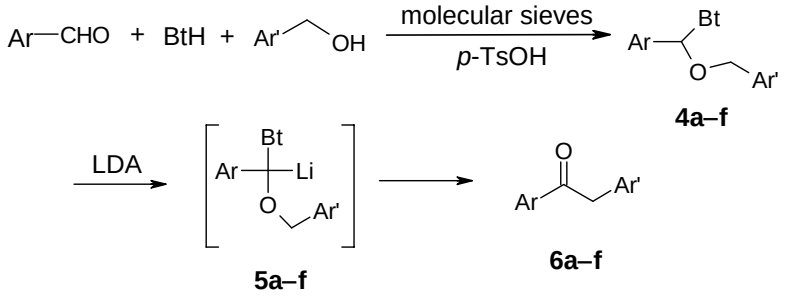
Novel ethers **4b–f** were fully characterized by their ^{1}H, ^{13}C NMR spectra and elemental analyses or HRMS data.



G = cyano, imidazolium or benzimidazolium; R^1, R^2 = alkyl or aryl

Scheme 1

The acidic benzotriazole-activated α-proton in the α-(benzotriazol-1-yl)alkyl benzyl ethers **4a–f** on treatment with LDA at –78 °C readily gives the α-lithiated intermediates **5a–f**, which eliminate the benzotriazole anion to give, by [1,2]-Wittig rearrangement, the carbonyl products **6a–f** in 53–63% yield. The structures of **6a–f** were confirmed by ^{1}H and ^{13}C NMR spectroscopy. ^{1}H NMR spectra of all of the ketones **6a–f** displayed a similar pattern including the disappearance of the α-proton and benzotriazolyl signals from the aromatic region. The benzylic protons in **6a–f** resonated around 4.2 ppm and the ^{13}C NMR signal for this carbon appeared around 45 ppm. The aromatic signals in all of the ketones **6a–f** experienced a negligible change in the chemical shift values from those in the ^{1}H and ^{13}C NMR spectra of starting ethers **4a–f**. The disappearance of the α-carbon signal around 88 ppm and the appearance of a carbonyl signal near 197 ppm in the ^{13}C NMR spectra further confirmed the formation of ketones **6a–f** (Scheme 2), (Table 1).



Bt = benzotriazol-1-yl

Scheme 2

Table 1. Synthesis of α-(benzotriazol-1-yl) ethers **4a–f** and aryl benzyl ketones **6a–f**

Entry	Ar	Ar′	**4** (%yield)[a]	**6** (%yield)[a]
a	Ph	Ph	78	63
b	4-F-C_6H_4	Ph	63	54
c	4-Cl-C_6H_4	Ph	60	62
d	3-MeO-C_6H_4	Ph	72	53
e	Ph	4-MeO-C_6H_4	73	61
f	4-Cl-C_6H_4	4-MeO-C_6H_4	63	63

[a] Isolated yields.

General methods for the preparation of ketones from aldehydes include (i) nucleophilic addition of an organometallic reagent followed by oxidation of the secondary alcohol;[10] (ii) transformation into a carbonyl anion equivalent such as an (α-benzotriazol-1-ylalkyl)methyl ether followed by lithiation, alkylation and deprotection.[9] The present two-step [1,2]-Wittig rearrangement procedure provides access to aryl benzyl ketones from an aromatic aldehyde and a benzyl alcohol.

Experimental Section

General Procedures. Melting points were determined using a Bristoline hot-stage microscope and are uncorrected. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Gemini 300 NMR spectrometer in $CDCl_3$ (with TMS for ^{1}H and chloroform-*d* for ^{13}C as the internal reference). HRMS were measured on an AEI-30 mass spectrometer. Elemental analyses were performed on a Carlo Erba-1106 instrument. THF was distilled from sodium/benzophenone and dichloromethane from calcium hydride prior to use. All of the reactions were carried out under N_2.

General procedure for the preparation of α-(benzotriazol-1-yl)alkyl ethers 4

A mixture of an aldehyde (20 mmol), an alcohol (20 mmol), benzotriazole (25 mmol), *p*-TsOH (10 mmol) and 4Å molecular sieves (10 g) in dry methylene chloride (60 mL) was stirred at 25 °C for 2 days. After filtration, the undissolved solid was washed with methylene chloride (3×30 mL). The solvent of the combined filtrate was removed in vacuo and the residue was purified by column chromatography using hexanes/EtOAc (9:1) as eluent to afford the pure products **4a–f**.

