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Heteroaromatic benzyl ethers as intermediates for palladium-catalysed transfer hydrogenolysis of benzyl alcohols

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Abstract

A chemoselective and easy to carry procedure for the hydrogenolysis of benzyl alcohols is described. Benzyl alcohols are readily converted into tetrazolyl and benzisothiazolyl ethers that can be catalytically hydrogenolysed to toluenes over palladium-on-charcoal using hydrogen donors. The effect of electronwithdrawing heteroaromatic substituents is interpreted on the basis of chrystallographic structure determinations and molecular orbital calculations.

Keywords: Palladium-on-charcoal; Transfer hydrogenolysis; Tetrazoles; Benzisothiazoles

1. Introduction

Benzyl alcohols **1** are widely used in organic synthesis, either as starting materials or as protecting groups [1,2]. Continuing the research on the development of synthetic methods using heterogeneous catalytic transfer reduction, [3] we report the selective transfer hydrogenolysis of benzyl alcohols **1** to toluenes **4** via heteroaromatic ethers **3**, under mild conditions (Scheme 1). High yields and low reaction times can be achieved with a careful selection of the reaction conditions.

Heterogeneous catalytic transfer hydrogenolysis of aryloxy- and allyloxytetrazoles has been used in the hydrogenolysis of phenols and allyl alcohols and presents a practical and selective synthetic alternative to other methods [4,5]. The hydrogenolysis of the C–OH bond is achieved after convertion of the hydroxyl group into an ether with the electronwithdrawing heteroaromatic tetrazole. Derivatization weakens the original C–O bond and increases the nucleophilic susceptibility of the carbon atom. The methodology has been extended to the hydrogenolysis of arylpseudosaccharyl ethers and to cross-coupling with organometalic reagents [6]. The effect of the heterocyclic part of these ethers on the C–O bond strength has been clarified through X-ray studies [7]. Hydrogenolysis of the C–O bond in benzyl alcohols is possible with molecular hydrogen using noble metals as catalysts [8]. The extent of cleavage depends on the nature of the catalyst. Palladium is normally used, because it is known as a good catalyst for hydrogenolysis and, unlike rhodium or platinum catalysts, does not dearomatise the ring [9]. The hydrogenolysis of the C–O bond can also be achieved through prior derivatization of the alcohol followed by catalytic hydrogenation. However, this methodology often presents problems of selectivity related to the use of molecular hydrogen. Hydride reduction is generally more selective, but coupled or dimeric products may be obtained. Another methodology is reduction by dissolving metals, but this strategy often leads to over-reduction [2].

In the present work, benzyl alcohols **1** are derivatized with heteroaromatic chlorides **2a** or **2b** to give high yields of the corresponding tetrazolyl or benzisothiazolyl ethers, **3a** or **3b** which are stable crystalline compounds, easy to prepare and to isolate. These ethers undergo easy and selective hydrogenolysis in high yields, by heterogeneous catalytic transfer reduction over palladium-on-charcoal. Reactions can be carried out without requiring the use of molecular hydrogen or anhydrous conditions. The side

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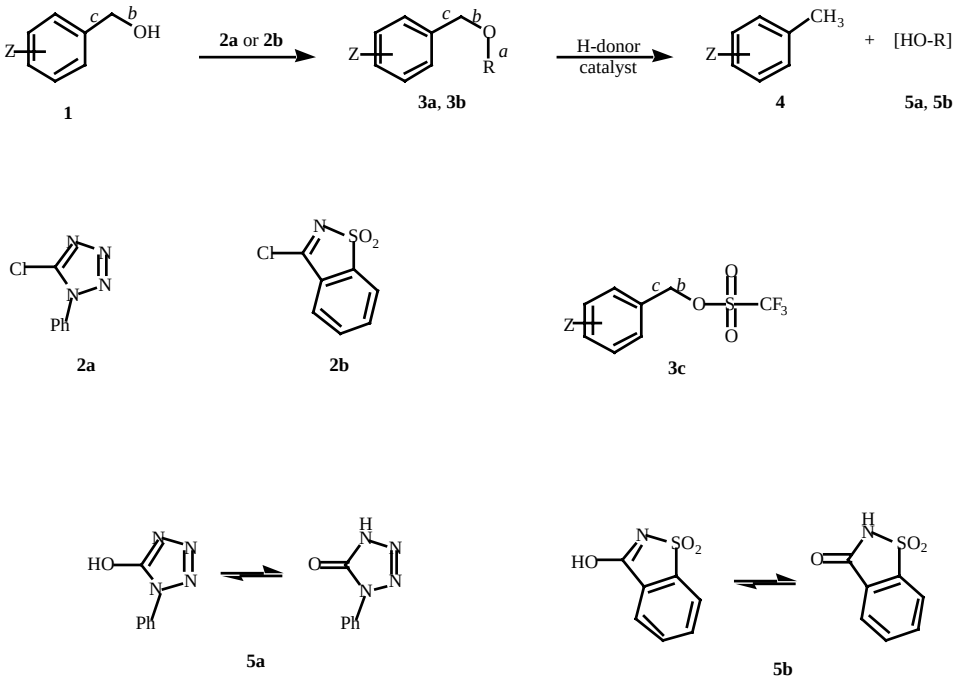


Scheme 1.

products, tetrazolone **5a** or saccharin **5b**, are water-soluble and the catalyst can simply be filtered off and may be re-used. Ethers **3** are stable solids that are amenable to full characterization including X-ray crystallography. An interpretation of the reactivity of these ethers is provided, based on their structural and electronic features and also on comparative adsorption abilities onto the catalyst surface. The procedures reported for easy to carry and selective hydrogenolysis of benzyl ethers are of interest to many preparative organic and bio-organic chemists.

