Synthesis C. Behloul et al. Paper

Reductive Removal of the Pivaloyl Protecting Group from Tetrazoles by a Naphthalene-Catalyzed Lithiation Process

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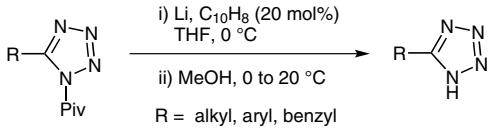

Dedicated to the memory of Professor Alan R. Katritzky

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Abstract The reaction of various 1-pivaloyl-1*H*-tetrazoles with excess lithium and a catalytic amount of naphthalene (20 mol%) led, after treatment with methanol, to the corresponding free tetrazoles through reductive C–N bond cleavage. This methodology represents a reasonable alternative to other nonreductive protocols.

Keywords tetrazoles, pivaloyl, lithium, deprotection

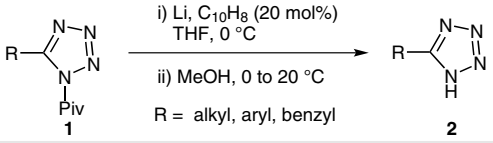
The pivaloyl group is widely used in organic synthesis to protect alcohols, amines, and thiols, due to its easy introduction, stability under a variety of reaction conditions, and relatively easy removal to give the corresponding depivalated compounds.[1] Among the different methodologies reported for the deacylation of protected alcohols and amines, we can find hydrolysis under basic or acidic conditions,[2] reduction with alkali metals in liquid ammonia,[3] reductive cleavage using an arene-catalyzed lithiation,[4] reaction with hydride sources,[5] electrolysis,[6] and enzymatic methods.[7]

The tetrazole moiety is present in several biologically active compounds, such as sartans, which are pharmaceuticals that are efficient for the treatment of hypertension, kidney damage caused by diabetes, and heart failure. The synthesis of sartans generally requires protection and deprotection steps to the tetrazole ring.[8] The effective protection caused by the high steric demand of the pivaloyl group, together with the ease of its introduction into and its removal from the nitrogen atom, are features that potentially make the pivaloyl group useful in the preparation of this interesting family of drugs. Thus, the development of procedures that remove the pivaloyl protecting group without affecting the tetrazole ring would be very interesting.[8]

In the last few years our research group has been using arene-catalyzed lithiation to perform metalations under very mild reaction conditions.[9–12] This lithiation methodology has been applied to the reductive cleavage of trityl ethers[13] and amines,[14] the desilylation of silylated alcohols, amines, and thiols,[15] the cleavage of carbonates, carbamates, and thiocarbonates,[16] and the deacylation of esters, thioesters, and amides.[17] Very recently, we have reported a reductive cleavage of tritylated tetrazoles using this lithiation methodology, which leads to the deprotected tetrazoles without affecting the heterocyclic ring.[18]

In this paper we wish to report the use of a naphthalene-catalyzed lithiation to perform the removal of the pivaloyl protecting group from tetrazoles under very mild conditions.

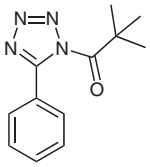
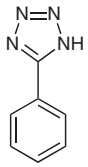
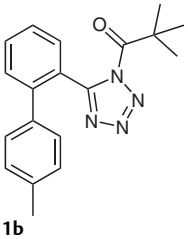
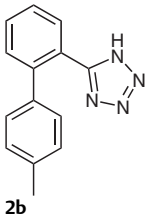
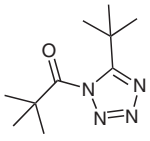
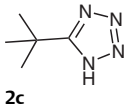
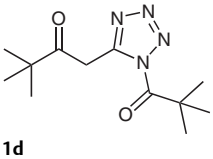
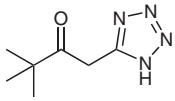
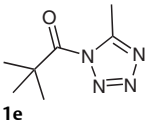
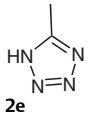
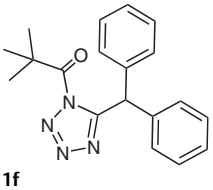
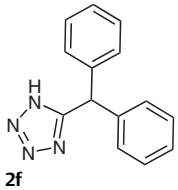
The reaction of various 5-substituted 1-pivaloyltetrazoles **1a**–**f** with excess lithium powder (1:20 molar ratio) and a catalytic amount of naphthalene (1:0.4 molar ratio) in tetrahydrofuran at 0 °C for three hours led, after quenching with methanol, to the corresponding free tetrazoles **2a**–**f** (Equation 1, Table 1).



