

Improved Synthesis of Benzotriazoles and 1-Acylbenzotriazoles by Ultrasound Irradiation

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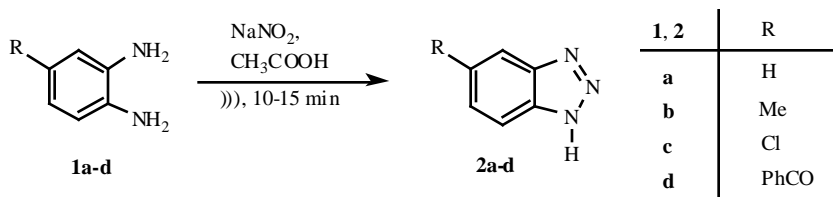
Abstract: Some 1*H*-benzotriazoles have been synthesised in good yields in short times by reaction of *o*-phenylenediamine with sodium nitrite in acetic acid under ultrasound irradiation. Also, the ultrasound-assisted preparation of 1-acylbenzotriazoles is described.

Keywords: Benzotriazoles, acylbenzotriazoles, ultrasound irradiation, sonochemistry, heterocycles.

INTRODUCTION

1*H*-Benzotriazoles are a significant class of compounds because of their wide use in organic synthesis and pharmaceutical chemistry [1]. The benzotriazoles there of are known to be important intermediates in the preparation of organic products: β-amido ketones, aldehydes [2], β-keto

microwaves and sonochemistry [9-15]. The beneficial effects of ultrasound irradiation are playing an increasing role in process chemistry, especially in cases where classical methods require drastic conditions or prolonged reactions times. When processes involve sensitive reagents, or there is the possibility of compound decomposition under prolonged



Entry	Reaction time (min.)	Product 2	Yield (%) ^a
1	10	a	91
2	12	b	65
3	12	c	60
4	15	d	90

^aYields of isolated products

Scheme 1.

esters [3], ionic liquid and as reagents for acylation and thioacylation reactions [4-6]. 1*H*-Benzotriazoles are also known to exhibit a broad spectrum of pharmacological activities [7]. *N*-Acylbenzotriazoles are powerful acylation agents, such as in the anionic polymerization of lactams to obtain polymers in the acetylation of proteins [8].

Recently, we described the synthesis of many organic molecules by non-traditional conditions, as aqueous media,

reactions conditions, ultrasound has also an advantage [12-14]. The use of ultrasound irradiation to decrease reaction times and improve yields has been demonstrated. As part of our programme to investigate organic reactions amenable to sonochemistry, we report to the ultrasound-assisted synthesis of 1*H*-benzotriazoles **2** and 1-acylbenzotriazoles **3**. The general procedure for synthesis of 1*H*-benzotriazoles is the reaction of the *o*-phenylenediamine with HNO₂ and prolonged reaction times [16]. In our procedure the benzotriazoles **2** were prepared by the reaction of the *o*-phenylenediamine with sodium nitrite in acetic acid under ultrasound irradiation (Scheme 1).

The reaction proceeded in a water bath of an ultrasonic cleaner at the frequency of 40 KHz and a nominal power 130

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Watts at 5° C within 10–15 min. The mixture was sonicated until the condensation had been completed. 1*H*-benzotriazoles **2a–d** were isolated in 60–91% yields.

In a recent paper was reported the preparation of *N*-acylbenzotriazoles by the reaction of benzotriazole with acid chloride and triethylamine under nitrogen atmosphere, in 30 minutes of reaction and posterior work-up with hydrochloridric acid [17]. Wang and Chen describe the synthesis of *N*-acylbenzotriazoles in basic media, via palladium catalyst in DMF and a reaction time of 10 h at 50 °C [18]. Our procedure is very simple and does not require a catalyst, base or long reaction times. For the acylation reaction of 1-*H*-benzotriazole **3** the influence of the reaction solvent was investigated: with acetone the acylated product was obtained in 92% yield (Entry **5–7**, Scheme **2**). Thus, careful analysis of the optimised reaction revealed that the optimum conditions for the acylation, the 1-*H*-benzotriazole (1 mmol), acyl chloride or anhydride (3 mmol) and acetone as solvent (8mL) to produce *N*-acylbenzotriazoles **3**. The reaction mixture was irradiated in a water bath of an ultrasonic cleaner at 10°C for 10 min (Scheme **2**). The *N*-acylbenzotriazoles were obtained with good results (see Scheme **2**, Table **1**).

Our methodology offers several advantages including mild reaction conditions, cleaner reaction, good yields of products as well as a simple experimental and isolated procedure which makes it a useful and attractive process for the synthesis of these compounds. The reaction flasks (Scheme **1–2**) were located in the maximum energy area in the cleaner bath. The progress of the reactions was monitored by CG/MS. The products were identified by ¹H and ¹³C NMR spectroscopy and confirmed by mass spectrometry (Table **1**). For the compounds **2**, **3aa**, **3ab**, **3ac** were verified the molecular ion (M⁺) and for the 1-acylbenzotriazoles **3ad** was verified the M+2 (217, see Table **1**). All products gave satisfactory elemental analysis: C, ± 0.30; H, ± 0.20.