2. Experimental section

2.1. General procedures

Melting points were recorded on a Stuart Scientific SMP3 melting point apparatus and are uncorrected. Mass spectra were obtained on a VG 7070E mass spectrometer by electron ionization (EI) at 70 eV. Proton NMR spectra were obtained on a Varian Gemini 300 FT spectrometer using TMS as the internal standard. Gas chromathography was carried out on a Chompack CP9001 instrument fitted with a flame ionization detector and a CP-SIL 5CB capillary column (25 m × 0.35 mm), using 1,4-dimethylbenzene as internal standard for measurement of relative retention times and for quantification of product yields. Adsorption experiments were determined by analysis of HPLC chromatograms, obtained on a Merck-Hitachi L-500 liquid chromatograph, equipped with a UV-visible detector set to 254 nm, and a Merck LiChrospher RP-18 HPLC column, 5 μm, i.d. 125–4 mm (acetonitrile–water [40:60] was used as the eluent). All chemicals were used as purchased from Aldrich. Theoretical calculations were performed using DFT methods available in Gaussian 98, [8] as described in the results and discussion section and in Table 1. Synthesis of 5-phenoxy-1-phenyltetrazole has been previously described [18].

Typical procedure for the preparation of benzyl ethers **3a**. A solution of 4-α, α, α-trifluoromethylphenylmethanol (0.8 g, 4.5 mmol) in dry THF (10 ml) was added to a slurry of sodium hydride (0.3 g, 8 mmol) in dry THF (20 ml) under anhydrous conditions. When effervescence had ceaced (30 min) a solution of 5-chloro-1-phenyltetrazole (0.8 g, 4.4 mmol) in THF (10 ml was added. The mixture was refluxed for one hour, then ice-water was added (30 ml). The organic product was extracted with diethylether (3 × 30 ml) and the ethereal solution dried over anhydrous sodium sulphate, filtered, and the filtrate evaporated to dryness to give a colourless solid which was recrystallized from ethanol to give **5-(4-α, α, α-trifluoromethyl)benzyloxy-1-phenyltetrazole** as colourless needles (89% yield; m.p. 421–422 K). Found: C 56.5, H 3.5, N 17.3%. $C_{15}H_{11}F_3N_4O$ requires C 56.3, H 3.4, N 17.4%. ^{1}H NMR (200 MHz, $CDCl_3$): *δ*, 5.70 (2H, s), 7.46 (2H, d), 7.51–7.70 (5H, m), 7.70 (2H, d); MS (EI, *m*/*z*) 320 (M^+). **5-Benzyloxy-1-phenyltetrazole**. Prepared as described above, from benzyl alcohol (0.6 g, 5.6 mmol), under reflux, for 2 h. Colourless needles from ethanol (90% yield; m.p. 421–422 K). Found: C 66.7, H 4.8, N 22.4%. $C_{14}H_{12}N_4O$ requires C 66.7, H 4.8, N 22.2%. ^{1}H NMR (200 MHz, $CDCl_3$): δ, 5.66 (2H, s), 7.38–7.58 (8H, m), 7.68–7.75 (2H, d); MS (EI, *m*/*z*) 252 (M^+). **5-(3-Methoxybenzyloxy)-1-phenyltetrazole**. Prepared from 3-methoxybenzyl alcohol (0.2 g, 1.6 mmol), as

Table 1
Selected structural data for compounds **3a-c** [14–16]

Entry	Compound (R)	Z	*c* (pm)	*b* (pm)	*a* (pm)	Method
1	**3a** (1-phenyltetrazol-5-yl)	H	150.3	147.0	132.4	B3LYP/6-311G*
2	**3a** (1-phenyltetrazol-5-yl)	H	149.8	146.7	132.6	X-ray
3	**3a** (1-phenyltetrazol-5-yl)	4-CF_3	150.2	145.8	132.7	B3LYP/6-311G*
4	**3a** (1-phenyltetrazol-5-yl)	4-MeO	149.3	146.9	131.8	X-ray
5	**3b** (3-*pseudo*-saccharyl)	H	150.7	145.0	131.0	B3LYP/6-311G*
6	**3b** (3-*pseudo*-saccharyl)	H	150.0	145.4	131.5	X-ray
7	**3b** (3-*pseudo*-saccharyl)	Cl	150.2	146.7	132.8	B3LYP/6-311G*
8	**3b** (3-*pseudo*-saccharyl)	4-CF_3	149.8	147.2	131.8	X-ray
9	**3b** (3-*pseudo*-saccharyl)	4-MeO	149.7	148.5	131.7	B3LYP/6-31G
10	**3c** (trifluorosulphonate)	H	149.7	148.5	–	B3LYP/6-311G*
11	**1** (hydrogen)	H	151.1	142.1	–	B3LYP/6-311G*

