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Palladium-catalysed reduction of heteroaromatic naphthyl ethers: Structural effects on reactivity

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Abstract

Tetrazolyl and benzisothiazolyl naphthylmethylic ethers **3** and **4(a–e)** are stable crystalline compounds that can be synthesised in high yields by reaction of the corresponding naphthyl methanols (**1a–e**) with the derivatizing agents **2a** and **2b**. Experimental conditions for palladium-catalysed hydrogenolysis of ethers **3**, **4**, with a hydrogen donor and with molecular hydrogen, were investigated. Analysis of the structure and reactivity indicates that naphthylmethylic ethers **3** and **4** are structurally similar to the corresponding benzyloxyderivatives around the ether bond but exhibit different reactivity. Structural analysis for these compounds is based on crystallographic structure determinations, for 5-(2-naphthylmethoxy)-1-phenyltetrazole (**3a**) and 3-(2-naphthylmethoxy)-1,2-benzisothiazole 1,1-dioxide (**4a**), and molecular orbital DFT(B3LYP)/6-311G(d) calculations, for all ethers. It can be concluded from this investigation that 5-chloro-1-phenyltetrazole **2a** acts as a better derivatizing agent for naphthyl methanols than 3-chloro-1,2-benzisothiazole-11-dioxide **2b**, this contrasting with what has been observed with phenols, allylic and benzylic alcohols.

Keywords: Tetrazoles; Benzisothiazoles; Naphthylmethylic ethers; Palladium-on-charcoal; Hydrogenolysis; Hydrogenation

1. Introduction

Naphthols and naphthyl derivatives are widely used in organic synthesis, as starting materials, protecting groups or synthetic intermediates [1,2]. A large variety of compounds containing the naphthalene unit show important applications in crucial areas, mainly in pharmaceutical and biotechnological industries [3,4].

Tetrazoles and benzisothiazoles have also received much attention due to their important applications. Many medical applications of tetrazoles [5–8] derive from the fact that the tetrazolic acid fragment, $-CN_4H$, has similar acidity to the carboxylic acid group, $-CO_2H$, and is almost isosteric with it, but is metabolically much more stable at physiologic pH [9]. In addition, tetrazoles also found application in agriculture [10], as stabilizers in photography and photoimaging [11] and as gas-generating agents for airbags [12].

1,2-Benzisothiazole-3-one 1,1-dioxide (saccharin) has been frequently used as a key element of biologically active compounds [13,14]. Also, it is a cheap and versatile starting material for the synthesis of related heterocyclic derivatives [15]. Benzisothiazolyl and isothiazolyl compounds are used in agriculture, as herbicides, fungicides and pesticides [16] and in medicine [17].

Heterogeneous catalytic transfer hydrogenolysis of aryloxy and allyloxy-tetrazoles and -benzisothiazoles has been used in the hydrogenolysis of phenols and allylic alcohols, and presents a practical and selective synthetic alternative to other methods [18,19]. The hydrogenolysis of the C–OH bond is achieved after conversion of the hydroxyl group into an ether with the electron-withdrawing heteroaromatic tetrazole or benzisothiazole. Derivatization weakens the original C–O bond and increases the nucleophilic susceptibility of the carbon atom. The effect of the heterocyclic part of these ethers on the C–O bond strength has been clarified through X-ray studies [20,21]. The extent of cleavage and selectivity depends on the nature of the catalyst. We have also devised experimental conditions for easy

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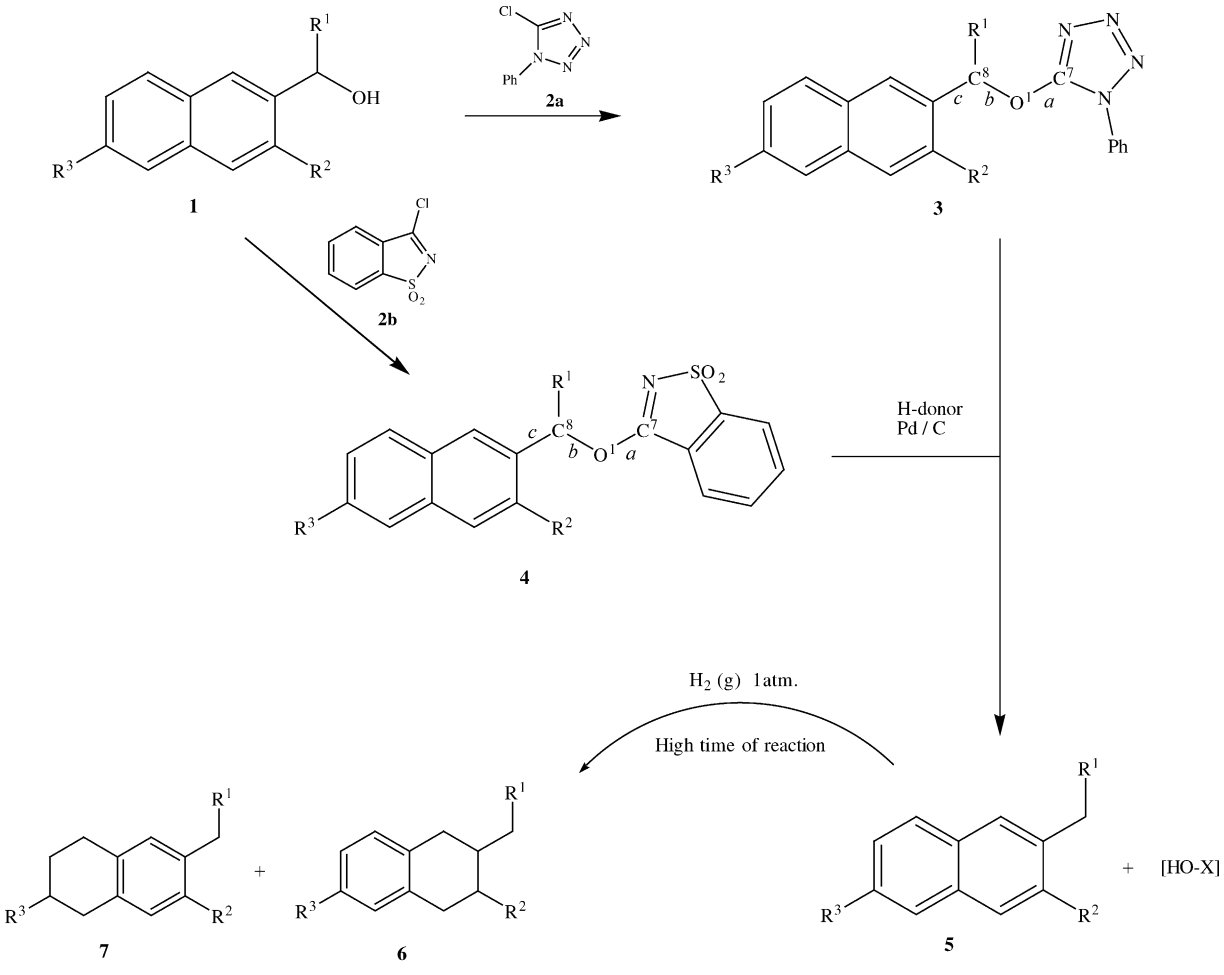
to carry and selective conversion of benzyl alcohols to toluenes in good yields, over Pd/C, via transfer hydrogenolysis of the corresponding benzyl tetrazolyl and benzisothiazolyl ethers, using hydrogen donors. High yields, low reaction times and selectivity can be achieved for the reduction, and tetrazolyl and saccharyl ethers exhibit similar reactivity [22], interpreted on the basis of structural data obtained by X-ray crystallography and molecular orbital calculations. 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 [23].

