Synthesis of 3-alkyl-1,2,3-triazol-1-ium hydrogen sulphate derivatives

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Abstract
An array of 3-alkyl-1,2,3-triazol-1-ium hydrogen sulphate derivatives was obtained from the reaction between some 1,4-disubstituted-1,2,3-triazoles and H₂SO₄ through a simple protocol in good yields. The molecular structure of a triazolium salt (R¹=PhCH₂, R²=CH₂O(4-CHO)C₆H₄) was unambiguously determined from X-ray diffraction studies, showing a remarkable triazole N3–H bond.

Keywords
1,2,3-triazole, crystal structure, CuAAC reaction, protonation, triazolium salt

Introduction
1,2,3-Triazolium salts are a promising class of molecules due to their growing number of uses as ionic liquids as well as metal ligands for catalysis.¹⁻⁵ Nonetheless, the structural diversity presented by 1,2,3-triazolium salts is rather limited as a consequence of the few methods available for the preparation of these compounds which are based on methylation and arylation at the triazole N3 nitrogen,⁶ as well as cycloadditions between 1,3-diaza-2-azoniaallene salts and alkynes.⁷ This constraint is attributed to the low basicity/nucleophilicity of 1,2,3-triazole compared to other heterocycles.⁸,⁹ Moreover, there are only a few examples of N–H 1,2,3-triazolium salts reported in literature. Drake and coworkers reported the formation of unsubstituted 1,2,3-triazole nitrate and perchlorate.¹⁰ However, substituted 1,2,3-triazoles have not been studied.

Despite these serious drawbacks, the idea of the synthesis of 1,2,3-triazolium salts from 1,2,3-triazoles is still attractive due to their high availability provided by the copper-catalyzed azide-alkyne cycloaddition (CuAAC) reaction and click chemistry approaches.¹¹ Hence, we decided to investigate the formation of 1,2,3-triazolium salts from simple protonation reactions.

Thus, an array of 1,2,3-triazoles prepared by our group¹²,¹³ through CuAAC reactions was used in this study. Initial experiments with hydrohalic acids afforded no evidence about 1,2,3-triazolium salt formation. On the other hand, straightforward treatment of diverse 1,2,3-triazoles with H₂SO₄ gave the corresponding 1,2,3-triazolium hydrogen sulphate derivatives 1–8 in 72%–98% yields (Scheme 1, Table 1). Triazolium salts 1–8 are stable compounds at ambient temperatures up to 30 °C, not hygroscopic, insoluble in water but in most cases soluble in polar solvents as methanol, acetone and dimethyl sulfoxide among others. Although pKa/ acidity for N3–H was not determined, the value of this parameter could be close to other similar acidic azolium salts,¹⁴,¹⁵ representing a challenging task for future investigations.

1,2,3-Triazolium hydrogen sulphate derivatives 1–8 were characterized by conventional spectroscopic techniques and compound 3 was a crystalline solid which was studied by X-ray crystallography. Crystallographic data and structural refinement parameters of compound

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3 are summarized in Table 2. From single-crystal X-ray diffraction analysis, the crystal structure of 3 presents a noteworthy N–H bond with a distance between triazole N3 nitrogen and hydrogen atoms, N3–H = 0.869 Å and angles H3–N3–N2 (119.07°), H3–N3–C2 (127.79°) and N2–N3–C2 (112.98°). These features not only corroborate the triazolium salt formation and the proposed structure for this compound but also show a reactivity pattern and indicate selective protonation of the N3 position of the 1,2,3-triazole ring (Figure 1). Selected bond distances and angles are given in Table 3 and are shown in Figure 2.

The compounds shown herein represent the first substituted 1,2,3-triazolium salts as well as the earliest examples of 1,2,3-triazolium salts containing a hydrogen sulphate anion. These facts are important because they demonstrate that 1,2,3-triazoles derived from CuAAC reactions are susceptible of being converted into 3-substituted 1,2,3-triazolium salts by a mild and simple methodology. In addition, interesting applications are envisioned for these compounds. For instance, in medicinal chemistry, triazolium salts are worthy of investigation as anticancer agents and could play a relevant role in the delivery of antifungal compounds by enhancing the solubility and biological activity of some azolium salts compared to other azole antifungal drugs.

In brief, 3-alkyl-1,2,3-triazol-1-ium hydrogen sulphate derivatives are readily synthesized from 1,4-disubstituted-1,2,3-triazoles which in turn are prepared from CuAAC reactions through a facile synthetic protocol which allows a fast access to this class of compounds which will increase the research in this area. The simplicity of the method suggests that this route to 3-alkyl-1,2,3-triazol-1-ium hydrogen sulphate derivatives will enjoy widespread application.