described above, under reflux, for 3 h. Colourless crystals from ethanol (83% yield; m.p. 364–365 K). Found: C 63.9, H 5.0, N 20.0%. $C_{15}H_{14}N_4O_2$ requires C 63.8, H 5.0, N 19.9%. ^{1}H NMR (200 MHz, $CDCl_3$): δ, 3.82 (3H, s), 5.62 (2H, s), 6.92–6.96 (1H, d), 7.03–7.09 (2H, m), 7.29–7.37 (1H,m), 7.43–7.56 (3H, m), 7.69–7,74 (2H, d); MS (EI, *m*/*z*) 282 (M^+). **5-(4-Chlorobenzyloxy)-1-phenyltetrazole**. Prepared as described above, from 4-chlorobenzyl alcohol (0.27 g, 1.9 mmol), under reflux, for 1,5 h. Colourless crystals from ethanol (93% yield; m.p. 371–372 K). Found: C 58.6, H 3.9, N 19.6%. $C_{14}H_{11}ClN_4O$ requires C 58.6, H 3.9, N 19.5%. ^{1}H NMR (200 MHz, $CDCl_3$): δ, 5.62 (2H, s), 7.6–7.51 (7H, m), 7.66–7.72 (2H, d); MS (EI, *m*/*z*) 286, 288 (3:1) (M^+ for chlorine isotopes). **5-(4-Methoxybenzyloxy)-1-phenyltetrazole**. Prepared as described above, from 4-methoxybenzyl alcohol (0.2 g, 1.6 mmol), under reflux, for 2,5 h. Colourless crystals from ethanol (87% yield; m.p. 406–407 K). Found: C 64.1, H 5.1, N 20.1%. $C_{15}H_{14}N_4O_2$ requires C 63.8, H 5.0, N 19.9%. ^{1}H NMR (200 MHz, $CDCl_3$): δ, 3.83 (3H, s), 5.59 (2H, s), 6.91–6.95 (2H, d, $J = 8.8$ Hz), 7.42–7.53 (5H, m), 7.66–7.72 (2H, d, $J = 6.6$ Hz); MS (EI, *m*/*z*) 282 (M^+).

Typical procedure for the preparation of benzyl ethers **3b**. A mixture of 3-chloro-1,2-benziothiazole 1,1-dioxide (0.72 g, 3.8 mmol), 4-chlorobenzyl alcohol (0.53 ml, 3.7 mmol) and triethylamine (2 ml) in toluene (20 ml) was stirred at room temperature until TLC analysis (DCM as eluent) indicated the absence of starting material (3 h). Dichloromethane (100 ml) was then added to the reaction mixture and the whole was washed with diluted hydrochloric acid (1M, 3 × 50 ml), then with a saturated aqueous solution of sodium hydrogencarbonate (3 × 50 ml), then with brine (3 × 50 ml) and finally dried over sodium sulphate. The filtrate was evaporated to dryness at room temperature. Recrystallization from toluene gave **3-(4-chlorobenzyloxy)-1,2-benziothiazole 1,1-dioxide** as colourless crystals (91% yield; m.p. 412–413 K). Found: C 54.3, H 3.3, N 4.5%. $C_{14}H_{10}ClNO_3S$ requires C 54.6, H 3.3, N 4.6%. ^{1}H NMR (300 MHz, $CDCl_3$): δ, 4.87 (2H, s), 7.29–7.36 (2H, d), 7.41–7.49 (2H, d), 7.82–7.97 (3H, m), 8.03–8.09 (1H, m); MS (EI, *m*/*z*) 307,309 (3:1) (M^+ for chlorine isotopes). **3-Benzyloxy-1,2-benziothiazole 1,1-dioxide**. From a mixture of 3-chloro-1,2-benziothiazole 1,1-dioxide (0.44 g,2.2 mmol), benzyl alcohol (0.3 g, 2.3 mmol) and triethylamine, in toluene, under reflux, for 1 h. Pale yellow crystals from toluene (90% yield; m.p. 401–402 K). Found: C 61.5, H 4.1, N 5.1%. $C_{14}H_{11}NO_3S$ requires C 61.5, H 4.1, N 5.1%. ^{1}H NMR (300 MHz, $CDCl_3$): δ, 5.56 (2H, s), 7.38–7.49 (5H, m), 7.68–7.82 (3H, m), 7.87–7.93 (1H, m); MS (EI, *m*/*z*) 273 (M^+). **3-(4-Methoxybenzyloxy)-1,2-benziothiazole 1,1-dioxide**. From a mixture of 3-chloro-1,2-benziothiazole 1,1-dioxide (0.5 g, 2.7 mmol), 4-methoxybenzyl alcohol (0.3 g, 2.4 mmol) and triethylamine, in toluene, under reflux, for 3 h. Pale yellow crystals from toluene (55% yield; m.p. 395–396 K). Found: C 59.3, H 4.3, N 4.6%. $C_{15}H_{13}NO_4S$ requires C 59.3, H 4.3, N 4.6%. ^{1}H NMR (300 MHz, $CDCl_3$): δ, 3.81 (3H, s), 4.86 (2H, s), 6.83–6.92 (2H, m), 7.42–7.50 (2H, d), 7.80–7.96 (3H, m), 8.01–8.09 (1H, M); MS (EI, *m*/*z*) 303 (M^+). **3-(3-Methoxybenzyloxy)-1,2-benziothiazole 1,1-dioxide**. From a mixture of 3-chloro-1,2-benziothiazole 1,1-dioxide (0.4 g, 2.0 mmol), 3-methoxybenzyl alcohol (0.3 g, 2.1 mmol) and triethylamine, in toluene, under reflux, for 1 h. Pale yellow crystals from toluene (76% yield; m.p. 401–402 K). Found: C 59.4, H 4.2, N 4.5%. $C_{15}H_{13}NO_4S$ requires C 59.4, H 4.3, N 4.6%. ^{1}H NMR (300 MHz, $CDCl_3$): δ, 3.83 (3H, s), 5.59 (2H, s), 6.92–6.96 (1H, d, $J = 8.5$ Hz), 7.03–7.09 (2H, m), 7.29–7.34 (1H, s) 7.71–7.75 (3H, m), 7.87–7.89 (1H, d, $J = 7.5$ Hz); MS (EI, *m*/*z*) 303 (M^+). **3-(4-**α, α, α**-Trifluoromethylbenzyloxy)-1,2-benziothiazole 1,1-dioxide**. From a mixture of 3-chloro-1,2-benziothiazole 1,1-dioxide (0.3 g; 1.49 mmol), (4-α, α, α-trifluoromethyl)benzyl alcohol (0.26 g; 1.48 mmol) and triethylamine (2 ml), in toluene (15 ml), at 343 K, for 1 h. Pale yellow crystals from ethyl acetate (72% yield; m.p. 436–437 K). Found: C 52.7, H 2.9, N 4.1%. $C_{15}H_{10}F_3NO_3S$ requires C 52.8, H 3.0, N 4.1%. ^{1}H NMR (300 MHz, $CDCl_3$): δ, 5.65 (2H, s), 7.63 (2H, d), 7.67–7.80 (5H, m), 7.90 (1H, d); MS (EI, *m*/*z*) 341 (M^+).