Continuing our ongoing research program on the synthesis and reactivity of tetrazolyl [24] and benzisothiazolyl derivatives, we have now investigated the efficiency of tetrazole and benzisothiazole as leaving groups for heterogeneous catalytic reduction of the π-extended 2-naphthylic methanols, over 10% Pd/C, using a hydrogen donor or molecular hydrogen. These alcohols are easily derivatized with heteroaromatic chlorides 5-chloro-1-phenyl-tetrazole **2a** [25] or 3-chloro-1,2-benzisothiazole 1,1-dioxide **2b**, affording high yields of the corresponding tetrazolyl or benzisothiazolyl ethers **3** and **4**, which are stable crystalline compounds amenable to full characterization. A methodology for selective hydrogenolysis of naphthyl methanols **1**, via heteroaromatic ethers **3** and **4**, under mild conditions, (Scheme 1) is provided. Toluene, THF, ethyl acetate and dichloromethane were tested as solvents. The effect of substituents on the naphthylic ring and on the benzylic carbon was also investigated. From the results obtained, it is clear that the heteroaromatics tetrazole and benzisothiazole behave differently as derivatizing agents in the hydrogenolysis of naphthyl methanol, in sharp contrast to what was observed with other hydroxylic compounds. The solvent nature and the introduction of substituents close to the ether linkage were also found to affect reactivity. An interpretation of the reactivity of ethers **3** and **4** is based on their structural and electronic features, obtained through solid-state analysis and theoretically, and on comparative adsorption abilities onto the catalyst surface. Considering the observed structural similari-



a : R^1=H; R^2=H; R^3=H
b : R^1=H; R^2=OMe ; R^3=H
c : R^1=Me; R^2=H; R^3=H
d : R^1=Me; R^2=H; R^3=OMe
e : R^1=Ph; R^2=H; R^3=H

Scheme 1.

ties in ethers **3** and **4** around the reactive center, in keeping with what had been observed previously with the corresponding benzylic derivatives, the presently observed difference in reactivity cannot be ascribed to ground state structural features.

2. Experimental

2.1. General

All chemicals were used as purchased from Aldrich. Solvents for extraction and chromatography were of technical grade. When required, the solvents used in reactions were freshly distilled from appropriate drying agents before use. Analytical TLC was performed with Merck silica gel 60 F_{254} plates and visualization was accomplished with UV light. Flash chromatography was carried out using Merck silica gel 60 (230–400 mesh ASTM). Melting points were recorded on a Stuart Scientific SMP3 Melting Point Apparatus and are uncorrected. Proton NMR (300, 400 MHz) spectra were obtained on a Varian Gemini 300 FT or a Bruker AM-400 spectrometers using $CDCl_3$, with TMS as an internal reference ($\delta = 0.0$ ppm). Mass spectra were obtained on a VG 7070E mass spectrometer by electron ionisation (EI) at 70 eV. Data are reported in the form *m*/*z* (intensity relative to base = 100). Infrared spectra (IR) were obtained on a Mattson 1000 FTIR spectrophotometer, over KBr. Elemental analyses were performed in an EA1108-Elemental Analyser (Carlo Erba Instruments). Gas chromatography was carried out on a Chrompack CP9001 instrument fitted with a flame ionisation detector and a CP-SIL 5CB capillary column (25 m × 0.35 mm), using 1,2,4,5-tetramethylbenzene as internal standard for measurement of relative retention times and for quantification of product yields. GC–MS analyses were performed using a Hewlett Packard 5890 Series II gas chromatograph with a 5971 series mass selective detector (EI 70 eV). A CP-WAX 58CB capillary column with 25 m length and 0.25 mm i.d. (Chrompack) was used. The initial temperature of 70 °C was maintained during 3 min and then a heating rate of 5 °C/min was used until a final temperature of 250 °C was reached. Adsorption experiments were determined by analysis of HPLC chromatograms, obtained on an Agilent 1100 Series chromatograph with a 655A-22 UV detector and Shimadzu SPD-M6A Photodiode Array. A Merck LiChroCART 125 column (RP-18, 5 μm) was used and the runs were performed using a mixture of water and acetonitrile (40:60) as the eluent.

2.2. Preparation of alcohols *1b* and *1e*

2.2.1. 2-Hydroxymethyl-(3-methoxy)-naphthalene (*1b*)

A solution of $NaBH_4$ (0.96 g, 30.00 mmol) in dry ethanol (25 mL) was added slowly (during 20 min) to a solution of 2-methoxy-1-naphthaldehyde (2.81 g, 15.00 mmol) in dry ethanol (25 mL) under anhydrous conditions. The mixture was stirred at room temperature until TLC analysis (dichloromethane as eluent) indicated the absence of starting material (1 h). Dichloromethane (100 mL) was added to the reaction mixture and the whole was washed with brine (3 × 50 mL) and the organic extract was dried over sodium sulphate. The filtrate was evaporated to dryness at room temperature to give a brown solid. Recristallization from toluene gave compound **1b** (2.54 g, 13.49 mmol, 90% yield) as pale yellow crystals; mp 383–384 K; IR (KBr) ν_{max} 3280 (O–H), 2966, 1625, 1513, 1471, 1251, 1085, 983, 804 cm^{-1}; MS (EI): *m*/*z* 188 ($[M]^+$, 100). Similarly, 2-naphthyl phenylmethanol (**1e**) was obtained from 2-naphthyl-phenyl-ketone (3.00 g, 12.90 mmol). Recristallization of the resulting pale yellow solid from toluene gave compound **1e** as yellow crystals (2.52 g, 10.76 mmol, 84% yield); mp 365–367 K; IR ν_{max} 3370 (O–H), 3058, 3027, 2871, 1600, 1492, 1452, 1270, 1120, 1022, 813 cm^{-1}; MS (EI): *m*/*z* 234 ($[M]^+$, 100).

