

Synthesis of Sulphur Containing Fused Ring Heterocycles by Intramolecular 1,3-Dipolar-Cycloadditions

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Sulfur containing fused triazoles and pyrazoles are synthesized through intramolecular cycloadditions of properly functionalized azides and nitrileimines, respectively.

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In connection with our studies on intramolecular 1,3-dipolar cycloadditions (1-4), we were interested in utilizing this type of reaction for the synthesis of sulphur containing fused ring heterocycles. The present paper describes the preparation of compounds **3**, **6**, **9**, and **12** through the reaction sequences illustrated in Schemes I and II, which involve intramolecular cycloadditions of properly functionalized 1,3-dipoles. Compounds **3** and **6** are the first representatives of hitherto unreported ring systems.

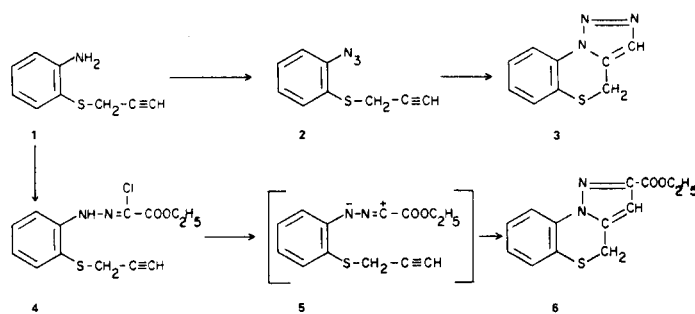
Diazotization of anilines **1** and **7** and treatment of the corresponding diazonium salts with sodium azide afforded azido compounds **2** and **8**, respectively. While the latter

was obtained as analytically pure crystals, the former slowly decomposes at room temperature and thus was only available in *ca.* 90% purity (by nmr spectrum).

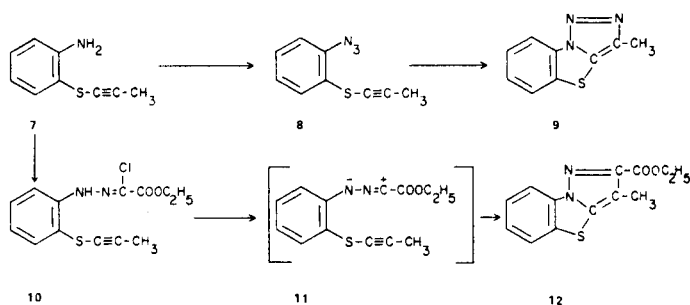
Azides **2** and **8** were refluxed in benzene at 0.05 *M* concentration, with the reaction progress monitored by tlc. Although very different times were required to consume all the starting substrate (0.5 and 24 hours respectively), in both cases the reaction gave a practically pure product. Elemental analyses and ir and nmr spectra are consistent with structures **3** and **9**.

Diazotization of the same anilines **1** and **7** and subsequent coupling with ethyl α -chloroacetate afforded

Scheme I



Scheme II



1-chlorohydrazone **4** and **10**. The nitrile imines **5** and **11**, generated on treatment of **4** and **10** with a large excess of triethylamine in refluxing benzene (72 and 96 hours, respectively), gave a mixture of products, which was chromatographed on silica gel column to isolate pyrazoles **6** and **12** in 42 and 12% yield. A small amount of unchanged hydrazone **10** was recovered.

The above results show that the intramolecular cycloaddition is the only reaction pathway for azides **2** and **8**, while it occurs to a minor extent in the case of nitrile imines **5** and **11**. The prolonged boiling in basic medium, necessary for the disappearance of the starting 1-chlorohydrazone, causes the formation of sizable amounts of intractable tar.

The lower yield of formation of **12** in comparison with **6** may reasonably be attributed to the more strain in the transition state leading to **12**. Analogous explanation can account for the lower reactivity of azide **8** with respect to **2**. A similar gap of reactivity has been reported for the intramolecular cycloadditions of 5-azido-1-pentene and 6-azido-1-hexene (**5**).

EXPERIMENTAL

Melting points were taken on a Büchi apparatus and are uncorrected. Ir spectra were recorded on a Perkin-Elmer Model 377 spectrophotometer. Nmr spectra were obtained on a Varian A-60A instrument in deuterochloroform solutions, with tetramethylsilane as an internal standard.

In all preparations, sodium sulphate was used as the drying agent.

2-(3-Propynylthio)aniline (**1**).

A mixture of sodium 2-aminothiophenoxide (9.1 g.) and 3-bromopropyne (7.4 g.) in dry benzene (150 ml.) was refluxed under stirring for 5 hours. Ether and water were then added. The organic solution was dried and evaporated under reduced pressure to give amine **1** (5 g., 50%), b.p. 120-125°/0.6 mm; ir (film): 3330-3500 cm^{-1} ; nmr: δ 2.18 (1H, t, $J = 2.5$ Hz), 3.42 (2H, d, $J = 2.5$ Hz), 4.35 (2H, broad s), 6.5-7.6 (4H, m).

Anal. Calcd. for $\text{C}_9\text{H}_9\text{NS}$: C, 66.24; H, 5.56; N, 8.58. Found: C, 66.04; H, 5.62; N, 8.90.