2.1.1. Typical procedure for transfer reduction of ethers *3a,b*

The 10% Palladium-on-charcoal (36 mg) was added to a stirred solution of 5-benzyloxy-1-phenyltetrazole (50 mg,

Table 2
Experimental conditions and yields for the transfer reduction of heteroaromatic benzyl ethers **3a** and **3b** to give toluenes **4**

Entry	Z	3	Solvent	Hydrogensource	Reaction time	Yield[a] (%)
1	H	**b**	THF	NaH_2PO_2/H_2O	15 min	85
2	H	**a**	THF	NaH_2PO_2/H_2O	10 min	90
3	H	**a**	Toluene	NaH_2PO_2/H_2O	120 min	42
4	4-OCH_3	**b**	THF	NaH_2PO_2/H_2O	30 min	82
5	4-OCH_3	**b**	THF	NH_2–NH_2/H_2O	10 min	75
6	4-OCH_3	**a**	THF	NaH_2PO_2/H_2O	30 min	85
7	3-OCH_3	**b**	THF	NH_2–NH_2/H_2O	75 min	55
8	3-OCH_3	**a**	THF	NaH_2PO_2/H_2O	30 min	85
9	4-CF_3	**b**	THF	NaH_2PO_2/H_2O	30 min	84
10	4-CF_3	**b**	THF	H_2 (1 atm)	2 days	70
11	4-CF_3	**a**	THF	NaH_2PO_2/H_2O	10 min	50
					180 min	55
12	4-CF_3	**a**	Toluene	NaH_2PO_2/H_2O	75 min	56
13	4-CF_3	**a**	THF	NaHCOO	90 min	77
14	4-CF_3	**a**	THF	NH_2–NH_2	30 min	77
15	4-Cl	**b**	THF	NaH_2PO_2/H_2O	25 min	70
16	4-Cl	**b**	THF	NH_2–NH_2/H_2O	15 min	86
17	4-Cl	**a**	THF	NaH_2PO_2/H_2O	10 min	89

[a] Yields determined with reference to an internal standard.

0.19 mmol) and an internal standard (xylene, 101 mg) in tetrahydrofuran (20 ml) and the mixture was heated to reflux. Sodium hypophosphite (161 mg, 1.52 mmol) in distilled water (3 ml) was added and the progress of the reaction was monitored for formation of toluene by gas chromatography, and for the disappearance of the starting material by thin layer chromathography. Yields of transfer hydrogenolysis of ethers **3a** and **3b** to form only the corresponding toluene and 5-phenyl-1-tetrazolone or 1,2 benzisothiazole-1,1-dioxide-3-one are presented in Table 2.