1-[(Benzyloxy)(phenyl)methyl]-1*H*-1,2,3-benzotriazole (4a). Colorless oil;[11] yield, 78%; ^{1}H NMR δ 8.10–8.04 (m, 1H), 7.44–7.42 (m, 2H), 7.34–7.25 (m, 12H), 4.58 (s, 2H); ^{13}C NMR δ 147.0, 136.0, 131.1, 129.0, 128.6, 128.5, 128.2, 128.1, 127.5, 126.0, 124.2, 119.9, 111.7, 88.3, 70.7.

1-[(Benzyloxy)(4-fluorophenyl)methyl]-1*H*-1,2,3-benzotriazole (4b). Colorless oil; yield, 63%; ^{1}H NMR δ 8.12–8.05 (m, 1H), 7.46–7.22 (m, 11H), 7.04 (t, *J* = 8.5 Hz, 2H), 4.57 (s, 2H); ^{13}C NMR δ 163.1 (d, *J* = 248.5 Hz), 147.3, 136.1, 132.2 (d, *J* = 3.4 Hz), 131.2, 128.9, 128.3 (d, *J*

= 23.5 Hz), 128.4, 128.1, 127.9, 124.6, 120.3, 115.8, 111.7, 88.0, 71.0. HRMS calcd for $C_{20}H_{17}FN_3O_2$: 334.1356 (M+1), found: 334.1346.

1-[(Benzyloxy)(4-chlorophenyl)methyl]-1*H*-1,2,3-benzotriazole (4c). Colorless oil; yield, 60%; ^{1}H NMR δ 8.12–8.05 (m, 1H), 7.40–7.24 (m, 13H), 4.57 (s, 2H); ^{13}C NMR δ 147.3, 136.0, 135.3, 134.9, 131.2, 129.0, 128.8, 128.6, 128.4, 127.9, 127.7, 124.6, 120.3, 111.7, 87.9, 71.1. Anal. Calcd for $C_{20}H_{16}ClN_3O$: C, 68.67; H, 4.61; N, 12.01. Found: C, 68.54; H, 4.83; N, 12.16.

1-[(Benzyloxy)(3-methoxyphenyl)methyl]-1*H*-1,2,3-benzotriazole (4d). Colorless oil; yield, 72%; ^{1}H NMR δ 8.10–8.04 (m, 1H), 7.40–7.20 (m, 10H), 7.04 (s, 1H), 6.98 (d, *J* = 7.7 Hz, 1H), 6.86 (dd, *J* = 8.2, 2.2 Hz, 1H), 4.57 (s, 2H), 3.74 (s, 3H); ^{13}C NMR δ 159.9, 147.2, 137.8, 136.2, 131.3, 129.9, 128.7, 128.4, 128.3, 127.7, 124.5, 120.1, 118.4, 114.5, 112.0, 111.9, 88.3, 71.0, 55.5. Anal. Calcd for $C_{21}H_{19}N_3O_2$: C, 73.03; H, 5.54; N, 12.17. Found: C, 72.79; H, 5.69; N, 11.96.

1-{[(4-Methoxybenzyl)oxy](phenyl)methyl}-1*H*-1,2,3-benzotriazole (4e). Colorless oil; yield, 73%; ^{1}H NMR δ 8.20–8.00 (m, 1H), 7.45–7.37 (m, 2H), 7.35–7.22 (m, 9H), 6.86 (d, *J* = 7.5 Hz, 2H), 4.53 (d, *J* = 11.7 Hz, 1H), 4.47 (d, *J* = 11.7 Hz, 1H), 3.77 (s, 3H); ^{13}C NMR δ 159.8, 147.1, 136.4, 131.3, 130.2, 129.1, 128.7, 128.2, 127.7, 126.1, 124.4, 120.1, 114.1, 111.9, 88.1, 70.6, 55.4. Anal. Calcd for $C_{21}H_{19}N_3O_2$: C, 73.03; H, 5.54; N, 12.17. Found: C, 72.84; H, 5.75; N, 12.17.

1-{(4-Chlorophenyl)[(4-methoxybenzyl)oxy]methyl}-1*H*-1,2,3-benzotriazole (4f). Colorless oil; yield, 63%; ^{1}H NMR δ 8.12–8.04 (m, 1H), 7.40–7.20 (m, 10H), 6.86 (d, *J* = 8.5 Hz, 2H), 4.53 (d, *J* = 11.7 Hz, 1H), 4.46 (d, *J* = 11.7 Hz, 1H), 3.79 (s, 3H); ^{13}C NMR δ 159.9, 147.2, 135.2, 135.0, 131.2, 130.2, 129.0, 127.9, 127.8, 127.6, 124.6, 120.2, 114.1, 111.7, 87.4, 70.7, 55.4. Anal. Calcd for $C_{21}H_{18}ClN_3O_2$: C, 66.40; H, 4.78; N, 11.06. Found: C, 66.04; H, 4.66; N, 10.84.

