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Revisiting benzyne chemistry: Synthesis of 4(7)-hydroxy benzotriazoles and 2-methylsulfanyl-benzene-1,3-diol

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ABSTRACT

Benzotriazoles are prepared by the formation of benzyne under dimsyl anion conditions. 2-methyl sulfinyl benzene 1, 3-diol derivatives were prepared and characterized by the solvent participated benzyne reactions.

Keywords: Benzyne, 1, 3- dipolar cycloaddition**,** Triazoles, Solvent participation

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INTRODUCTION

1, 2, 3-Benzotriazoles are interesting molecules. There are four primary uses of benzotriazoles, i) corrosion inhibitors ii) ultraviolet light stabilizer for plastics iii) antifogging agent in photography and iv) as forming a part of interestingly biologically active molecules. The triazoles may display a wide range of biological activity such as anti HIV, anti-microbial agents and selective β_3 adrenergic receptor agonist and anti allergic agents.[1-5] Additionally 1, 2, 3-triazoles are found in herbicides, fungicides and dyes.[6, 7]

Huisgen's 1, 3-dipolor cycloaddition of alkynes and azides yielding triazoles is undoubtedly the premier example of click chemistry reactions. The other synthetic methods are multi step processes. Punniyamurthy[8] et al reported a new route to 1-Aryl-1H-benzotriazole by Pd-catalyzed C-H activation/C-N bond formation method. Faraji[9] et al reported microwave assisted 1, 3-dipolar cycloaddition of azide to a benzyne derivative for the preparation of 1H-phenanthro [9, 10-d] [1, 2, 3] triazole.

MATERIALS AND METHODS

General: Most of the reagents used in this work were obtained from commercial suppliers and were of LR/AR grade. Solvents were purified before use by standard procedures. Melting points were determined using open capillary tubes on POLMON melting points apparatus (Model-96) and are uncorrected. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded by using a Bruker 400 Spectrometer with TMS as internal standard. IR spectra were recorded on a Perkin-Elmer Spectrum 100 FTIR Spectrophotometer as KBr pellets or with the neat products. Mass spectra were recorded on an API 2000 LCMS/MS Applied BioSystems MDS Sciex spectrometer. Analytical TLC was conducted on E-Merck 60F254 aluminum-packed plates of silica gel (0.2 mm). Developed plates were visualized by using UV light or in an iodine chamber. HPLC was performed by using a Shimadzu 2010 instrument.

General procedure for preparation of 4(7)-Benzyloxy-1H-benzotriazole 2 and 3-Benzyloxy-2-methylsulfanyl-phenol 3.
To a stirred solution of NaH (2.20 gm, 0.091 moles) and DMSO (50 ml), 1-Benzyloxy-3-chloro-benzene (5.0 gm, 0.02 moles) and Sodium azide (NaN_3) (7.45 gm, 0.114 moles) were added at ambient temperature for 10 minutes. The reaction mixture was heated to 45-50 °C and stirred for 1h. At the end of the reaction [monitored by TLC] the reaction mass was cooled to room temperature and the solvent was evaporated under reduced pressure. A solution of HCl (125 ml of water and 75 ml of 32% HCl) was added to the residue. An off white solid was obtained. The product was purified by column chromatography to get pure 4(7)-Benzyloxy-1H-benzotriazole **2** as a white solid. Yield 2.6 gm (50%) and 3-Benzyloxy-2-methylsulfanyl-phenol **3** as a white solid. Yield 1.25 gm (22%).

4(7)-Benzyloxy-1H-benzotriazole (2) : Off white color solid; M.p.: 166.8- 170.0 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.36 (s, 2H, CH_2), 6.94 (d, *J* =4.0 Hz, 1H, ArH), 7.43-7.32 (m, 5H, ArH), 7.54(d, *J* = 7.2 Hz, 2H, ArH) 11.60 (br, s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 70.38, 106.04, 106.56, 127.10, 128.26, 128.28, 128.39, 128.80, 128.82, 136.93 ppm; IR (KBr): 3038, 2881, 1618, 1524, 1403, 1386, 1309, 1231, 1112, 974 cm^{-1}. Anal. Calcd for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.66 Found: C, 69.11; H, 4.71; N, 18.38. MS: m/z = 226.3 (M^+)