In summary, we developed a new synthetic route to prepare benzotriazoles and *N*-acylbenzotriazoles using

ultrasound irradiation. The present method has many advantages to those reported in the literature, including avoiding the use of catalysts, the procedure is carried out in a shorter time, easier work-up and good yields. The method reported here is not only simple to operate but also efficient.

General procedures

Synthesis of 1*H*-benzotriazoles **2a–d**

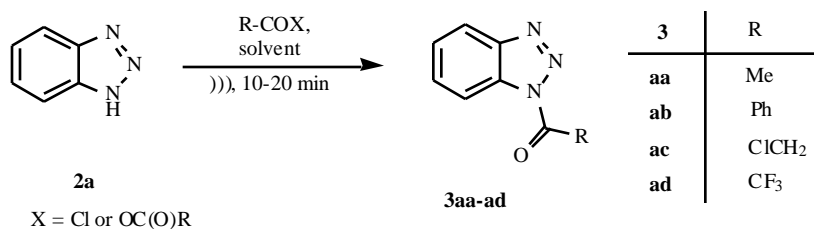
In a solution of *o*-fenylenodiamine **1** (2 mmol), in acetic acid (10 mL) was added at 5° C the sodium nitrite (0.30 g, 4.34 mmol) and irradiated in a water bath of the ultrasonic cleaner at 5–10 °C for the appropriate time (see Scheme **1**). After the indicated time, the solvent was removed, the organic phase extracted with methylene dichloride (20 mL), washed with water (3 X 10 mL) and dried with MgSO₄. The solvent was removed under reduced pressure and the products were isolated with satisfactory purity.

Synthesis of 1-acylbenzotriazoles **3aa–ad**

A mixture of benzotriazole (0.119 g, 1 mmol), acyl chloride or anhydride (3 mmol), in acetone (8 mL) was irradiated in a water bath of the ultrasonic cleaner at 10 °C for 10 minutes. After the indicated time (see Scheme **2**), the solvent was removed, the organic phase extracted with ethyl acetate (10 mL), washed with water (3 x 10mL) and dried with MgSO₄. The solvent was removed under reduced pressure to afford 1-acylbenzotriazoles **3**.

Material and Instruments

¹H and ¹³C spectra were acquired on a Bruker DPX 300 instrument (300.13 MHz for ¹H, 75.48 MHz for ¹³C), at 300 K. Low resolution mass spectra were obtained on a Shimadzu QP5050 spectrometer operating at 70 eV. IR spectra were recorded on a Varian 3100 FT-IR spectrometer. Standard flash chromatography procedures were followed using 230–400 mesh silica gel 60Å.

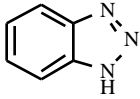
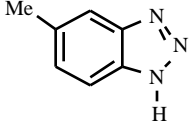
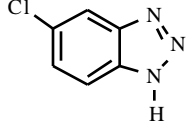
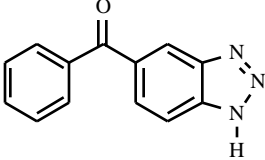
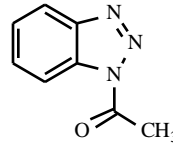
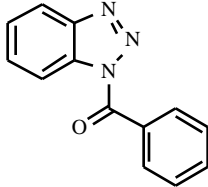
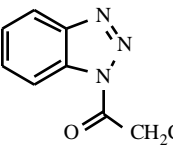
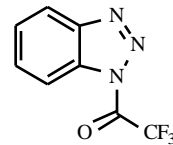


Entry	X	Solvent	Reaction time (min.)	Product 3	Yield (%) ^a
5	OC(O)CF ₃	acetone	10	ad	92
6	OC(O)CF ₃	dichloromethane	10	ad	55
7	OC(O)CF ₃	dichloromethane	20	ad	65
8	Cl	acetone	10	aa	85
9	Cl	acetone	10	ab	70
10	Cl	acetone	10	ac	94

^aYields of isolated products

Scheme 2.