2.3. General procedure for the preparation of ethers *3*

The required naphthylmethylic alcohol **1** (7.00 mmol) in dry THF (10 mL) was added to a suspension of sodium hydride (55–60%, 0.50 g, 12.50 mmol) in dry THF (20 mL), at room temperature, under an inert atmosphere. When effervescence had ceased (30 min), a solution of 5-chloro-1-phenyltetrazole (1.50 g, 8.30 mmol) in dry THF (10 mL) was added slowly. The mixture was refluxed with stirring until TLC analysis (toluene/acetone 5:1) indicated the absence of starting material. The crude was extracted with dichloromethane (3 × 30 mL) and the organic layer was dried over anhydrous sodium sulfate. Evaporation of solvent to dryness under reduced pressure and recrystallization from toluene afforded ethers **3**.

2.3.1. 5-(2-Naphthylmethoxy)-1-phenyltetrazole (*3a*)

From 2-(hydroxymethyl)naphthalene (1.11 g, 7.00 mmol). The reaction mixture was refluxed for 2 h. Recrystallization from toluene gave compound **3a** as colourless crystals (1.70 g, 5.63 mmol, 80% yield); mp 412–413 K; ^{1}H NMR (300 MHz, $CDCl_3$): δ, 5.80 (2H, s), 7.40–7.60 (6H, m), 7.69–7.72 (2H, d), 7.85–7.91 (3H, m), 7.98 (1H, s) ppm; IR ν_{max} 2964 (C–H, CH_2), 1593 (C=N), 1566, 1099, 1070 (C–O–C), 1024, 764 cm^{-1}; MS (EI): *m*/*z* 302 ($[M]^+$, 100).

2.3.2. 5-[(2-Naphthyl-(3-methoxy))methoxy]-1-phenyltetrazole (*3b*)

From (2-hydroxymethyl-3-methoxy)-naphthalene (1.32 g, 7.00 mmol). The reaction mixture was refluxed for 6 h. Recrystallization gave compound **3b** as pale yellow crystals (1.54 g, 4.63 mmol, 66% yield); mp 366–368 K; ^{1}H NMR (400 MHz, $CDCl_3$): δ, 3.95 (3H, s), 6.20 (2H, s), 7.20 (1H, s), 7.25–7.45 (4H, m), 7.55–7.58 (1H, t), 7.65–7.67 (2H, d), 7.80–7.83 (1H, d), 7.85–7.95 (2H, m) ppm; IR ν_{max} 2966 (C–H, CH_2), 1590 (C=N), 1556, 1504, 1456, 1251, 1095 (C–O–C), 921, 746 cm^{-1}; MS (EI): *m*/*z* 332 ($[M + H]^+$, 100). Calculated for $C_{19}H_{16}N_4O_2$: C, 68.66; H, 4.85; N, 16.86. Found: C, 68.38; H, 4.87; N, 16.81.

2.3.3. 5-[1-(2-Naphthyl)ethoxy]-1-phenyltetrazole (*3c*)

From 1-(2-naphthyl) ethanol (1.21 g, 7.00 mmol). The reaction mixture was refluxed for 20 h. Recrystallization from toluene gave compound **3c** as yellow crystals (1.75 g, 5.54 mmol, 79% yield); mp 420–422 K; ^{1}H NMR (400 MHz, $CDCl_3$): δ, 1.95–1.98 (3H, d), 6.30–6.35 (1H, q), 7.30–7.55 (5H, m),

7.58–7.68, (2H, d), 7.73–8.93 (5H, m) ppm; IR ν_{max} 2981 (C–H, CH_3), 1594 (C=N), 1554, 1498, 1382, 1351, 1126, 1055 (C–O–C), 901, 756 cm^{-1}; MS (EI): *m/z* 317 ($[M + H]^+$, 66).

*2.3.4. 5-{1-[2-Naphthyl-(6-methoxy)]ethoxy}-1-phenyltetrazole (**3d**)*

From 1-(2-methoxynaphthalen-6-yl)ethanol (1.42 g, 7.00 mmol). The reaction mixture was refluxed for 20 h. Recrystallization from toluene gave compound **3d** as pale yellow crystals (1.60 g, 4.62 mmol, 66% yield); mp 408–409 K; ^{1}H NMR (400 MHz, $CDCl_3$): δ, 2.00–2.05 (3H, d), 3.95 (3H, s), 5.70–5.75 (1H, q), 7.05–7.25 (3H, m), 7.35–7.38 (2H, t), 7.42–7.45 (1H, d), 7.70–7.73 (2H, d), 7.80 (1H, s), 7.85–7.88 (2H, d) ppm; IR ν_{max} 2967 (C–H, CH_3), 1610 (C=N), 1492, 1378, 1265, 1164, 1027 (C–O–C), 744 cm^{-1}; MS (EI): *m/z* 347 ($[M + NH_4]^+$, 17). Calculated for $C_{20}H_{18}N_4O_2$: C, 69.35; H, 5.34; N, 16.17. Found: C, 69.25; H, 5.30; N, 15.93.

*2.3.5. 5-(2-Naphthylbenzyloxy)-1-phenyltetrazole (**3e**)*

From (naphthalene)(phenyl)methanol (1.64 g, 7.00 mmol). The mixture was refluxed for 36 h. Recrystallization from toluene gave compound **3e** as pale yellow crystals (1.44 g, 3.81 mmol, 54% yield); mp 398–400 K; ^{1}H NMR (400 MHz, $CDCl_3$): δ, 6.88–6.90 (1H, s), 7.16–7.20 (1H, d), 7.24–7.26 (2H, t), 7.38–7.44 (3H, m), 7.45–7.65 (5H, m), 7.80–7.87 (2H, m), 7.88–8.05 (4H, m) ppm; IR ν_{max} 2956, 1621 (C=N), 1565, 1498, 1393, 1354, 1156, 1067 (C–O–C), 755 cm^{-1}; MS (EI): *m/z* 395 ($[M + NH_4]^+$, 10).