Equation 1

The deprotected tetrazoles **2a**–**f** were isolated generally in good yields (Equation 1 and Table 1). In general, moderate to good yields were obtained in the deprotection of 5-aryl-1-pivaloyltetrazoles **2a**,**b** (entries 1 and 2), 5-alkyl-1-pivaloyltetrazoles **2c**,**e** (entries 3 and 5), or 5-benzhydryl-1-pivaloyltetrazole **2f** (entry 6). Interestingly, 5-(3,3-dimethyl-2-oxobutyl-1-pivaloyl)-1*H*-tetrazole (**1d**), containing a carbonyl group in the 5-substituent that could undergo re-

Table 1 Reductive Removal of the Pivaloyl Group from Protected Tetrazoles **1**

Entry	Substrate	Time (h)	Product	Yield[a] (%)
1	 **1a**	3	 **2a**	63
2	 **1b**	3	 **2b**	56
3	 **1c**	3	 **2c**	55
4	 **1d**	3	 **2d**	62
5	 **1e**	3	 **2e**	61
6	 **1f**	3	 **2f**	61

[a] Yield of isolated product after extraction and recrystallization, based on the starting material **1**.

duction under these reaction conditions, underwent solely depivalation to give **2d** in 62% yield (entry 4). All the lithiation processes were complete in a reaction time of three hours.

The starting tetrazoles were prepared by reaction of sodium azide with the corresponding nitriles in the presence of an amine. The isolated tetrazoles were then pivalated on N1 by reaction with pivaloyl chloride, giving the expected protected tetrazoles **1** in good yields.

In conclusion, we report an efficient method to remove the pivaloyl protecting group from various 1-pivaloyl-1*H*-tetrazoles bearing various aliphatic, aromatic, or benzylic substituents in the 5-position under very mild reaction conditions. This procedure is an alternative to other methodologies, especially those involving hydrolysis, which usually require harsh reaction conditions.

FT-IR spectra were obtained on a Nicolet Impact 400D spectrophotometer using KBr plates (for solid compounds). NMR spectra were recorded on a Bruker spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C) using $CDCl_3$, DMSO-d_6, CD_3OD as solvents and TMS (δ = 0.00, ^{1}H) and $CDCl_3$ (δ = 77.0, ^{13}C), DMSO-d_6 (δ = 2.50, ^{1}H and δ = 39.75, ^{13}C), CD_3OD (δ = 4.87, ^{1}H and δ = 49.0, ^{13}C) as internal standards. Elemental analysis were measured by the Technical Services at the University of Alicante. Column chromatography was performed using silica gel 60 (35–70 mesh) or basic alumina (50–160 µm particle size). Li powder was prepared according to the procedure described.[19] Commercially available BuLi was titrated with a 1 M solution of *s*-BuOH in xylene using 1,10-phenanthroline as indicator.[20] Commercially available anhyd THF (99.9%, water content ≤ 0.006%, Acros) was used as solvent in all the lithiation reactions.

All reagents used for the synthesis of substrates **1** and naphthalene were commercially available (Acros, Aldrich) and were used without further purification. All glassware was dried in an oven at 100 °C and cooled to r.t. under argon before use.

Tetrazoles **2a**–**f** were prepared following the procedure recently described by us.[18] Physical and spectroscopic data of the obtained compounds **2a**–**f** were identical with those previously reported.[18]

CAUTION! Several tetrazole derivatives or their salts have been shown to have explosive properties, especially tetrazoles with electron-withdrawing substituents in position 5 of the ring.[21] Although we had no problems during the synthesis of any of the tetrazoles included in this paper, proper protective measures should be taken.

Protected Tetrazoles 1a–f; General Procedure

To a stirred solution of the tetrazole (10.0 mmol) in anhyd THF (10 mL) under argon at 0 °C was added dropwise 2.5 M BuLi in hexane (4 mL, 10.0 mmol); the mixture was stirred at this temperature for 10 min. Pivaloyl chloride (1.23 mL, 10.0 mmol) was added to the mixture over ca. 5 min and it was stirred at r.t. overnight. The reaction was quenched with H_2O (5 mL) and extracted with EtOAc (3 × 15 mL). The combined organic phases were washed with brine (5 mL), dried (Na_2SO_4), filtered, and the solvent evaporated to give a residue that was purified by recrystallization (hexane–EtOAc) to afford pure product.

2,2-Dimethyl-1-(5-phenyl-1*H*-tetrazol-1-yl)propan-1-one (1a)

White solid; yield: 1.497 g (65%); mp 218–220 °C.

IR (KBr): 1701, 1608, 1562, 1484, 1409, 1256, 685 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 1.06 (s, 9 H), 7.45–7.90 (m, 5 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 27.6 (3 CH_3), 39.3 (C), 125.6 (C), 128.2 (2 CH), 130.5 (2 CH), 132.5 (CH), 157.7 (C).

Anal. Calcd for $C_{12}H_{14}N_4O$: C, 62.69; H, 6.13; N, 24.33. Found: C, 62.66; H, 6.15; N, 24.37.

2,2-Dimethyl-1-[5-(4′-methylbiphenyl-2-yl)-1*H*-tetrazol-1-yl]propan-1-one (1b)

Yellow solid; yield: 1.986 g (62%).