2.1.2. Reduction of 3-(4-α, α, α-trifluoromethylbenzyloxy)-1,2-benzisothiazole 1,1-dioxide using molecular hydrogen

Palladium-on-charcoal (10%; 0.02 g) was added to a stirred solution of 3-(4-α, α, α-trifluoromethylbenzyloxy)-1,2-benzisothiazole 1,1-dioxide (0.03 g, 0.088 mmol) and *p*-xylene (0.05 g; 0.47 mmol) in tetrahydrofuran (15 ml). The final mixture was transferred to a pressure reactor and kept under hydrogen (1 atm). The reaction was monitored by gas chromathography. A maximum conversion of 70% was obtained after 48 h.

2.1.3. Comparative adsorption experiment

A solution of 5-benzyloxy-1-phenyltetrazole (20 ml, $1.025 \times 10 - 4$ M in toluene) was vigorously stirred with palladium-on-charcoal (15 mg) in a round bottom flask for 10 min. The catalyst was filtered off and the remaining solution analysed by HPLC. The percentage of adsorption was inferred by the decrease in the peak area at 366 nm. This experiment was repeated with a solution of 5-phenoxy-1-phenyltetrazole (20 ml, $1.012 \times 10 - 4$ M in toluene) and palladium-on-charcoal (15 mg). The percentage of adsorption was 2.8 times greater for 5-phenoxy-1-phenyltetrazole (26.5%) than for 5-benzyloxy-1-phenyltetrazole (8.7%).

2.1.4. X-ray crystallographic studies

Experimental data for the X-ray diffraction studies of crystalline 5-(4-methoxybenzyloxy)-1-phenyltetrazole (**3a**; Z = OCH_3) and 3-(4-α, α, α-trifluoromethylbenzyloxy)-1,2-benzisothiazole 1,1-dioxide (**3b**; Z = CF_3) are presented in Tables 3 and 4 (supplementary material).

3. Results and discussion

It has been found that the heteroaromatic halides 5-chloro-1-phenyltetrazole **2a** and 3-chloro-1,2-benzisothiazole 1,1-dioxide (*pseudo*saccharyl chloride) **2b** react efficiently with a variety of allylic alcohols and phenols, affording high yields of stable crystalline heteroaromatic ethers. These ethers are excellent substrates for heterogeneous catalytic transfer reduction and cross-coupling reactions [4–6]. In the present investigation we show that heterogeneous catalytic transfer reduction can also be successfully used in the hydrogenolysis of benzylic heteroaromatic derivatives **3a** and **3b**, therefore presenting a good alternative to other synthetic methodologies for the conversion of benzyl alcohols in toluenes (Scheme 1) [2].

Benzyl ethers **3a** and **3b** are easily synthesised by reaction of benzyl alcohols with the heteroaromatic halides. 5-Benzyloxy-1-phenyltetrazoles **3a** were obtained by initial reaction of a benzylic alcohol with sodium hydride followed by reaction with 5-chloro-1-phenyltetrazole **2a**. 3-Benzyloxy-1,2-benzisothiazole 1,1-dioxides **3b** were obtained by direct reaction of the benzylic alcohol with 3-chloro-1,2-benzisothiazole 1,1-dioxide **2b** in the presence of base.

Ground state structural features are often used for predicting and interpreting reactivity [10]. The effect of converting benzyl alcohols into ethers **3a**,**b** may be assessed through structural analysis obtained by X-ray crystallography and/or molecular orbital calculations. In the present work we report crystal structures of 3-(4-α,α,α-trifluoromethylbenzyloxy)-1,2-benzisothiazole 1,1-dioxide and 5-(4-methoxybenzyloxy)-1-phenyltetrazole (Figure 1). Selected geometric parameters for these compounds, and for the corresponding non-substituted benzyloxy derivatives, are presented in Table 1. In this publication we discuss bond lengths around the central ether linkage (sequence of atoms C7–O3–C8–C9). For the four compounds considered (Table 1, entries 2, 4, 6 and 8), the heteroaromatic carbon-oxygen bond lengths *a* (C7–O3) range from 131.5 to 132.6 pm (mean 131.9 pm) and the benzylic carbon-oxygen bond length *b* (C8–O3) ranges from 146.7 to 149.8 pm (mean 147.2 pm). Thus, the bond to be hydrogenolysed, C8–O3, is longer than the corresponding C–O bond in the original benzyl alcohol (142 pm), whereas bond C7–O3 is

Table 3
Experimental data for the X-ray diffraction studies on crystalline 3-(4-α,α,α-triflurometylbenzyloxy)-1,2-benzisothiazole 1,1-dioxide (**3b**; Z = CF_3) and 5-(4-methoxybenzyloxy)-1-phenyltetrazole (**3a**; Z = OCH_3)[a]