*2.4. General procedure for the preparation of ethers **4***

A mixture of the required naphthylmethylic alcohol **1** (6.00 mmol), 3-chloro-1,2-benzisothiazole 1,1-dioxide (1.21 g, 6.00 mmol) and anhydrous sodium carbonate (3.82 g; 35.90 mmol) in toluene (60 mL), was refluxed with stirring until TLC analysis (DCM as eluent) indicated the absence of starting material. The excess of base was filtered off and then dichloromethane (100 mL) was added to the reaction mixture. The crude was washed with diluted hydrochloric acid (1 M, 3 × 50 mL), then with brine (3 × 50 mL) and finally dried over anhydrous sodium sulphate. Evaporation of solvent to dryness under reduced pressure and recrystallization from a mixture of toluene/dichloromethane (3:2) afforded compounds **4**.

*2.4.1. 3-(2-Naphthylmethoxy)-1,2-benzisothiazole 1,1-dioxide (**4a**)*

From 2-(hydroxymethyl)-naphthalene (0.95 g, 6.00 mmol). The reaction mixture was refluxed for 4 h. Recrystallization gave compound **4a** as colourless crystals (1.10 g, 3.38 mmol, 56% yield); mp 423–425 K; ^{1}H NMR (400 MHz, $CDCl_3$): δ, 5.10 (2H, s), 7.10–7.15 (1H, s), 7.45–7.50 (2H, d), 7.58–7.63 (1H, d), 7.80–7.90 (4H, m), 7.92–7.97 (2H, m) 8.05–8.10 (1H, d) ppm; IR ν_{max} 3029 (C–H, CH_2), 1427, 1311, 1184, 1043, 748, 582 cm^{-1}; MS (EI): *m/z* 323 ($[M]^+$, 100). Calculated for $C_{18}H_{13}NO_3S$: C, 66.86%; H, 4.05%; N, 4.49%. Found: C, 66.70%; H, 4.17%; N, 4.51%.

*2.4.2. 3-[(2-Naphthyl-(3-methoxy))methoxy]-1,2-benzisothiazole 1,1-dioxide (**4b**)*

From (2-hydroxymethyl-3-methoxy)-naphthalene (1.13 g, 6.00 mmol). The reaction mixture was refluxed for 4 h. Recrystallization gave compound **4b** as pale yellow crystals (1.16 g, 3.29 mmol, 47% yield); mp 373–375 K; ^{1}H NMR (400 MHz, $CDCl_3$): δ, 4.12–4.15 (3H, s), 5.65–5.68 (2H, s), 7.32–7.40 (2H, t), 7.52–7.56 (1H, d), 7.72–7.85 (4H, m), 7.82–7.87 (1H, s), 8.02–8.05 (1H, d), 8.29–8.32 (1H, d) ppm; IR ν_{max} 2952 (C–H, CH_2), 1594, 1450, 1336, 1247, 1182, 1095, 817, 746 cm^{-1}; MS (EI): *m/z* 323 ($[M + NH_4]^+$, 38).

*2.4.3. 3-[1-(2-Naphthyl)ethoxy]-1,2-benzisothiazole 1,1-dioxide (**4c**)*

From 1-(2-naphthyl) ethanol (1.03 g, 6.00 mmol). The reaction mixture was refluxed for 6 h. Recrystallization from toluene/dichloromethane (3:2) gave compound **4c** as pale yellow crystals (1.05 g, 3.12 mmol, 45% yield); mp 348–350 K; ^{1}H NMR (400 MHz, $CDCl_3$): δ, 1.45–1.55 (3H, d), 4.20–4.26 (1H, q), 7.25–7.27 (1H, s), 7.45–7.63 (4H, m), 7.75–7.80 (2H, d), 7.83–8.10 (4H, m) ppm; IR ν_{max} 2926 (C–H, CH_2), 1658, 1599, 1450, 1277, 1276, 1116, 819, 754 cm^{-1}; MS (EI): *m/z* 354 ($[M + NH_4]^+$, 34).

*2.4.4. 3-{1-[2-Naphthyl-(6-methoxy)]ethoxy}-1,2-benzisothiazole 1,1-dioxide (**4d**)*

From 1-(2-methoxynaphthalen-6-yl)ethanol (1.21 g, 6.0 mmol). The reaction mixture was refluxed for 6 h. Recrystallization gave compound **4d** as pale yellow crystals (1.12 g, 3.05 mmol, 44% yield); mp 377–380 K; ^{1}H NMR (400 MHz, $CDCl_3$): δ, 1.55–1.58 (3H, d), 3.91 (3H, s), 5.05–5.11 (1H, q), 7.10–7.12 (1H, d), 7.13–7.15 (1H, s), 7.45–7.54 (2H, d), 7.73–7.82 (3H, m), 7.90–8.05 (4H, m) ppm; IR ν_{max} 2962, 1606, 1460, 1261, 1162, 1074, 1030, 893, 843, 815 cm^{-1}; MS (EI): *m/z* 384 ($[M + NH_4]^+$, 43). Calculated for $C_{20}H_{17}NO_4S$: C, 65.38%; H, 4.66%; N, 3.81%. Found: C, 65.43%; H, 4.65%; N, 3.74%.

*2.4.5. 3-(2-Naphthylbenzyloxy)-1,2-benzisothiazole 1,1-dioxide (**4e**)*

From (naphthalene)(phenyl)methanol (1,41 g, 6.00 mmol). The reaction mixture was refluxed for 24 h. Recrystallization gave compound **4e** as pale yellow crystals (0.95 g, 2.38 mmol, 34% yield); mp 362–365 K; ^{1}H NMR (400 MHz, $CDCl_3$): δ, 5.62 (1H, s), 7.41 (1H, d), 7.50–7.62 (5H, m), 7.65–7.67 (1H, d), 7.70–7.82 (5H, m), 7.94–8.12 (4H, m) ppm; IR ν_{max} 3059, 1334, 1290, 1249, 1184, 748 cm^{-1}; MS (EI): *m/z* 417 ($[M + NH_4]^+$, 21).

*2.5. Typical procedure for transfer hydrogenolysis of ethers **3** and **4** using sodium hypophosphite*

Palladium-on-charcoal (10%, 0.10 g) was added to a stirred solution of 3-(2-naphthylmethoxy)-1,2-benzisothiazole 1,1-dioxide (**3a**) (0.10 g, 0.31 mmol) and an internal standard (1,2,4,5-tetramethylbenzene, 0.10 g) in THF (25 mL) and the mixture was heated to reflux. Sodium hypophosphite (0.20 g,

1.89 mmol) in distilled water (5 mL) was added, and the progress of the reaction was monitored for formation of 2-methyl-naphthalene by gas chromatography, and for the disappearance of the starting material by thin layer chromatography. Other ethers were treated similarly. Yields for transfer hydrogenolysis of ethers **3** and **4** are presented in Table 3.