IR (KBr): 1712, 1482, 1244, 1078, 823, 754 cm^{-1}.

^1H NMR (400 MHz, CD_3OD): δ = 0.92 (s, 9 H), 2.27 (s, 3 H), 6.93–7.08 (m, 4 H), 7.45–7.63 (m, 4 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 21.1 (CH_3), 27.6 (3 CH_3), 124.2 (C), 128.7, 129.9, 130.2, 131.6, 131.8, 132.5 (8 CH), 137.6 (C), 138.8 (2 C), 143.6 (2 C), 156.8 (C).

Anal. Calcd for $C_{19}H_{20}N_4O$: C, 71.23; H, 6.29; N, 17.49. Found: C, 71.23; H, 6.32; N, 17.53.

1-(5-*tert*-Butyl-1*H*-tetrazol-1-yl)-2,2-dimethylpropan-1-one (1c)

White solid; yield: 1.472 g (70%); mp 104–106 °C.

IR (KBr): 1732, 1264, 1218, 1045, 703 cm^{-1}.

^1H NMR (400 MHz, CD_3OD): δ = 1.42 (s, 18 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 29.5 (3 CH_3), 31.8 (3 CH_3), 165.7 (C), 214.1 (CO).

Anal. Calcd for $C_{10}H_{18}N_4O$: C, 57.12; H, 8.63; N, 26.64. Found: C, 57.12; H, 8.62; N, 26.66.

3,3-Dimethyl-1-(1-pivaloyl-1*H*-tetrazol-5-yl)butan-2-one (1d)

Brown solid; yield: 2.018 g (80%).

^1H NMR (400 MHz, CD_3OD): δ = 2.74 (s, 18 H), 2.80 (s, 2 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 26.4, 26.8, 27.5 (3 CH_3), 27.6, 27.7, 27.9 (3 CH_3), 31.7 (CH_2), 39.3 (C), 45.5 (C), 152.5 (C), 182.5 (C=O), 210.1 (C=O).

Anal. Calcd for $C_{12}H_{20}N_4O_2$: C, 57.12; H, 7.99; N, 22.21. Found: C, 57.10; H, 8.01; N, 22.24.

2,2-Dimethyl-1-(5-methyl-1*H*-tetrazol-1-yl)propan-1-one (1e)

White solid; yield: 1.430 g (85%); mp 152–157 °C.

^1H NMR (400 MHz, CD_3OD): δ = 0.92 (s, 9 H), 2.31 (s, 3 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 8.4 (CH_3), 26.8 (CH_3), 27.6 (2 CH_3), 39.3 (C), 154.1 (C), 182.5 (CO).

Anal. Calcd for $C_7H_{12}N_4O$: C, 49.99; H, 7.19; N, 33.31. Found: C, 49.96; H, 7.14; N, 33.33.

1-[5-(Diphenylmethyl)-1*H*-tetrazol-1-yl]-2,2-dimethylpropan-1-one (1f)

White solid; yield: 2.884 g (90%); mp 154–158 °C.

^1H NMR (400 MHz, CD_3OD): δ = 1.07 (s, 9 H), 5.80 (s, 1 H), 7.23–7.38 (m, 10 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 26.8, 27.5, 27.6 (3 CH_3), 39.3 (C), 47.8 (CH), 128.6 (2 CH), 129.6 (4 CH), 129.9 (4 CH), 140.8 (2 C), 159.9 (C), 182.5 (C=O).

Anal. Calcd for $C_{19}H_{20}N_4O$: C, 71.23; H, 6.29; N, 17.49. Found: C, 71.24; H, 6.26; N, 17.45.

Naphthalene-Catalyzed Lithiation of Compounds 1: Preparation of Products 2; General Procedure

To a green suspension of Li powder (70 mg, 10 mmol) and naphthalene (26 mg, 0.2 mmol) in THF (5 mL) under argon at 0 °C was added dropwise a solution of the protected tetrazole **1** (0.5 mmol) in THF (2 mL) and the mixture was stirred at this temperature for 3 h. MeOH (5 mL) was carefully added to the mixture, the cooling bath was removed, and the mixture was stirred until it reached r.t. The mixture was extracted with EtOAc (3 × 15 mL) and the combined organic phases were washed with brine (5 mL), and then dried (Na_2SO_4). After evaporation of the solvents, the resulting residue was purified by recrystallization (hexane–EtOAc), giving the corresponding free tetrazoles **2** in the following yields: **2a** (46 mg, 63%), **2b** (66 mg, 56%), **2c** (35 mg, 55%), **2d** (52 mg, 62%), **2e** (26 mg, 61%), and **2f** (72 mg, 61%) (see also Table 1). The obtained tetrazoles **2** were characterized by comparison of their physical and spectroscopic data with those previously synthesized.

Acknowledgement

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379457.

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