Table 1. Data Spectra of 1H-benzo[d][1,2,3]triazoles^a

 <p>1H-benzo[d][1,2,3]triazole</p>	<p>2a: C₆H₅N₃; white powder, yield 91%. Mwt. 119.0; mp = 95-96 °C; IR (KBr) 1727, 1376, 1194, 753 cm⁻¹; ¹H NMR (Acetone-<i>d</i>₆, 300 MHz) 8.05 (d, <i>J</i> = 5 Hz, 2H, Ph), 7.49 (d, <i>J</i> = 5, 2H, Ph); ¹³C NMR (Acetone-<i>d</i>₆, 75 MHz) 112.0, 126.9, 139.2 (Ph, 6C); MS (m/z, %) 119 (M⁺, 100).</p>
 <p>5-methyl-1H-benzo[d][1,2,3] triazole</p>	<p>2b: C₇H₇N₃; brown powder, yield 65 %. M wt. 133.1; mp = 136-138 °C; IR (KBr) 2347, 1734, 1378, 1225, 1062 cm⁻¹; ¹H NMR (DMSO-<i>d</i>₆, 300 MHz) 3.07 (s, CH₃, 3H), 7.74-8.26 (m, 3H, Ar), 16.0 (NH); ¹³C NMR (DMSO-<i>d</i>₆, 75 MHz) 16.2 (Me), 116.6, 124.8, 125.8, 138.6 (Ar, 6C); MS (m/z, %) 133 (M⁺, 80)..</p>
 <p>5-chloro-1H-benzo[d][1,2,3]triazole</p>	<p>2c: C₆H₄ClN₃; brown powder, yield 60 %. M wt. 153.0; mp = 153-154 °C; IR (KBr) 2347, 1397, 1339, 1062, 885 cm⁻¹; ¹H NMR (DMSO-<i>d</i>₆, 300 MHz) 7.41 – 8.02 (m, 3H, Ar); ¹³C NMR (DMSO-<i>d</i>₆, 75 MHz) 114.7, 117.2, 126.3, 130.6, 138.4, 139.6 (Ar, 6C); MS (m/z, %) 153 (M⁺, 100).</p>
 <p>(1H-benzo[d][1,2,3] triazol-5-yl) (phenyl)methanone</p>	<p>2d: C₁₃H₉N₃O; orange powder, yield 90 %. M wt. 223.1; mp = 132-133 °C; IR (KBr) 2347, 1663, 1397, 1055, 1062 cm⁻¹; ¹H NMR (Acetone-<i>d</i>₆, 300 MHz) 7.51 – 8.53 (m, 8H, Ar); ¹³C NMR (Acetone-<i>d</i>₆, 75 MHz) 120.8, 128.5, 129.8, 134.5, 134.7 (12C, Ar), 195.3 (C=O); MS (m/z, %) 224 (M+1, 100).</p>
 <p>1-(1H-benzo[d][1,2,3] triazol-1-yl)ethanone</p>	<p>3aa: C₈H₇N₃O; white powder, yield 85 %. M wt. 161.1; mp = 53-57 °C; IR (KBr) 1744, 1389, 1248, 1061, 764 cm⁻¹; ¹H NMR (Acetone-<i>d</i>₆, 300 MHz) 2.91 (s, 3H, CH₃), 7.40 – 8.22 (m, 4H, Ph); ¹³C NMR (Acetone-<i>d</i>₆, 75 MHz) 23.3 (CH₃), 114.6, 119.5, 125.9, 129.9, 139.0, 146.1 (6C, Ph), 169.5 (C=O); MS (m/z, %) 161 (M⁺, 40).</p>
 <p>(1H-benzo[d][1,2,3]triazol-1-yl)(phenyl)methanone</p>	<p>3ab: C₁₃H₉N₃O; white powder, yield 70 %. M wt. 223.1; mp = 112-113 °C; IR (KBr) 2347, 1733, 1060, 878 cm⁻¹; ¹H NMR (DMSO-<i>d</i>₆, 300 MHz) 7.42 – 8.31 (m, 9H, 2 Ph); ¹³C NMR (Acetone-<i>d</i>₆, 75 MHz) 146.1, 131.0, 130.2, 126.1, 120.0, 114.2 (12C, 2Ph), 169.6 (C=O); MS (m/z, %) 223 (M⁺, 10).</p>
 <p>1-(1H-benzo[d][1,2,3]Triazol-1-yl)-2-chloro ethanone</p>	<p>3ac: C₈H₆ClN₃O; white powder, yield 94 %. M wt. 195.0; mp = 98-101 °C; IR (KBr) 1744, 1387, 1234, 764 cm⁻¹; ¹H NMR (Acetone-<i>d</i>₆, 300 MHz) 7.40 – 8.30 (m, 4H, Ph); ¹³C NMR (Acetone-<i>d</i>₆, 75 MHz) 43.0 (CH₂), 113.4, 120.2, 126.6, 131.2 (6C, Ph), 165.4 (C=O); MS (m/z, %) 195 (M⁺, 30).</p>
 <p>1-(1H-benzo[d][1,2,3]Triazol-1-yl)-2,2,2-tri fluoroethanone</p>	<p>3ad: C₈H₄F₃N₃O; white powder, yield 90 %. M wt. 215.0 mp = 90-91 °C; IR (KBr) 1785, 1686, 1170, 1061 cm⁻¹; ¹H NMR (Acetone-<i>d</i>₆, 300 MHz) 7.33 (d, <i>J</i> = 6 Hz, 2H, Ph), 7.74 (d, <i>J</i> = 6 Hz, 2H, Ph); ¹³C NMR (DMSO-<i>d</i>₆, 75 MHz) 115.0 (q, <i>J</i> = 360 Hz, CF₃), 157.0 (q, <i>J</i> = 84 Hz, C=O) 108.8, 125.9, 138.4 (Ph, 6C); MS (m/z, %) 217 (M+2, 100).</p>

^aYields of isolated products.

