Sodium Hydroxide: a Mild and Inexpensive Catalyst for the Regioselective Synthesis of 2-Substituted 5-Methylthiazolo[3,2-*b*]-*s*-triazoles†‡

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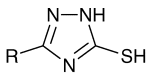
The facile and regioselective synthesis of 2-substituted 5-methylthiazolo[3,2-*b*]-*s*-triazoles has been performed by the catalytic action of NaOH on 3-propynylthio-*s*-triazoles.

Thiazolo[3,2-*b*]-*s*-triazoles **3** were first synthesized by Potts and Hussain[1] *via* the reaction of **1** with chloroacetone and subsequent dehydration of the corresponding ketone in the presence of $POCl_3$. In 1978, Srinvasan and co-workers[2] reported the synthesis of 5-arylprop-3-ynlthio-*s*-triazoles **2** in moderate yields, through the reaction of **1** with propynyl bromide, in the presence of sodium acetate. Further annulation of **2** to give thiazolo [3,2-*b*]-*s*-triazoles has been also reported under mercury(II) acetate catalysis in poor to moderate yields.[2]



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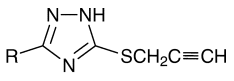

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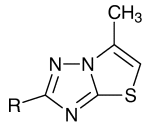

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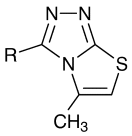

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In the above attempt to prepare **2**[2], through use of **1**, propynyl bromide and alkali, the moderate yields obtained perhaps is due to formation of 3-allenylthio substituted *s*-triazole derivatives *via* the intermediacy of an *s*-propynyl derivative **2**.

Here, we report a simple and efficient synthesis of 3-propynylthio-s-triazoles **2** and regioselective cyclization of the latter to give **3** in moderate to high yields.

When compound **1** (R = Me) was condensed with propynyl bromide in refluxing absolute ethanol in the absence of base, prop-3-ynylthio-s-triazole **2** (R = Me) was obtained, mp = 126 °C. In the ^{1}H NMR spectrum of this compound methylene protons appear as a doublet and the acetylenic proton as triplet showing a long range coupling (J = 2.4 Hz). To establish the generality of method, several 5-substituted 3-thio-*s*-triazoles **1** were employed and condensed with propynyl bromide to afford **2** in good to excellent yields (Table 1).

For cyclization of **2** (R = Ph) in moderate yield, Srinvasan and co-workers used mercury(II) acetate which is poisonous and expensive. However the use of 1 M sodium hydroxide solution for cyclization obviated these disadvantages and regioselective cyclization occurred to give the desired products in much better yield. Thus when **2** (R = Me) was refluxed in 1 M sodium hydroxide solution with subsequent neutralization a single (TLC) compound was obtained. Its ^{1}H NMR showed signals at δ 2.5 (d, J = 1.5 Hz 3 H, Me), 2.6 (s, 3 H, Me), 6.5 (q, J = 1.5 Hz, CH of thiazole).

Table 1 Synthesis of prop-3-ynylthio-*s*-triazoles (**2a–g**)

Product	R	Yield (%)	Mp[a]/°C	Recrystallisation solvent
2a	H	68	109	ethanol
2b	Me	59	126	ethanol
2c	Ph	72	127 (128)	benzene
2d	*o*-MeC_6H_4	71	144 (145)	benzene
2e	*p*-MeC_6H_4	68	92 (90)	benzene
2f	*o*-ClC_6H_4	75	85 (84)	benzene
2g	*p*-ClC_6H_4	67	144 (145)	benzene

[a]1st values, 2nd in parentheses.

Although fusion of thiazole and the triazole nuclei can occur in two different ways to give thiazolo[3,2-*b*]-*s*-triazole **3** and thiazolo[2,3-*c*]-s-triazole **4**, from analytical, spectral and melting point data as well as by comparison with an authentic sample, the product was identified as 2,5-dimethylthiazolo[3,2-*b*]-*s*-triazole **3** (R = Me). This indicates that sodium hydroxide has smoothly catalyzed regioselective cyclization and isomerization of the acetylenic moiety of the propynylthio group. The reaction proceeds *via* 5-exo-diagonal cyclization[3] followed by isomerization and aromatization[4–6] A mechanism is suggested in Scheme 1.

Various prop-3-ynylthio-*s*-triazoles **2** were employed in order to prepare condensed thiazoles and to establish the generality of method. We found that one-pot cyclization and aromatization of **2** to **3** can be carried out in high regioselectivity and excellent yields. Melting points are reported in Table 2.

In conclusion in comparison with the presently available synthetic methods[1,2] which show drawback's from the stand point of yields, price and limited availability of catalyst or low regioselectivity, the efficiency of the present method is apparent from the availability of inexpensive sodium hydroxide and the unique regioselectivity as well as high yield with lack of side products. Owing to the simplicity of the conditions and use of inexpensive catalyst this methodology should find utility in organic synthesis.