3-Benzyloxy-2-methylsulfanyl-phenol (3) : White color solid; M.p.: 81.9-84.1° C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.29 (s, 3H, CH_3), 5.17 (s, 2H, CH_2), 6.50-6.52 (d, 1H, *J* = 8.24 Hz, ArH), 6.66-6.68 (d, 1H, *J* = 8.20 Hz, ArH), 7.06(s, 1H, OH), 7.16-7.20 (t, 1H, *J* = 8.21 Hz, ArH), 7.32-7.42 (m, 3H, ArH), 7.47-7.49 (d, 2H, *J* = 7.32 Hz, ArH) ppm. ^{13}C-NMR(100 MHz, $CDCl_3$): δ = 17.88, 70.42, 104.09, 107.55, 108.98, 126.95, 127.85, 128.56, 130.59, 136.84, 157.69, 159.81ppm. IR (KBr): 3337, 2921, 1591, 1569, 1450, 1218, 1060, 780 cm^{-1}. Anal. Calcd for $C_{14}H_{14}O_2S$: C, 68.26; H, 5.73. Found: C, 68.12; H, 5.48. MS: (m/z) = 246 (M^+).

General procedure for the synthesis of 4(7) Hydroxy benzotriazole (1):
2.0 gm of 4(7)-Benzyloxy-1H-benzotriazole **2,** 0.5 gm of 10% Pd/C and 100 ml ethanol are heated to 60-65°C in a steel auto clave with 3 Kg hydrogen pressure for 2-3 h. At the end of the reaction [monitoring by TLC] the reaction mass was cooled to room temperature. The reaction mass was filtered on hyflow bed and washed with ethanol. The solution was evaporated under reduced pressure. The crude product was purified by column chromatography to get pure 4(7)-hydroxy benzotriazole. Off white solid; M.p.: 220.8-222.1°C (lit 224°C); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.66 (s, 1H), 7.20 (s, 2H), 10.61 (s, br, 1H), 15.41 (s, br, 1H) ppm. IR (KBr): 3176, 3116, 1600, 1319, 1235, 1094, 865 cm^{-1}. MS: m/z = 154.9 (M^+)

General procedure for the synthesis of 3-Benzyloxy-2-methylsulfanyl-phenol (3):
A solution of 16.5 gm (0.411 moles) sodium hydride (60%) and 100 ml of DMSO were taken in a 1.0 lt 4necked round-bottomed flask fitted with a reflux condenser and N_2 atmosphere. The reaction mixture was heated to 50-60°C and stirred for 1 hr and cooled to 25-30°C. 1-Benzyloxy-3-chloro-benzene 30.0 gm (0.137 moles) was dissolved in 50 ml of DMSO and added to the reaction mass at 25-30°C. The reaction mixture was heated to 50-60°C and stirred for 3-4 hr. After completion of TLC, the reaction mixture was cooled to 25-30°C. The reaction mass quenched into ice water and extracted with ethyl acetate (300 ml X 3). The collected organic extracts were washed with water (200 ml X 2). The solvent was dried over Na_2SO_4 and evaporated under reduced pressure to get residue. The residue was purified on column chromatography to get pure 3-Benzyloxy-2-methylsulfanyl-phenol **3** as a white solid. Yield 13 gm (58%). M.p.: 81.9-84.1° C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.29 (s, 3H, CH_3), 5.17 (s, 2H, CH_2), 6.50-6.52 (d, 1H, *J* = 8.24 Hz, ArH), 6.66-6.68 (d, 1H, *J* = 8.20 Hz, ArH), 7.06(s, 1H, OH), 7.16-7.20 (t, 1H, *J* = 8.21 Hz, ArH), 7.32-7.42 (m, 3H, ArH), 7.47-7.49 (d, 2H, *J* = 7.32 Hz, ArH) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 17.88, 70.42, 104.09, 107.55, 108.98, 126.95, 127.85, 128.56, 130.59, 136.84, 157.69, 159.81 ppm. IR (KBr): 3337, 2921, 1591, 1569, 1450, 1218, 1060, 780 cm^{-1}. Anal. Calcd for $C_{14}H_{14}O_2S$: C, 68.26; H, 5.73. Found: C, 68.12; H, 5.48. MS: (m/z) = 246 (M^-).