2.6. Typical procedure for reduction of ethers *3* and *4* using molecular hydrogen

Palladium-on-charcoal (10%, 0.02 g) was added to a stirred solution of 3-(2-naphthylmethoxy)-1,2-benzisothiazole 1,1-dioxide (**3a**) (0.05 g, 0.16 mmol) and an internal standard (durene, 0.07 g) in THF (25 mL). The final mixture was transferred to a pressure reactor and kept under molecular hydrogen (1 atm). The reaction was monitored by gas chromatography. Reduction products were identified by GC–MS and by comparison with standard samples. Other ethers were exposed to similar reaction conditions. Yields for reduction of ethers **3** and **4** are presented in Table 3.

2.7. Comparative adsorption experiment

A solution of 5-(2-naphthylmethoxy)-1-phenyltetrazole **3a** (20 mL, 1.0×10^{-4} M in THF) 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 calculated by the decrease in the peak area for the compound. This experiment was repeated with a solution of 5-((2-naphthylmethoxy)-3-methoxy)-1-phenyltetrazole **3b** (20 mL, 1.0×10^{-4} M in THF) and palladium-on-charcoal (15 mg). The percentage of adsorption was three times greater for 5-(2-naphthylmethoxy)-1-phenyltetrazole (8.5%) than for 5-((2-naphthylmethoxy)-3-methoxy)-1-phenyltetrazole (2.8%).

2.8. Computational details

The equilibrium geometries for naphthylmethylic ethers **3**–**4**(**a**–**e**) were fully optimized at the DFT level of theory with the standard 6-311G(d) basis set, using the Gaussian 98 program [26]. DFT calculations were carried out with the three-parameter density functional abbreviated as B3LYP, which includes Becke's gradient exchange correction [27] and the Lee, Yang and Parr correlation functional [28]. No symmetry restrictions were imposed on the initial structures. Selected results for compounds **3**–**4**(**a**–**e**) obtained with Gaussian 98 are presented in Table 1.

2.9. X-ray crystallographic studies

Experimental data for the X-ray diffraction studies of crystalline 5-(2-naphthylmethoxy)-1-phenyltetrazole (**3a**) and 3-(2-naphthylmethoxy)-1,2-benzisothiazole 1,1-dioxide (**4a**) are presented in Tables 2 and 3.

Table 1
Selected structural data obtained from X-ray crystallographic analysis and molecular orbital calculations for heteroaromatic naphthylmethylic ethers **3**(**a**–**e**) and **4**(**a**–**e**)[a]

Structure	Bond distances (Å)			Angles (°) C7—O1—C8	Method
	a	*b*	*c*		
3a	1.328	1.472	1.494	113.9	X-ray
3a	1.324	1.468	1.498	115.2	B3LYP/6-311G*
3b	1.345	1.453	1.508	115.1	B3LYP/6-311G*
3c	1.340	1.495	1.513	117.3	B3LYP/6-311G*
3d	1.344	1.503	1.524	116.3	B3LYP/6-311G*
3e	1.324	1.472	1.519	116.0	B3LYP/6-311G*
4a	1.314	1.459	1.495	116.2	X-ray
4a	1.324	1.454	1.506	119.2	B3LYP/6-311G*
4b	1.341	1.486	1.505	119.6	B3LYP/6-311G*
4c	1.343	1.494	1.514	120.2	B3LYP/6-311G*
4d	1.338	1.500	1.519	118.6	B3LYP/6-311G*
4e	1.335	1.493	1.508	119.7	B3LYP/6-311G*

[a] Atom numbering as in Scheme 1.

3. Results and discussion

Ground state structural features are often used for predicting and interpreting reactivity [29]. The effect of converting naphthyl methanols in ethers **3**, **4** may be assessed through structural analysis obtained by X-ray crystallography. Crystal structures of 3-(2-naphthylmethoxy)-1,2-benzisothiazole 1,1-dioxide (**4a**, Fig. 1) and of 5-(2-naphthylmethoxy)-1-phenyltetrazole (**3a**, Fig. 2) were determined (Tables 2 and 3).

Solid-state analysis of compound **4a** shows that there are two molecules in the unit cell, but only one will be discussed because they are identical to within three times the error limits. Crystallographic analysis of **4a** reveals that the geometry of the naphthalene skeleton is very similar to that of naphthalene [30], the same holding for that of the saccharyl skeleton compared with saccharin [31]. Analysis of the bond lengths around the central ether linkage (sequence of atoms C7–O1–C8–C9; Fig. 1 and Table 2) shows that the heteroaromatic C–O bond (C7–O1) has a length of 131.4 pm and the "benzylic" C–O bond length (C8–O3) is 145.9 pm (mean 131.9 and 147.2 pm, respectively, for benzyloxy tetrazoles and benzisothiazoles). The bond angle C7–O1–C8 is 116.2°, near the value required for an sp^2 hybrid. The length for bond C8–C9 is 149.5 pm (mean 149.8 for benzylic derivatives) and is unexceptional for a CH_2 connected to an aryl ring [32]. Thus, the bond to be hydrogenolysed, C8–O1, is very long, whereas bond C7–O1 is very short.

Crystallographic analysis of **3a** reveals general features similar to **4a**. Analysis of the bond lengths around the central ether linkage in **3a** (sequence of atoms C7–O1–C8–C9; Fig. 2 and Table 2) shows that the heteroaromatic C–O bond (C7–O1) has a length of 132.8 pm and the "benzylic" C–O bond length (C8–O1) is 147.2 pm (mean 131.9 and 147.2 pm, respectively, for benzyloxy tetrazoles and benzisothiazoles) [22]. The length for bond C8–C9 is 149.4 pm (mean 149.8 for benzylic derivatives) and is again unexceptional for a CH_2 connected to an aryl ring [31]. Thus, for the tetrazolyl derivative **3a** the bond

Table 2
Selected bond lengths and angles for 5-(2-naphthylmethoxy)-1-phenyltetrazole (**3a**) and 3-(naphthalen-2-methoxy)-1,2-benzisothiazole 1,1-dioxide (**4a**) (Å, °)