General procedure for the preparation of ketones (6a–f) via [1,2]-Wittig rearrangement

To a solution of **4a–f** (2 mmol) in dry THF (10 mL) at –78 °C was added dropwise LDA (2.2 mmol). The solution was stirred at –78 °C for 3 hours and then allowed to warm up to room temperature overnight. The reaction was quenched using water (5 mL) and then extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4. After removal of the solvent *in vacuo* the residue was purified by column chromatography using hexanes/EtOAc (20:1) as eluent to afford the pure ketones **6a–f**.

1,2-Diphenyl-1-ethanone (6a). White prisms (pentane); mp 53.0–55.0 °C (Lit.[12] mp 55.0–56.0 °C); yield, 63%; ^{1}H NMR δ 8.01 (d, *J* = 7.7 Hz, 2H), 7.57–7.42 (m, 3H), 7.35–7.24 (m, 5H), 4.28 (s, 2H); ^{13}C NMR δ 197.4, 136.4, 133.0, 129.3, 128.5, 128.5, 128.4, 126.7, 45.3.

1-(4-Fluorophenyl)-2-phenyl-1-ethanone (6b). White microcrystals (hexane); mp 77.5–78.5 °C (Lit.[13] mp 83.0 °C); yield, 54%; ^{1}H NMR δ 8.03 (dd, *J* = 8.8, 5.5 Hz, 2H), 7.38–7.22 (m, 5H), 7.11 (t, *J* = 8.5 Hz, 2H), 4.25 (s, 2H); ^{13}C NMR δ 196.2, 165.9 (d, *J* = 254.8 Hz), 134.5, 133.1, 131.5, 131.4, 129.2 (d, *J* = 48.1 Hz), 127.2, 115.9 (d, *J* = 11.8 Hz), 45.7.

1-(4-chlorophenyl)-2-phenyl-1-ethanone (6c). White needles (hexane); mp 102.0–103.0 °C (Lit.[14] mp 107.5 °C); yield, 62%; ^{1}H NMR δ 7.94 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.5 Hz, 2H),

7.38–7.20 (m, 5H), 4.25 (s, 2H); ^{13}C NMR δ 196.6, 139.8, 135.0, 134.4, 130.2, 129.6, 129.2, 129.0, 127.2, 45.8.

1-(3-Methoxyphenyl)-2-phenyl-1-ethanone (6d). Colorless oil;[15] yield, 53%; ^{1}H NMR δ 7.60 (d, *J* = 7.7 Hz, 1H), 7.55–7.51 (m, 1H), 7.40–7.22 (m, 6H), 7.10 (dd, *J* = 8.2, 2.2 Hz, 1H), 4.27 (s, 2H), 3.84 (m, 3H); ^{13}C NMR δ 197.7, 160.0, 138.2, 134.8, 129.8, 129.6, 128.9, 127.1, 121.5, 119.9, 113.0, 55.6, 45.8.

2-(4-Methoxyphenyl)-1-phenyl-1-ethanone (6e). White powder (hexane); mp 92.0 °C (Lit.[16] mp 99.5-100.5 °C); yield, 61%; ^{1}H NMR δ 8.01 (d, *J* = 7.1 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.20 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 4.22 (s, 2H), 3.78 (s, 3H); ^{13}C NMR δ 198.1, 158.7, 136.8, 133.3, 130.7, 128.8, 128.7, 126.7, 114.3, 55.4, 44.8.

1-(4-Chlorophenyl)-2-(4-methoxyphenyl)-1-ethanone (6f). White prisms (hexane); mp 107.5 °C (Lit.[17] mp 111.0 °C); yield, 63%; ^{1}H NMR δ 7.93 (d, *J* = 8.5 Hz, 2H), 7.42 (d, *J* = 8.5 Hz, 2H), 7.16 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 4.19 (s, 2H), 3.78 (s, 3H); ^{13}C NMR δ 196.7, 158.6, 139.6, 134.9, 130.4, 130.1, 129.0, 126.1, 114.2, 55.3, 44.7.

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