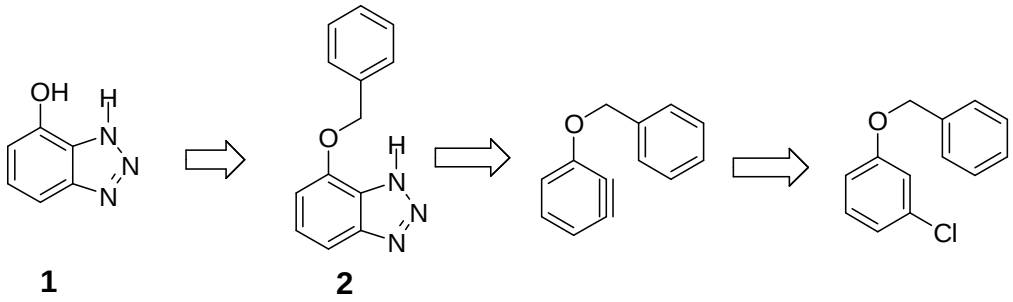
General procedure for the synthesis of 2-Methylsulfanyl-benzene-1,3-diol (4):
3-Benzyloxy-2-methylsulfanyl-phenol 3 (10 g, 0.040 mol) was dissolved in Conc. HCl (100 mL) at room temperature and stirred for 5 min. Reaction mass temperature was heated to 60°C and maintained for 24 h. After completion of the reaction (monitor by TLC) the reaction mass was cooled to room temperature. Charged ethyl acetate (200 mL X 2) and separated the organic layers, combined organic layers were washed with water (100 mL), dried over anhydrous sodium sulfate. Evaporated solvent completely to get crude. The crude was purified though silica gel (100-200 mesh) column chromatography to afford pure 2-Methylsulfanyl-benzene-1,3-diol **4** as a white

solid. Yield 5.0 gm (79 %). M.p.: 52.1-54.4°C ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.18 (s, 3H, S-CH_3), 6.33 (d, *J* = 8.24 Hz, 2H, ArH), 6.92 (t, *J* = 8.08 Hz, 1H, ArH), 9.27 (s, 2H, Ar-OH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 18.25, 106.44, 106.61, 131.65, 157.21 ppm; IR (KBr): 3395, 3365, 2927, 2459, 1609, 1578, 1472, 1346, 1319, 1174, 1148, 971, 781 cm^{-1}. Anal. Calcd for $C_7H_8O_2S$: C, 53.82; H, 5.16. Found: C, 53.58; H, 5.05. MS: m/z 154.9 (M^-)

RESULTS AND DISCUSSION

4(7) hydroxyl benzotriazole is identified as a critical intermediate for different biological disorders of phase-I drug candidates. It is prepared [10] by Lane et al starting from benzotriazole in a two step process with moderate yields.

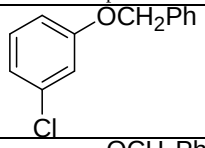
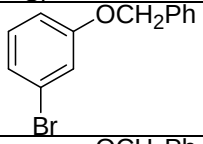
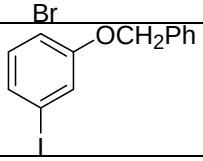
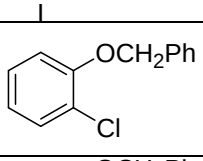
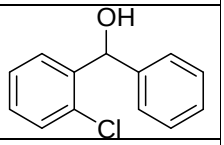
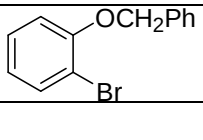
In our efforts to synthesize 4(7)-Hydroxy benzotriazole **1** in a better way; we realized that benzyne [11] chemistry may be an alternative methodology as described Scheme 1.

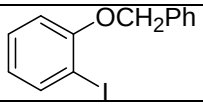
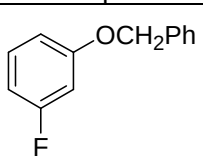
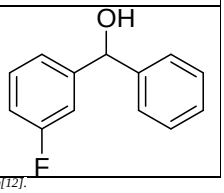


Scheme 1: Retro analysis of 4(7) Hydroxy benzotriazole

We studied benzyne chemistry with halo substituted phenyl benzyl ethers. We found that except fluoro all the halo phenyl benzyl ethers gave the expected product **2**.