3a				**4a**			
N(3)–N(4)	1.370(2)	N(3)–N(4)–C(1)	122.31(17)	C(1)–C(6)	1.380(4)	C(2)–C(1)–C(6)	122.6(3)
N(3)–N(2)	1.294(2)	C(7)–N(4)–C(1)	130.83(18)	C(1)–S(1)	1.768(3)	C(2)–C(1)–S(1)	130.1(2)
N(4)–C(7)	1.339(3)	N(2)–N(3)–N(4)	106.47(17)	C(6)–C(7)	1.469(4)	C(6)–C(1)–S(1)	107.3(2)
C(7)–N(1)	1.312(3)	N(1)–C(7)–O(1)	128.40(2)	C(7)–N(1)	1.293(4)	N(1)–C(7)–O(3)	123.7(3)
C(7)–O(1)	1.328(3)	N(1)–C(7)–N(4)	111.00(2)	C(7)–O(1)	1.314(4)	N(1)–C(7)–C(6)	118.4(3)
C(8)–O(1)	1.472(3)	O(1)–C(7)–N(4)	120.61(19)	C(8)–O(1)	1.459(4)	O(3)–C(7)–C(6)	117.8(3)
C(8)–C(9)	1.494(3)	O(1)–C(8)–C(9)	106.71(18)	C(8)–C(9)	1.495(5)	O(3)–C(8)–C(9)	107.8(3)
C(9)–C(10)	1.363(3)	C(7)–N(1)–N(2)	104.26(18)	C(9)–C(10)	1.406(5)	C(7)–N(1)–S(1)	108.9(2)
C(10)–C(11)	1.427(4)	C(7)–O(1)–C(8)	113.93(17)	C(9)–C(18)	1.359(5)	C(7)–O(1)–C(8)	116.2(2)
N(1)–N(2)	1.380(2)	N(3)–N(2)–N(1)	111.40(17)	N(1)–S(1)	1.663(3)	N(1)–S(1)–C(1)	95.88(14)
N(2)–N(3)–N(4)–C(1)	−179.8(2)			S(1)–C(1)–C(2)–C(3)	−177.4(3)		
N(2)–N(3)–N(4)–C(7)	−0.3(2)			C(2)–C(1)–C(6)–C(7)	178.5(3)		
N(3)–N(4)–C(7)–N(1)	−0.3(2)			S(1)–C(1)–C(6)–C(7)	−2.7(3)		
N(3)–N(4)–C(7)–O(1)	179.6(2)			C(4)–C(5)–C(6)–C(7)	−179.7(3)		
O(1)–C(8)–C(9)–C(10)	68.3(2)			C(1)–C(6)–C(7)–N(1)	1.9(5)		
O(1)–C(7)–N(1)–N(2)	−179.4(2)			C(1)–C(6)–C(7)–O(1)	−178.4(3)		
N(4)–C(7)–N(1)–N(2)	−0.1(2)			O(1)–C(8)–C(9)–C(10)	80.1(5)		
N(1)–C(7)–O(1)–C(8)	3.2(2)			S(1)–N(1)–C(7)–O(1)	−179.6(3)		
N(4)–C(7)–O(1)–C(8)	−175.9(2)			C(6)–C(7)–N(1)–S(1)	0.07(16)		
C(9)–C(8)–O(1)–C(7)	−175.9(2)			N(1)–C(7)–O(1)–C(8)	−0.9(2)		
C(7)–N(1)–N(2)–N(3)	0.0(2)			C(8)–O(1)–C(7)–C(6)	179.3(4)		
N(4)–N(3)–N(2)–N(1)	0.2(2)			C(7)–O(1)–C(8)–C(9)	−175.5(3)		

to be hydrogenolysed, C8–O1, is also very long, whereas bond C7–O1 is considerably shortened.

Theoretical calculations for the naphthylmethylic ethers **3**, **4** were performed with the Gaussian 98 program package as described in the experimental section. Selected results presented in Table 1 are in perfect agreement with data obtained by X-ray crystallography for compounds **3a** and **4a**. Also, the values obtained for the bond lengths and angles (C7–O1–C8) throughout the series of naphthyl ethers **3b**–**e** and **4b**–**e** (Table 1, bonds *a*, *b* and *c* in Scheme 1), are very similar to those obtained by X-ray crystallography for derivatives **3a** and **4a**. Thus, all ethers are structurally similar around the central ether linkage.

The favourable delocalisation of the ether oxygen lone pair on the heteroaromatic system by an effective p-conjugation in

Table 3
Experimental data for the X-ray diffraction studies on crystalline 5-(2-naphthylmethoxy)-1-phenyltetrazole (**3a**) and 3-(naphthalen-2-methoxy)-1,2-benzisothiazole 1,1-dioxide (**4a**)[a]

Formula	$C_{17}H_{12}N_4O$	$C_{18}H_{13}NO_3S$
Formula weight	288.31	323.35
Crystal system	Triclinic	Orthorhombic
Cell parameters at 213 K		
a (Å)	6.4787(13)	14.504
b (Å)	9.4652(19)	12.884
c (Å)	12.824(3)	16.040
α (°)	98.72(3)	90
β (°)	100.03(3)	90
γ (°)	97.28(3)	90
Volume (Å^3)	755.9(3)	2997.3
Z	2	8
Calculated density (mg m^{-3})	1.267	1.433
Linear absorption coefficient (mm^{-1})	0.083	0.231
F(0 0 0)	300	1344
θ range (°)	2.20–24.25	2.11–22.99
Reflections collected, unique	4164, 2259 [R(int) = 0.0392]	16226, 4087 [R(int) = 0.0537]
Completeness to Refinement method	2θ = 26.06, 92.6% full-matrix least-squares on F^2	θ = 22.99, 100.0% full-matrix least-squares on F^2
Data, restraints, parameters	2259/0/208	4087/1/415
Goodness of fit on F^2	0.868	0.906
Final R indeces [$I > 2\sigma(I)$]	$R1$ = 0.0413, w$R2$ = 0.0907	$R1$ = 0.0345, w$R2$ = 0.0688
R indeces	$R1$ = 0.0783, w$R2$ = 0.1030	$R1$ = 0.0463, w$R2$ = 0.0715
Absolute structure parameter	−0.03(5)	0.08(7)
Largest diff. peak and hole (e. Å^{-3})	0.179 and −0.206	0.330 and −0.257

[a] SHELXL 97: Program for the Refinement of Crystal Structures, Universitu og Göttingen, 1997.