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REFERENCES

- [1] Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles*, Wiley-VCH GmbH & Co. KGaA, Weinheim, **2003**.
- [2] Katritzky, A. R.; Fang, Y.; Silina, A. *J. Org. Chem.*, **1999**, *64*, 7622.
- [3] Katritzky, A. R.; Wang, Z.; Wang, M.; Wilkerson, C. R.; Hall, C. D.; Akhmedov, N. G. *J. Org. Chem.*, **2004**, *69*, 6617.
- [4] Zhang, S.; Hou, Y.; Huang, W.; Shan, Y. *Electrochim. Acta*, **2005**, *50*, 4097.
- [5] Katritzky, A. R.; Yang, B.; Semenzin, D. *J. Org. Chem.*, **1997**, *62*, 726.
- [6] Katritzky, A. R.; Witek, R. M.; Rodriguez-Garcia, V.; Mohapatra, P. P.; Rogers, J. W.; Cusido, J.; Abdel-Fattah, A. A. A.; Steel, P. J. *J. Org. Chem.*, **2005**, *70*, 7867.
- [7] (a) Al-Soud, Y. A.; Al-Masoudi, N. A.; Ferwanah, A. S. *Bioorg. Med. Chem.*, **2003**, *11*, 1701; (b) Katarzyna, K.; Najda, A.; Justyna, Z.; Chomicz, L.; Piekarczyk, J.; Myjak, P.; Bretner, M. *Bioorg. Med. Chem.*, **2004**, *12*, 2617; (c) Swamy, S. N.; Sarala, B. G.; Priya, B. S.; Gaonkar, S. L.; Prasad, J. S.; Rangappa, K. S. *Bioorg. Med. Chem.*, **2006**, *16*, 999.
- [8] (a) Reimschuessel, H. K.; Boardman, F. *US Pat.* 3, 350, 364 **1967**. *Chem. Abstr.*, **1968**, *68*, 357m; (b) Reboud-Ravaux, M.; Ghelis, C. *Eur. J. Biochem.*, **1976**, *65*, 25.
- [9] Stefani, H. A.; Pereira, C. M. P.; Dörr, F. A.; Cella, R. *ARKIVOC*, **2005**, *vi*, 19.
- [10] Stefani, H. A.; Gatti, P. M. *Synth. Commun.*, **2000**, *30*, 2165.
- [11] Stefani, H. A.; Cella, R.; Dörr, F. A.; Pereira, C. M. P.; Gomes, F.; Zeni, G. *Tetrahedron Lett.*, **2005**, *46*, 2001.
- [12] Stefani, H. A.; Pereira, C. M. P.; Almeida, R. B.; Braga, R. C.; Guzen, K. P.; Cella, R. *Tetrahedron Lett.*, **2005**, *46*, 6833.
- [13] Martins, M. A. P.; Pereira, C. M. P.; Cunico, W.; Moura, S.; Rosa, F.; Peres, R. L.; Machado, P.; Zanatta, N.; Boanacorso, H. G. *Ultrason. Sonochem.*, **2006**, *13*, 364.
- [14] (a) Stefani, H. A.; Oliveira, C. B.; Almeida, R. B.; Pereira, C. M. P.; Braga, R. C.; Cella, R.; Borges, V. C.; Savegnago, L.; Nogueira, C. W. *Eur. J. Med. Chem.*, **2006**, *41*, 513; (b) Guzen, K. P.; Cella, R.; Stefani, H. A. *Tetrahedron Lett.*, **2006**, *47*, 8133.
- [15] Martins, M. A. P.; Pereira, C. M. P.; Beck, P.; Machado, P.; Moura, S.; Teixeira, M. V. M.; Bonacorso, H. G.; Zanatta, N. *Tetrahedron Lett.*, **2003**, *44*, 6669.
- [16] Kreutzberger, A.; Stratmann, J. *Arch. Pharm.*, **1979**, *312*, 806.
- [17] Katritzky, A. R.; Pastor, A.; Voronkov, M. V. *J. Heterocycl. Chem.*, **1999**, *36*, 777.
- [18] Wang, L.; Chen, Z.-C. *Synth. Commun.*, **2001**, *31*, 1633.