Table 1: Preparation of benzotriazole 2 with different halo benzyl ethers under NaH/DMSO conditions

Entry	Compound	Temp/Time	Yield of **2**	Remarks*
01		60°C/1 h	58 %	--
02		60°C/1 h	47 %	--
03		60°C/1 h	51 %	--
04		60°C/1 h	40%	
05		60°C/1 h	50 %	--

06		60°C/1 h	49 %	--
07		60°C/1 h	--	

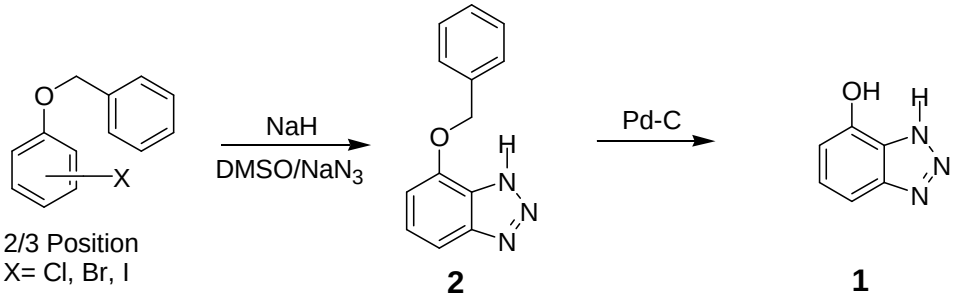
* *Wittig rearrangement product is obtained*[12].

We also found that benzyne reaction gave best results in DMSO/NaH basic conditions (compared to t-BuOK and NaOMe, Table 2).

Table 2: Preparation of benzotriazole 2 under different basic conditions

Entry	Base(eq)	Solvent	Temp/Time	Yields
01	NaH(4.0)	DMSO	60°C/1 h	50%
02	NaOMe(4.0)	DMSO	100°C/ 16 h	NR
03	t-BuOK	DMSO	100°C/ 16 h	NR
04	NaH(4.0)	DMA	100°C/ 16 h	NR
05	NaH(4.0)	THF	Reflux/ 16 h	NR
06	NaH(4.0)	NMP	100°C/ 16 h	NR
07	NaH(4.0)	DME	100°C/ 16 h	NR

NR: No Reaction, DMA: Dimethyl Acetamide, NMP: N-Methyl-2-pyrrolidone.



Scheme 2: Synthesis of 4(7) Hydroxy benzotriazole

When this reaction was studied in NaH with different solvents like THF, DMAC, Dimethoxy ethane (DME) the reaction did not give any triazole product (Table 2). compound **2** was hydrogenated to give 4(7) hydroxyl benzotriazole **1** .

During this 1, 3-cycloaddition reaction we also observed one new product in small percentage (~15%). The new compound has one –SMe (δ 2.5 ppm) functional group. We identified this compound as **3** and the structure was confirmed by single crystal X-ray (Fig 1). The mechanism for the formation of **3** is proposed as shown in Fig 2.