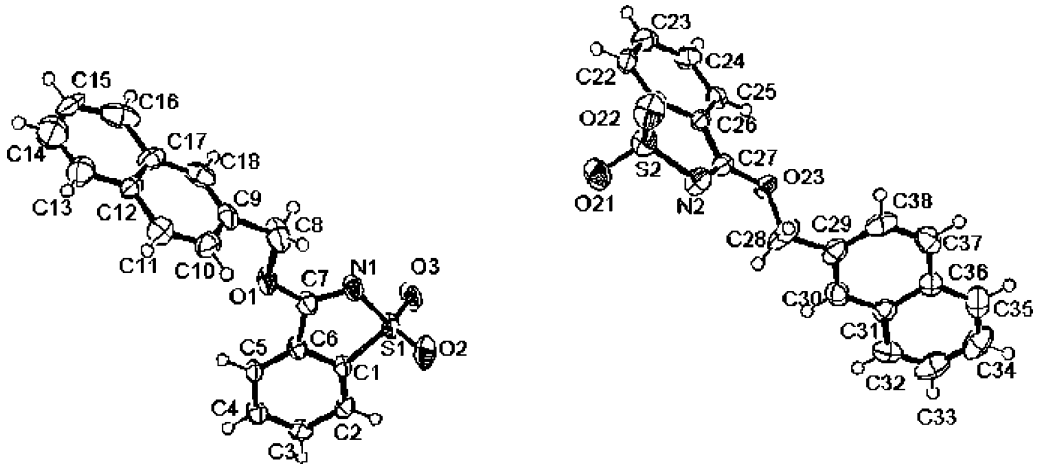


Fig. 1. Crystal structure of 3-(2-naphthylmethoxy)-1,2-benzisothiazole 1,1-dioxide **4a**.

ethers **3a** and **4a** is the cause for the increase in the "benzylic" bond lengths. From these data, it is clear that structural features around the ether linkage are similar for naphthyl derivatives **3**, **4** and for the benzylic analogues [22]. These results have provided further evidence that both tetrazolyl and saccharyl rings (X in ethers **3** and **4**; Scheme 1) exhert similar electron-withdrawing effects, resulting in an activation of the "benzylic" bond towards hydrogenolysis.

Experimental conditions were tuned for reduction of ethers **3**, **4** to naphthyl derivatives **5** over palladium on charcoal (10%), using a hydrogen donor or with molecular hydrogen (Scheme 1 and Table 4). The reaction times reported correspond to the maximum yields obtained for each set of reaction conditions. Sodium hypophosphite is known as an effective reducing agent for catalytic hydrogenolysis and hydrogenation of several functional groups and was also used in the present investigation [22,33]. Toluene, THF, ethyl acetate and dichloromethane were tested as solvents. The effect of substituents on the naphthylic ring and on the benzylic carbon was also investigated.

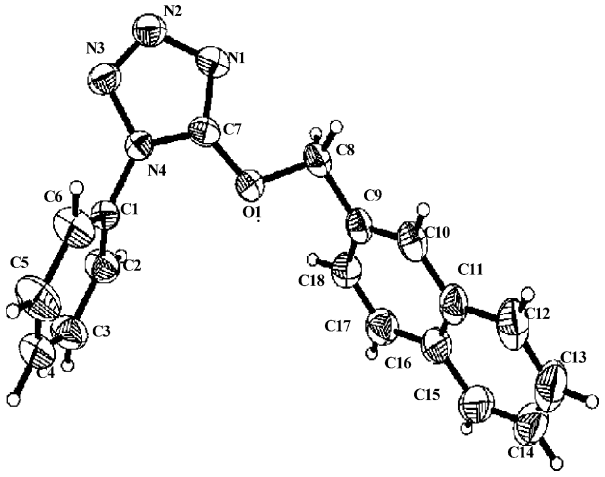


Fig. 2. Crystal structure of 5-(2-naphthylmethoxy)-1-phenyltetrazole **3a**.

For the unsubstituted 2-naphthyl tetrazolyl ether **3a**, transfer hydrogenolysis is achieved quantitatively after 5 min in THF, 10 min in ethyl acetate and 30 min in DCM, under reflux. At room temperature hydrogenolysis still occurs selectively in THF, but is slower (1 h; entries 1, 2). Using molecular hydrogen, hydrogenolysis of this ether also occurs selectively, in over 90% yield, in refluxing THF or at room temperature (2 h; entries 4, 6). On extended reaction times (18 h), hydrogenation of 2-methyl naphthalene **5a** is observed in high yield, at room temperature, but much less in refluxing THF (87% versus 8%; entries 5, 7). Thus, hydrogenolysis of **3a** can be achieved in excellent yields in refluxing THF, with sodium phosphinate or molecular hydrogen. With this source of hydrogen, further reduction of **5a** can be obtained in very high yields by extending the reaction time, at room temperature.

The introduction of a methoxy group on position 3 of the naphthyl ring (compound **3b**) appears to alter substantially the reactivity. Maximum yields of **5b** obtained are 59 and 35%, in THF and toluene respectively (5 h; entries 10, 11). In order to clarify the reasons for this difference in reactivity, comparative adsorption experiments for compounds **3a** and **3b** were carried out. From these experiments, it was observed that, in the same experimental conditions, the percentage of 5-(2-naphthylmethoxy)-1-phenyltetrazole adsorbed onto the catalyst surface was about 3 times greater than that of 5-((2-naphthylmethoxy)-3-methoxy)-1-phenyltetrazole (8.5% versus 2.8%). Thus, the methoxy group appears to hinder adsorption of ether **3b** onto the catalyst surface, resulting in a decrease in yield of hydrogenolysis. This effect is more pronounced in toluene than in THF, because the former competes more for active sites than the later.

The introduction of a methyl group on the benzylic carbon (compound **3c**) also results in a decrease in the yield of hydrogenolysis and an increase in time of reaction. Maxima of 55 and 47% yields of 5c are obtained after 6 h, in THF and toluene respectively (entries 12, 13). If the methyl group attached to the benzylic carbon is replaced by a phenyl (**3e**) the yields of hydrogenolysis are similar to those obtained for **3c** (entries 12,

Table 4
Experimental conditions and yield for the transfer reduction of heteroaromatic naphthylmethylic ethers **3** and **4(a–e)** to give compounds **5**, **6** and **7(a–e)**