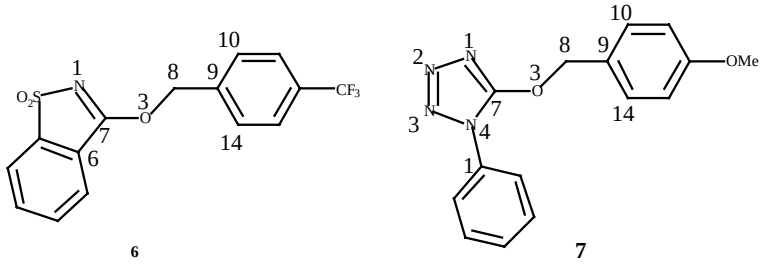
Formula	$C_{15}H_{10}F_3NO_3S$	$C_{15}H_{14}N_4O_2$
Formula weight	341.30	382.30
Crystal system	Monoclinic P21	Monoclinic P21
Cell parameters at 213 K		
a (Å)	24.0690(15)	11.2701(7)
b (Å)	8.8309(6)	13.4933(8)
c (Å)	15.5812(10)	9.1035(5)
a (°)	90	90
β (°)	119.0070(10)	95.2960(10)
γ (°)	90	90
Volume (Å^3)	2896.4(3)	1378.47(14)
Z, calculated density (mg m^{-3})	8, 1.565	4, 1.360
Linear absorption coefficient (mm^{-1})	0.271	0.094
F(0000)	1392	592
θ range (°)	1.93 to 28.25	1.81 to 28.30
Reflections collected, unique	6335, 3227 [*R*(int) = 0.0141]	8372, 316 [*R*(int) = 0.0135]
Completeness to 2*θ* = 26.06 (%)	90.1	92.7
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data, restraints, parameters	3227, 54, 236	3166, 0, 191
Goodness of fit on F^2	1.080	1.076
Final *R* indeces [I > 2*s* (I)]	*R*1 = 0.0380, *wR*2 = 0.1111	*R*1 = 0.0399, *wR*2 = 0.1054
R indeces	*R*1 = 0.0403, *wR*2 = 0.1129	*R*1 = 0.0428, *wR*2 = 0.1079
Absolute structure parameter	−0.03(5)	−0.03(5)
Largest diffraction peak, hole (e, Å^{-3})	0.429, −0.422	0.236, −0.304

[a] SHELXL 97: program for the refinement of crystal structures, Universitu og Göttingen, 1997.

exceptionally short. The favourable delocalization of the ether oxygen lone pair on the heteroaromatic systems by an effective p-conjugation is the responsible for the shortening of the C–O bond lengths *a*. In diaryl ethers, the C–O bond length (about 137–138 pm) is slightly longer because of delocalization in two aryl systems. In aryl tetrazolyl and aryl saccharyl ethers the short C–O bond is about 133–134 pm [7] and in allyl tetrazolyl and allyl saccharyl ethers is around 131–132 pm [11]. The lenght for the benzylic bond C8–C9 is around 149.8 pm, unexceptional for a CH_2 connected to an aryl ring [12]. In ethers **3a,b**, the non-conjugation of the oxygen lone pair with the benzyl system is responsible for the observed low dependence of bond lengths *a* and *b* in respect to benzyl substitution.

In keeping with previous observations [13], results presented in Table 1 show that both heteroaromatic moieties act as very strong electron-withdrawing groups, decreasing the *p*-character of the benzylic C–O bond *b* and consequently increasing the length of the bond to be hydrogenolysed from 142.1 pm in benzyl alcohol **1** to 146.7 pm in ether **3a** or to 145.4 pm in ether **3b**, while strengthening the heteroaromatic C–O bond *a*. The heteroaromatic, together with the benzylic oxygen, acts as a good leaving group in the ether.

Theoretical calculations for benzyl tetrazolyl (**3a**), benzyl saccharyl (**3b**) and benzyl trifluoromethylsulphonyl (**3c**) ethers and also for benzyl alcohol, were performed with the Gaussian 98 program package, [14] using the Beck-style three parameter density functional with the Lee–Yang–Parr correlation functional (B3LYP) [15] and the 6-311G* basis set [16]. Selected results presented in Table 1 agree with data obtained by X-ray crystallography and have provided further evidence that both heteroaromatic rings (R in ethers **3a** and **3b**) exert an electron-withdrawing effect similar to that observed for trifluoromethylsulfonyl in **3c** (Table 1, entry 10, *b* = 148.5 pm), commonly used as a nucleofuge in *ipso*-substitution reactions. This effect results in an activation of



6 7

Fig. 1. Structures 3-(4-α,α,α-trifluoromethylbenzyloxy)-1,2-benzisothiazole 1,1-dioxide and 5-(4-methoxybenzyl oxy)-1-phenyltetrazole.