Experimental

Melting points (uncorrected) were obtained on a Koffler Hazbank Rischart type 4841 apparatus. The ^{1}H NMR spectra were obtained on a Varian 60A spectrometer and mass spectra were scanned on a Varian Mat CH-7 instrument at 70 eV.

Preparation of 5-*Substituted* 3-*Propynylthio-s-triazoles* (**2**) (*Typical Procedure*).—An appropriate 3-thioxo-*s*-triazole (5 mmol) was dissolved in ethanol (50 ml) to which was added propynyl bromide (5 mmol) dropwise. This mixture was refluxed for 3 h. After evaporation of solvent and pouring the residue into crushed ice, the solid that separated was filtered and crystallized from a suitable solvent (see Table 1).

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†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1998, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.
‡This paper is dedicated to Professor A. Shafiee on the occasion of his 60th birthday.

Table 2 Synthesis of 2-substituted 5-methylthiazolo[3,2-*b*]-*s*-triazoles (**3a–g**)

Product	R	Yield (%)	Mp/°C	Recrystallisation solvent
3a	H	95	66–70	ethanol
3b	Me	92	69–70 (lit.,[1] 68–69)	ethanol
3c	Ph	90	124–125 (lit.,[1] 123)	chloroform
3d	*o*-MeC_6H_4	85	84–85 (lit.,[2] 85)	chloroform
3e	*p*-MeC_6H_4	80	142 (lit.,[2] 141)	methanol
3f	*o*-ClC_6H_4	90	84–85 (lit.,[2] 82)	chloroform
3g	*p*-ClC_6H_4	80	117–118 (lit.,[2] 118)	chloroform

Selected Data for **2a**.—δ_H ([$^2H_6$]DMSO) 3.05 (t, $J = 2.4$ Hz, 1 H, ≡CH), 3.9 (d, $J = 2.4$ Hz, 2 H, CH_2), 8.45 (s, 1 H, CH of triazole). IR (KBr disc), ν 3240, 2850, 2500, 2110 cm^{-1}; m/z (%) 139(4), 138(6), 137(48), 110(76), 84(51), 38(80), 32(67), 28(100).

Selected Data for **2b**.—δ_H ([$^2H_6$]DMSO) 2.5 (t, $J = 2.4$ Hz, 1 H, ≡CH), 2.7 (s, 3 H, CH_3), 4.0 (d, $J = 2.4$ Hz, 2 H, CH_2). IR (KBr disc), ν 3230, 2500, 2850, 2100 cm^{-1}; m/z (%) 153 (4), 159(20), 150 (79), 149 (65), 110 (70), 84 (54), 28 (100).

Selected Data for **2c**.—δ_H ($CDCl_3$), 2.35 (t, $J = 2.4$ Hz, 1 H, ≡CH), 4.0 (d, $J = 2.4$ Hz, 2 H, CH_2), 7.45–7.70 (m, 5 H, Ph). IR (KBr disc), ν 3300, 2500, 2850 cm^{-1}; m/z (%) 215 (10), 213 (3), 212 (18), 211 (18), 102 (19), 32 (27), 28 (100).

Preparation of 2-*Substituted* 5-*Methylthiazolo*[3,2-b]-*s-triazoles* (**3**) (*Typical Procedure*).—An appropriate prop-3-ynylthio compound **2** (0.01 mol) was dissolved in 1 M NaOH (20 ml) and the mixture refluxed for 2 h. The reaction mixture was cooled to room temperature and neutralized by addition of HCl. The solid was filtered off and crystallized from suitable solvent (see Table 2).

Selected Data for **3a**.—δ_H ($CDCl_3$), 2.6 (d, $J = 1.5$ Hz, 3 H, CH_3), 6.7 (q, $J = 1.5$ Hz, 1 H, CH of thiazole ring), 8.25 (s, 1 H, CH of triazole ring). IR (KBr disc), ν 3050, 1480, 1400, 1180, 650 cm^{-1}; m/z (%) 139 (2), 138 (13), 136 (100), 110 (70), 66 (67), 32 (39), 27 (25), 28 (98), 16 (30).

Selected Data for **3b**.—δ_H ($CDCl_3$) 2.5 (d, $J = 1.5$ Hz, 3 H, CH_3), 2.6 (s, 3 H, CH_3), 6.55 (q, $J = 1.5$ Hz, 1 H, CH of thiazole ring). IR (KBr disc), ν 3070, 3020, 3000, 1580, 1500 cm^{-1}; m/z (%) 153 (5), 152 (10), 151 (100), 110 (32), 70 (23), 66 (56), 44 (23), 28 (23).

Selected Data for **3c**.—δ_H($CDCl_3$) 2.55 (d, $J = 1.5$ Hz, 3 H, CH_3), 6.55 (q, $J = 1.5$ Hz, 1 H, CH of thiazole ring), 7.3–7.6 (m, 3 H of Ph), 8.83 (m, 2 H of Ph). IR (KBr disc), ν 3100, 1475, 1450, 1320, 1280, 710 cm^{-1}; m/z (%) 215 (4), 212 (100), 142 (35), 101 (46), 70 (95), 32 (54).

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