Entry	Ether	Solvent	Temp. (°C)	Hydrogen source	Reaction time	Yield[a] **5** (%)	Yield[a] **6**/**7** (%)
1	**3a**	THF	Reflux	NaH_2PO_2/H_2O	5 min	99	–
2	**3a**	THF	25	NaH_2PO_2/H_2O	1 h	83	–
3	**3a**	Toluene	25	NaH_2PO_2/H_2O	1 h	80	–
4	**3a**	THF	Reflux	H_2 (1 atm)	2 h	92	–
5	**3a**	THF	Reflux	H_2 (1 atm)	18 h	82	8
6	**3a**	THF	25	H_2 (1 atm)	2 h	90	–
7	**3a**	THF	25	H_2 (1 atm)	18 h	2	87
8	**3a**	DCM	Reflux	NaH_2PO_2/H_2O	30 min	96	–
9	**3a**	Ethyl acetate	Reflux	NaH_2PO_2/H_2O	10 min	91	–
10	**3b**	THF	25	NaH_2PO_2/H_2O	5 h	59	–
11	**3b**	Toluene	25	NaH_2PO_2/H_2O	5 h	35	–
12	**3c**	THF	25	NaH_2PO_2/H_2O	6 h	55	–
13	**3c**	Toluene	25	NaH_2PO_2/H_2O	6 h	47	–
14	**3d**	THF	25	NaH_2PO_2/H_2O	6 h	61	–
15	**3d**	Toluene	25	NaH_2PO_2/H_2O	6 h	44	–
16	**3e**	THF	25	NaH_2PO_2/H_2O	5 h	52	–
17	**3e**	Toluene	25	NaH_2PO_2/H_2O	5 h	33	–
18	**4a**	THF	Reflux	NaH_2PO_2/H_2O	15 h	70	–
19	**4a**	THF	25	NaH_2PO_2/H_2O	19 h	57	–
20	**4a**	Toluene	25	NaH_2PO_2/H_2O	24 h	40	–
21	**4a**	THF	Reflux	H_2 (1 atm)	2 h	84	–
22	**4a**	THF	Reflux	H_2 (1 atm)	18 h	81	3
23	**4a**	THF	25	H_2 (1 atm)	2 h	23	–
24	**4a**	THF	25	H_2 (1 atm)	18 h	5	16
25	**4a**	DCM	Reflux	NaH_2PO_2/H_2O	3 h	43	–
26	**4a**	Ethyl acetate	Reflux	NaH_2PO_2/H_2O	4 h	35	–
27	**4b**	THF	25	NaH_2PO_2/H_2O	15 h	42	–
28	**4b**	Toluene	25	NaH_2PO_2/H_2O	15 h	20	–
29	**4c**	THF	25	NaH_2PO_2/H_2O	19 h	46	–
30	**4c**	Toluene	25	NaH_2PO_2/H_2O	19 h	15	–
31	**4d**	THF	25	NaH_2PO_2/H_2O	19 h	37	–
32	**4d**	Toluene	25	NaH_2PO_2/H_2O	19 h	17	–
33	**4e**	THF	25	NaH_2PO_2/H_2O	23 h	37	–
34	**4e**	Toluene	25	NaH_2PO_2/H_2O	23 h	31	–

[a] Obtained by gas chromatography with reference to durene as internal standard.

13 and 16, 17). Comparing results obtained for compound **3c** with those obtained for compound **3d** indicates that the introduction of a methoxy group on the naphthylic ring in position 7 does not appear to further affect the reactivity (entries 12, 13 and 14, 15).

In all equivalent sets of experimental conditions, the hydrogenolysis of benzisothiazolyl ethers **4** is slower and lower yielding than that of the corresponding tetrazolyl ethers. This behaviour contrasts with what was observed for benzyloxytetrazoles and -benzisothiazoles [22], since these exhibited similar reactivity. For the unsubstituted benzisothiazolyl derivative **4a**, hydrogenolysis using sodium hypophosphite is also selective, but much slower and low yielding than for the tetrazolyl derivative **3a**. Maximum yields obtained are 70, 43 and 35%, in refluxing THF, DCM and ethyl acetate respectively (entries 18, 25 and 26). At room temperature, the product yield lowers to 57 and 40%, in THF and toluene respectively (entries 19, 20). For ether **4a**, the best product yield (84%) and lower reaction time (2 h) are obtained when using molecular hydrogen in refluxing THF. On extended heating to 18 h, dearomatization of **5a** occurs in only 3% yield (entries 21, 22). However, at room temperature the maximum product yield decreases to 23%, and on extending the time of reaction dearomatization of **5a** is favoured (entries 23, 24).

It appears from these results that the best set of conditions for selective hydrogenolysis of ether **4a** requires molecular hydrogen in refluxing THF.

As was observed for ethers **3**, the introduction of a methoxy group on the naphthylic ring, adjacent to the ether linkage (**4b**), a methyl, or a phenyl group on the benzylic carbon (**4c** and **4e**) results in a decrease in reactivity (entries 27, 28; 29, 30 and 33, 34, respectively). In keeping with what had been observed for the corresponding tetrazolyl derivatives, substituents in positions close to the reaction centre hinder the adsorption of the substrate onto the catalyst, inhibiting H-transfer. Again, the effect is more pronounced in toluene because less active sites are available, for substrate adsorption.

Dearomatization of **5** only occurs when using molecular hydrogen, and is only of some meaning in terms of yields if the system is kept at room temperature. Under reflux, the percentage of conversion of **5** in tetrahydronaphthalene (**6**/**7**) is very low (entries 5, 22). Yields of tetrahydronaphthalene are much higher from ether **3a** than from ether **4a**. For hydrogenation to occur, methylnaphthalene has to be adsorbed onto the catalyst surface.

If the by-product tetrazolone is more easily desorbed from the catalyst surface than benzisothiazolone, more active sites will be available for methylnaphthalene, leading to a higher rate of hydrogenation.

4. Conclusion

In keeping with what was observed for benzylic derivatives [22], THF is a better solvent for hydrogenolysis than toluene. In contrast to what was observed for benzyl alcohols, it is clear from the present investigation that the heteroaromatics tetrazole and benzisothiazole behave differently as derivatizing agents in the hydrogenolysis of naphthyl methanols. For derivatives **3** and **4**, reductive C–O cleavage over Pd/C can be achieved using sodium hypophosphite or molecular hydrogen as source of hydrogen. Under the reaction conditions tested, hydrogenolysis is generally faster and higher yielding for tetrazolyl than for benzisothiazolyl derivatives. For ether **3a**, hydrogenolysis is considerably faster than for benzyloxytetrazole, but for ether **4a** it is much slower and lower yielding. When using sodium hypophosphite as source of hydrogen, only hydrogenolysis is observed. However, when using molecular hydrogen, dearomatization of methylnaphthalene is observed after extended periods of time, at room temperature. Again, this behaviour is different from what is known to occur with benzyl derivatives. This difference in reactivity is ascribed to the higher affinity of the flat extended π-surface in 2-methylnaphthalene for the metal catalyst.

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