Table 4
Selected structural data for 3-(4-α,α,α-trifluromethylbenzyloxy)-1,2-benzisothiazole 1,1-dioxide **6** and 5-(4-methoxybenzyl oxy)-1-phenyltetrazole **7**(Å, °) [22]

6			
C(1)–C(6)	1.385(2)	C(2)–C(1)–C(6)	122.77(14)
C(1)–S(1)	1.7630(15)	C(2)–C(1)–S(1)	129.99(12)
C(6)–C(7)	1.4798(19)	C(6)–C(1)–S(1)	107.23(10)
C(7)–N(1)	1.2923(19)	N(1)–C(7)–O(3)	123.82(13)
C(7)–O(3)	1.3177(17)	N(1)–C(7)–C(6)	118.52(12)
C(8)–O(3)	1.4723(18)	O(3)–C(7)–C(6)	117.66(12)
C(8)–C(9)	1.498(2)	O(3)–C(8)–C(9)	106.61(12)
C(13)–C(14)	1.385(2)	C(7)–N(1)–S(1)	108.65(10)
N(1)–S(1)	1.6600(12)	C(7)–O(3)–C(8)	115.42(11)
		N(1)–S(1)–C(1)	96.53(7)
S(1)–C(1)–C(2)–C(3)	179.88(11)		
C(2)–C(1)–C(6)–C(7)	179.20(13)		
S(1)–C(1)–C(6)–C(7)	0.29(14)		
C(4)–C(5)–C(6)–C(7)	−179.81(14)		
C(1)–C(6)–C(7)–N(1)	−0.25(18)		
C(1)–C(6)–C(7)–O(3)	179.92(12)		
O(3)–C(8)–C(9)–C(14)	93.30(18)		
O(3)–C(7)–N(1)–S(1)	179.88(11)		
C(6)–C(7)–N(1)–S(1)	0.07(16)		
N(1)–C(7)–O(3)–C(8)	−0.9(2)		
C(6)–C(7)–O(3)–C(8)	178.95(12)		
C(9)–C(8)–O(3)–C(7)	−173.01(12)		
C(7)–N(1)–S(1)–C(1)	0.10(11)		
7			
N(3)–N(4)	1.3642(12)	N(3)–N(4)–C(1)	121.96(8)
N(3)–N(2)	1.2901(14)	C(7)–N(4)–C(1)	130.82(8)
N(4)–C(7)	1.3436(13)	N(2)–N(3)–N(4)	106.22(9)
C(7)–N(1)	1.3161(13)	N(1)–C(7)–O(3)	129.18(9)
C(7)–O(3)	1.3183(12)	N(1)–C(7)–N(4)	110.09(9)
C(8)–O(3)	1.4699(12)	O(3)–C(7)–N(4)	120.73(9)
C(8)–C(9)	1.4929(14)	O(3)–C(8)–C(9)	105.99(8)
C(13)–C(14)	1.3776(16)	C(7)–N(1)–N(2)	104.62(9)
N(1)–N(2)	1.3660(14)	C(7)–O(3)–C(8)	115.10(8)
		N(3)–N(2)–N(1)	111.85(9)
		N(2)–N(3)–N(4)–C(1)	179.54(9)
		N(2)–N(3)–N(4)–C(7)	−0.24(11)
		N(3)–N(4)–C(7)–N(1)	0.00(11)
		N(3)–N(4)–C(7)–O(3)	−179.61(9)
		O(3)–C(8)–C(9)–C(14)	−76.11(12)
		O(3)–C(7)–N(1)–N(2)	179.79(10)
		N(4)–C(7)–N(1)–N(2)	0.22(12)
		N(1)–C(7)–O(3)–C(8)	−1.40(16)
		N(4)–C(7)–O(3)–C(8)	178.12(9)
		C(9)–C(8)–O(3)–C(7)	172.40(8)
		C(7)–N(1)–N(2)–N(3)	−0.38(12)
		N(4)–N(3)–N(2)–N(1)	0.39(12)

bond C8–O3 towards transfer reduction. Full details and discussion of crystallographic and theoretical data will appear elsewhere.

Considered as “alkyl” ethers, benzylic compounds **3a,b** were expected to be inert to hydrogenolysis [3,7]. Benzyloxy carbonyl esters are easily catalytically hydrogenolysed, either with molecular hydrogen or by transfer methods [3] but benzyl ethers are known to be much more resistent to transfer reduction, requiring higher temperatures, longer reaction times and the additional use of Lewis acids [3]. Experimental conditions reported for heterogeneous catalytic transfer hydrogenolysis refer the use of biphasic toluene/water or benzene/water as solvent systems. Under these conditions, benzyl tetrazolyl ethers were found to be inert to hydrogenolysis even after extended periods of time, affording only benzyl alcohol as a result of hydrolysis [17]. In contrast, it was found that 5-benzyloxy-1-phenyl tetrazole gives quantitative formation of toluene in 10 min, also with Pd/C as catalyst and sodium hypophosphite as donor, but using a tetrahydrofuran/water bifasic solvent system [13]. Thus, by simply changing the solvent system, rates of heterogeneous catalytic transfer reduction may be altered substantially.

In heterogeneous catalytic processes, the solvent can affect rates of reaction through solvation of reactants and intermediates in solution, and also by competing with reactant molecules for active sites on the surface of the catalyst. It has been demonstrated that the adjustment of the competitive adsorption of both hydrogen donor and substrate on the catalyst active sites is essential in liquid phase heterogeneous catalytic transfer reduction, so that none of these adsorbates poisons the catalyst [18]. Solvents may exert a decisive role in balancing the competitiveness of the adsorbates, so as to induce chemisorption onto the catalyst in comparable extents. This influence has been demonstrated for the liquid heterogeneous catalytic hydrogenolysis of aryloxytetrazoles, where the solvent system was used to adjust the surface concentration of the adsorbates in order to promote catalysis [19]. For aryltetrazolyl and -saccharyl ethers, it was found that toluene was a better solvent for transfer reduction than THF [7]. Recently, adsorption isotherms in the liquid phase were used to determine relative binding strengths of aryl ether and hydrogen donor in different solvents [20]. Results indicated that rates of reaction can be varied by regulating the effective concentration of the hydrogen donor at the catalyst surface through variations in the proportion of water in a mixed-solvent system.