### Experimental

#### General remarks

The starting materials were purchased from Aldrich Chemical Co. and were used without further purification. Solvents were distilled before use. Silica plates of 0.20-mm thickness were used for thin-layer chromatography. Melting points were determined with a Krüss Optronic melting point apparatus and they are uncorrected. 1H and 13C NMR spectra were recorded using a Bruker Avance 300 MHz, and a Varian 500 MHz; the chemical shifts (δ) are given in ppm relative to tetramethylsilane (TMS) as an internal standard (0.00). For analytical purposes, the mass spectra were recorded on a Shimadzu GCMS-QP2010 Plus in the EI mode, 70 eV, 200 °C via direct inlet probe. Only the molecular and parent ions (m/z) are reported. Infrared (IR) spectra were recorded on a Bruker TENSOR 27 FT instrument. 1,2,3-triazoles were prepared according to the literature.

For the X-ray diffraction studies, crystals of compound 3 were obtained by slow evaporation of a dilute MeOH solution, and the reflections were acquired with a Bruker AXS SMART APEX2 diffractometer using Mo Kα radiation.
APEX DUO diffractometer equipped with an Apex II charge-coupled device (CCD) detector. Three standard reflections every 97 reflections were used to monitor the crystal stability. The structures were solved by direct methods; missing atoms were found by difference Fourier synthesis, and refined on F2 by a full-matrix least-squares procedure using anisotropic displacement parameters using SHELX-97. Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre (CCDC; No. 2043876 for compound 3). Copies of available materials can be obtained free of charge on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (facsimile: (44) 01223 336033); e-mail: deposit@ccdc.

**Synthesis of 3-alkyl-1,2,3-triazol-1-ium hydrogen sulphate derivatives.** Typical procedure: 98% H2SO4 (0.03 mL) was added to a solution of the appropriate 1,2,3-triazole (0.10 g) in CH2Cl2 (2 mL) at room temperature. The resulting reaction mixture was gently stirred at room temperature for 1 min, and the precipitate was collected by filtration, washed successively with cold ether and CH2Cl2 and dried under reduced pressure to afford the corresponding 3-alkyl-1,2,3-triazol-1-ium hydrogen sulphate derivative which was purified by crystallization (MeOH).

**Table 3.** Selected bond distances (Å) and bond angles (°) for 3-benzyl-5-(4-formylphenoxymethyl)-1,2,3-triazol-1-ium hydrogen sulphate 3, C17H17N3O6S.

| Bond | Distance (Å) | Bond | Angle (°) |
|------|--------------|------|-----------|
| N(1)–N(2) | 1.3229(17)  | N(2)–N(1)–C(1) | 112.91(12) |
| N(1)–C(1) | 1.3510(18)  | N(3)–N(2)–N(1) | 103.68(11) |
| N(2)–N(3) | 1.3209(17)  | N(2)–N(3)–C(2) | 112.99(12) |
| N(3)–C(2) | 1.3539(18)  | N(2)–N(3)–H(3) | 119.1(13)  |
| N(3)–H(3) | 0.869(9)    | C(2)–N(3)–H(3) | 127.8(13)  |
| C(1)–C(2) | 1.369(2)    | N(1)–C(1)–C(2) | 105.34(12) |
| C(1)–H(1) | 0.9500      | N(1)–C(1)–H(1) | 127.3       |

**Figure 1.** ORTEP diagram and atom labelling system for compound 3.

**Figure 2.** Molecular structure of 3 showing N(3)–H(3) distance and angle N(2)–N(3)–H(3).

3-Benzyl-5-(4-chlorophenoxymethyl)-1,2,3-triazol-1-ium hydrogen sulphate (1). White solid, m.p. 69 °C (80%). IR (ATR, cm−1): 3160, 3000, 1590, 1450, 1443. 1H NMR (300 MHz, DMSO-d6): δ 7.33–7.34, (m, 2H), 7.29 (s, 1H), 7.28 (m, 4H), 7.04, (m, 2H), 5.60, (s, 2H), 5.11, (s, 2H). 13C NMR (75 MHz, DMSO-d6): δ 157.0, 142.8, 136.09, 129.4, 128.9, 128.3, 128.1, 125.0, 116.7, 61.5, 53.0. Anal. calcd. for C16H16ClN3O5S (%): C 48.30, H 4.05, N 10.56; found: C 48.35, H 4.13, N 10.50.

3-Benzyl-5-(p-tolyloxymethyl)-1,2,3-triazol-1-ium hydrogen sulphate (2). White solid, m.p. 78 °C (72%). IR (ATR, cm−1): 3440, 2880, 2160, 2030, 1680, 1153. 1H NMR (300 MHz, DMSO-d6): δ 8.22 (s, 1H), 7.28 (m, 5H), 7.00, (d, J = 8.2 Hz, 2H), 6.85 (d, J = 8.2 Hz, 2H), 5.54, (s, 2H), 5.01, (s, 2H), 2.15 (s, 3H). 13C NMR (75 MHz, DMSO-d6): δ 156.5, 143.8, 136.5, 130.6, 130.4, 129.5, 129.0, 128.7, 125.5, 115.3, 61.5, 53.6, 20.7. Anal. calcd. for C17H19N3O5S (%): C 54.10, H 5.07, N 11.13; found: C 54.17, H 5.03, N 11.17.