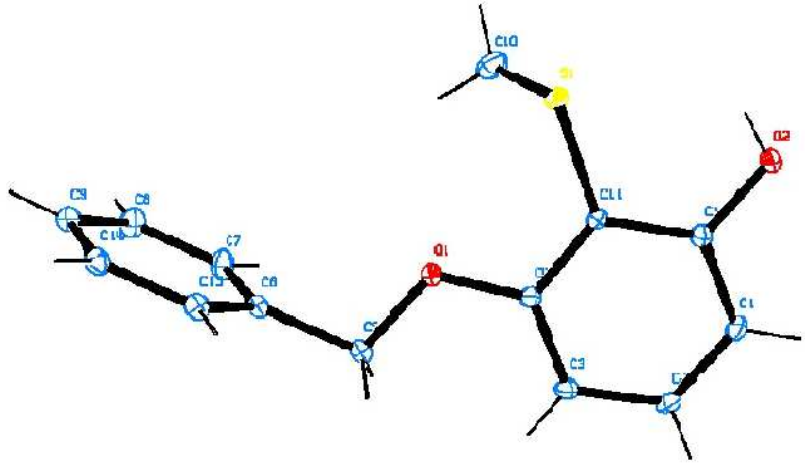


Fig 1: X-ray structure of compound 3

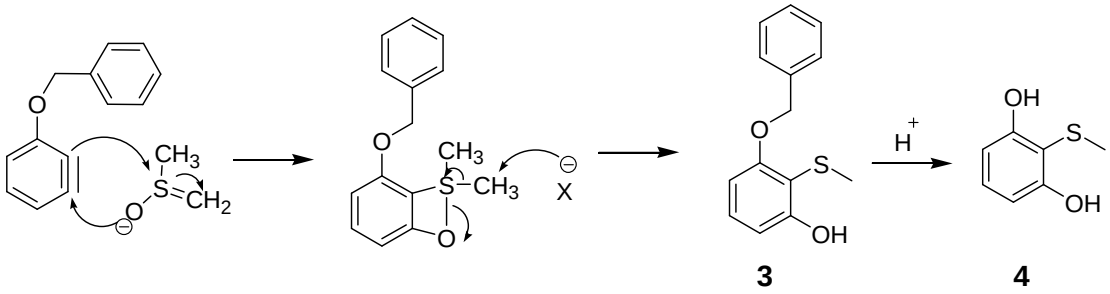


Fig 2: Proposed mechanism for the formation of 3

To confirm the mechanism, when we did the reaction without sodium azide, compound **3** was obtained as a major product (58%). This type of solvent formation was earlier observed by A. J. Birch et al on halo substituted anisole. This appears to be one of the best method to prepare 2, 6-disubstituted aryl thioethers. The debenzylation of **3** was best carried out with conc.HCl to give 2-methyl sulfinyl benzene 1, 3-diol **4 ,** in good yield.

CONCLUSION

In conclusion we have developed a simple method for 4(7) hydroxyl benzotriazoles and another simple method of making 2 , 6-disubstituted aryl thioethers and 2-thiomethyl resorcinol.

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REFERENCES

[1] L. Garanti.; G. Molteni. *Tetrahedron Lett.* **2003**, 44, 1133-1135.
[2] G. Molteni.; P. D. Buttero. *Tetrahedron.* **2005**, 61, 4983-4987.
[3] R. Alvarez.; S. Velazquez.; F. San.; S. Aquaro.; C. De.; C. Perno.; A. Karlsson.; J. Balzarini.; J. M. Camarasa. *J. Med. Chem.* **1994**, 37, 4185-4194.
[4] S. Velazquez.; R. Alvarez.; C. Perez.; F. Gago.; C. De.; J. Balzarini.; M. J. Camarasa. *Antivir Chem Chemoter*. **1998,** 9, 481-489.
[5] M. J. Genin.; D. A. Allwine.; D. J. Andersn.; M. R. Barbachyn.; K. C. Grega.; J. B. Hester.; D. K. Hutchinson.; J. Morris.; R. J. Reischer.; C. W. Ford.; G. E. Zurenko.; J. C. Hamel.; R. D. Schaadt.; D. Stapert.; B. H. Yagi. *J. Med. Chem.* **2000,** 43, 953-970.

[6] H. Wamhoff.; Comprehensive Heterocyclic Chemistry, A. R. Katritzky.; C. W. Rees. Eds. (1984) Pergamon press: New York . 1984, 5, 669.
[7] P. Appukkuttan.; W. Dehaen.; V. V. Fokin.; E. Van Der Eyken. *Org Lett.* **2004,** 6, 4223-4225
[8] R. K. Kumar.; Ali Amd.; T. Punniyamurthy. *Org Lett*. **2011,** 13, 2102-2105.
[9] A. A. Taherpour.; M. Faraji. *Molbank.* **2008**, M577
[10] E. S. Lane.; C. Williams. *J Chem Soc*. **1956**, 569
[11] A. J. Birch.; K. B. Chamberlain.; S. S. Oloyede. *Aus J Chem.* **1971**, 24, 2179-2180.
[12] A. Veerareddy.; A. Srinivasulureddy.; B. Sreenivasulareddy.; M. C. S. Subha. *Der Pharma chemica.* **2013**, 5, 227-231.