Experimental conditions were tuned for the heterogeneous catalytic transfer hydrogenolysis of a series of benzyl ethers **3a** and **3b** to toluenes **4** (Scheme 1). The hydrogenolysis byproducts, tetrazolone or saccharine, respectively, are easily separated from the reaction mixture. In view of optimizing the methodology, different combinations of solvents and hydrogen donors were used. Results obtained are summarised in Table 2 and show that both heteroaryl derivatives **3a** and **3b** exhibit similar reactivity and are good leaving groups for easy catalytic displacement by hydrogen. In all reactions, a 10% dispersion of palladium on charcoal was used as catalyst.

In a control experiment, direct transfer hydrogenolysis of benzyl alcohol was attempted, but did not occur even after extended reaction times. For comparative purposes, catalytic hydrogenation of 4-trifluoromethylbenzyloxy-1,2-benzisothiazole 1,1-dioxide with molecular hydrogen was carried out. Results show that a maximum yield of conversion of 70% was obtained after 2 days, whereas a conversion of 84% was achieved after 30 min in a transfer reduction process, using sodium hypophosphite as hydrogen donor (entries 9, 10). Thus, using catalytic transfer reduction, higher yields of the hydrogenolysed product are obtained at much lower reaction times.

It was found that transfer hydrogenolysis of ethers **3** is also very sensitive to the solvent system and that THF is a better solvent for hydrogenolysis than toluene, contrariwise to what was observed for the hydrogenolysis of the corresponding aryl ethers where the use of THF gave poor results [7]. This difference in behavior was thought to be due to a lower affinity of benzyl ethers to the catalytic surface than that of the aryl analogues. If benzyl ethers adsorb only weakly to the catalyst surface, a solvent that competes less for adsorption is required, so that the substrate is not desorbed before transfer of hydrogen from the donor. In order to test this hyppotesis, a simple experiment was carried out. The adsorption of two model compounds, 5-phenoxy-1-phenyltetrazole and 5-benzyloxy-1-phenyltetrazole, from toluene solutions, onto Pd–C 10%, was evaluated by determining the decrease in initial concentration upon stirring separate mixtures of substrate and catalyst for 10 min. It was found that the adsorption of the aryloxy derivative onto the catalyst was 3 times stronger than the one of its benzyloxy analogue **3a** (Z=H). Therefore, for benzyl ethers **3**, which adsorb more weakly onto the catalyst, a solvent that does not compete for adsorption is required, in order to avoid desorption of the substrate before transfer of hydrogen. For successful reduction, substrate and reducing agent have to be present on the catalyst surface. A stronger adsorption ability of one of the reactants over the other will lead to the poisoning of the catalyst or to auto-decomposition of the hydrogen donor.

Cyclohexene, 2-propanol, hydrazine, sodium formate and sodium hypophosphite were tested as hydrogen donors. Generally, higher yields of hydrogenolysis were obtained when using sodium hypophosphite. 2-Propanol and cyclohexene were completely inert in all cases. Hydrazine and sodium formate were generally less efficient than sodium hypophosphite (see for instance entries 7 and 8). For the specific hydrogenolysis of 5-(4-α, α, α-trifluoromethylbenzyloxy)-1-phenyltetrazole, 4-(α, α, α−trifluoromethyl)toluene was only obtained in poor yields using sodium hypophosphite (entry 11), but could be obtained in acceptable yield using formate or hydrazine as hydrogen donor, (entries 13 and 14).

Sodium hypophosphite is known to be an effective reducing agent for catalytic hydrogenation and hydrogenolysis of various functional groups [21]. The obvious advantages gained from the use of hydrogen donors are higher yields, lower reaction times, simplicity of execution avoiding the use of molecular hydrogen and enhanced selectivity. Hydrogenolysis of tetrazolyl and *pseudo*saccharyl derivatives of 4-chlorobenzyl alcohol (**3a** and **3b**; Z = Cl), gave exclusively 4-chlorotoluene in good yields (entries 15 to 17). In light of the possibility of slow release of hydrogen, sodium hypophosphite appears to be a mild hydrogen transfer agent suitable for use in scale-up processes. Furthermore, the hydrogen source is easily regulated.

4. Conclusion

In conclusion, experimental conditions were found for easy to carry and selective transfer hydrogenolysis of benzyl ethers **3a** and **3b** to toluenes in good yields. The reactivity of these ethers was interpreted on the basis of structural data obtained by X-ray crystallography and theoretical calculations.

In liquid phase catalysis, reactions very often need to be carried out at moderate temperatures, in order to preserve the integrity of other functional groups present and/or chirality. Therefore, the possibility of adjusting catalytic activity through solvent composition is of crucial importance.

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