3-Benzyl-5-(4-formylphenoxymethyl)-1,2,3-triazol-1-ium hydrogen sulphate (3). White solid, m.p. 87 °C (98%). IR (ATR, cm−1): 3355, 3145, 2352, 1748, 1600, 1582, 1510, 1450, 1400, 1365, 130.6, 130.4, 129.5, 129.0, 128.7, 125.5, 115.3, 61.5, 53.6, 20.7. Anal. calcd. for C17H17N3O6S (%): C 52.17, H 4.38, N 10.74; found: C 52.14, H 4.33, N 10.79.

**Figure 3.** Molecule of 3 showing N(3)–H(3) distance and angle N(2)–N(3)–H(3).

3-Benzyl-5-(p-tolyloxy)methyl)-1,2,3-triazol-1-ium hydrogen sulphate (4). White solid, m.p. 55 °C (81%). IR (ATR, cm−1): 3355, 3145, 2352, 1748, 1600, 1582, 1510, 1450, 1400, 1300, 1250, 1200, 1150. 1H NMR (300 MHz, DMSO-d6): δ 9.87 (s, 1H), 8.34, (s, 1H), 7.87, (d, J = 8.9 Hz, 2H), 7.40, (s, 3H), 7.25 (m, 2H), 5.61, (s, 2H), 5.26 (s, 2H), 3.84 (s, 3H). 13C NMR (75 MHz, DMSO-d6): δ 191.5, 163.0, 136.0, 131.9, 129.9, 128.3, 128.1, 125.9, 115.3, 61.5, 53.0. Anal. calcd. for C17H17N3O6S (%): C 52.17, H 4.38, N 10.74; found: C 52.14, H 4.33, N 10.79.

**Figure 4.** Molecule of 3 showing N(3)–H(3) distance and angle N(2)–N(3)–H(3).
DMSO-$d_6$): $\delta$ 160.2, 148.6, 130.9, 130.2, 129.3, 128.7, 126.2, 122.8, 118.2, 115.3, 56.5. Anal. calcd. for $C_{14}H_{12}N_4O_6S$ (%): C 51.57, H 4.33, N 12.03; found: C 51.54, H 4.38, N 12.08.

5-(4-Nitrophenyl)-1,2,3-triazol-1-ium hydrogen sulphate (5). White solid, m.p. 78°C (65%). IR (ATR, cm$^{-1}$): 3400, 3156, 1600, 1523, 1480, 1357, 1232, 1197. 1H NMR (300 MHz, DMSO-$d_6$): $\delta$ 8.47, (d, J = 8.0 Hz, 2H), 8.3, (s, 1H), 7.94, (m, 2H), 7.67, (m, 2H), 7.41-7.57, (m, 3H). 13C NMR (75 MHz, DMSO-$d_6$): $\delta$ 148.3, 147.1, 141.3, 130.3, 129.5, 128.5, 126.1, 125.9, 120.8, 120.4. Anal. calcd. for $C_{14}H_{12}ClN_3O_4S$ (%): C 47.53, H 4.8, N 15.38; found: C 47.52, H 3.47, N 11.92.

5-(4-Chlorophenoxymethyl)-3-(tetrahydrofuran-2-ylmethyl)-1,2,3-triazol-1-ium hydrogen sulphate (6). White solid, m.p. 154°C (Dec.) (77%). IR (ATR, cm$^{-1}$): 3400, 3156, 3120, 1600, 1523, 1480, 1357, 1232, 1197. 1H NMR (300 MHz, DMSO-$d_6$): $\delta$ 8.08, (s, 1H), 7.37, (d, J = 8.9 Hz, 2H), 6.95, (d, J = 8.9 Hz, 2H), 5.04, (s, 2H), 4.41, (m, 2H), 4.31, (dd, J = 9.0, 4.5 Hz, 1H), 3.62, (m 2H), 2.50, (m, 1H), 1.92, (m, 1H), 1.74, (m, 2H), 1.52 (m, 1H). 13C NMR (75 MHz, DMSO-$d_6$): $\delta$ 151.1, 137.9, 133.2, 131.3, 128.9, 128.2, 126.1, 126.1, 124.8, 122.3. Anal. calcd. for $C_{15}H_{12}ClN_3O_7S$ (%): C 48.11, H 5.30, N 10.52; found: C 48.17, H 5.36, N 11.41.

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