2-(1-Propynylthio)aniline (**7**).

A mixture of amine **1** (6.0 g.) and powdered potassium hydroxide (14 g.) in dry tetrahydrofuran (130 ml.) was stirred at 40° during 1 hour. The solvent was partly removed under reduced pressure and the residue was taken up by ether and water. The organic solution was dried and evaporated, and the residue was chromatographed on silica gel column (420 g.). Elution with ether/petroleum ether 1/1 gave amine **7** (3.1 g., 51.6%), b.p. 135-139°/0.7 mm; ir (film): 3320-3450 cm^{-1} ; nmr: δ 1.92 (3H, s), 4.15 (2H, broad s), 6.5-7.5 (4H, m).

Anal. Calcd. for $\text{C}_9\text{H}_9\text{NS}$: C, 66.24; H, 5.56; N, 8.58. Found: C, 65.95; H, 5.45; N, 8.40.

2-(3-Propynylthio)phenylazide (**2**).

A solution of sodium nitrite (0.80 g.) in water (5 ml.) was added dropwise to a solution of amine **1** (1.63 g.) in 2*N* hydrochloric acid (25 ml.) under vigorous stirring and ice cooling. The

mixture was neutralized by sodium hydrogen carbonate, then sodium azide (0.65 g.) in water (10 ml.) was slowly added at 0-3°. After 30 minutes, the mixture was extracted with ether and the organic solution was dried and evaporated *in vacuo* to give crude azide **2** (1.2 g., 60.8%), m.p. 32-35°; ir (nujol): 2130 cm^{-1} ; nmr: δ 2.18 (1H, t, $J = 2.5$ Hz), 3.63 (2H, d, $J = 2.5$ Hz), 6.9-7.6 (4H, m).

2-(1-Propynylthio)phenylazide (**8**).

Amine **7** (1.63 g.) was diazotized and treated with sodium azide as described in the above preparation. The resulting precipitate was collected by filtration to afford practically pure azide **8**, (1.05 g., 58.9%), m.p. 45° after recrystallization from chloroform/diisopropyl ether; ir (nujol): 2130 cm^{-1} ; nmr: δ 2.09 (3H, s), 7.0-7.3 (3H, m), 7.5-7.7 (1H, m).

Anal. Calcd. for $\text{C}_9\text{H}_7\text{N}_3\text{S}$: C, 57.14; H, 3.73; N, 22.21. Found: C, 57.44; H, 4.00; N, 22.45.

4*H*-[1,2,3]Triazolo[5,1-*c*][1,4]benzothiazine (**3**).

A solution of **2** (0.908 g.) in benzene (100 ml.) was refluxed for 30 minutes. After removal of the solvent under reduced pressure, a small amount of diisopropyl ether was added. Filtration gave compound **3** (0.81 g., 89.2%), m.p. 63° after recrystallization from ether/*n*-pentane; nmr: δ 4.10 (2H, s), 7.58 (1H, s), 7.2-7.6 (3H, m), 8.1-8.3 (1H, m).

Anal. Calcd. for $\text{C}_9\text{H}_7\text{N}_3\text{S}$: C, 57.14; H, 3.73; N, 22.21. Found: C, 57.01; H, 3.66; N, 22.11.

3-Methyl[1,2,3]triazolo[5,1-*b*]benzothiazole (**9**).

A solution of azide **8** (1.0 g.) in benzene (110 ml.) was refluxed for 24 hours. The solvent was removed and the residue was recrystallized from ether/*n*-pentane to afford compound **9** (0.89 g., 89%), m.p. 115°; nmr: δ 2.50 (3H, s), 7.3-7.8 (3H, m), 8.0-8.2 (1H, m).

Anal. Calcd. for $\text{C}_9\text{H}_7\text{N}_3\text{S}$: C, 57.14; H, 3.73; N, 22.21. Found: C, 57.40; H, 3.81; N, 21.98.

Ethyl 2-Chloro-2-[2-(3-propynylthio)phenylhydrazono]acetate (**4**).

Amine **1** (3.26 g.) was diazotized as described above, then the solution was adjusted to pH 4 by sodium acetate. Ethyl 2-chloroacetate (**6**) (3.22 g.) in methanol (30 ml.) was added dropwise under stirring and cooling at 0°. The ice-bath was removed and the mixture was stirred for 2 hours, then was extracted with ether. The organic solution was dried and evaporated and the residue was triturated with diisopropyl ether and filtered to give **4** (1.8 g., 30.3%), m.p. 75°; ir (nujol): 3280 and 1725 cm^{-1} ; nmr: δ 1.40 (3H, t), 2.18 (1H, t, $J = 2.5$ Hz), 3.43 (2H, d, $J = 2.5$ Hz), 4.34 (2H, q), 6.8-7.7 (4H, m), 9.6 (1H, broad s).

Anal. Calcd. for $\text{C}_{13}\text{H}_{13}\text{ClN}_2\text{O}_2\text{S}$: C, 52.61; H, 4.39; N, 9.45. Found: C, 52.35; H, 4.09; N, 9.65.

Ethyl 2-Chloro-2-[2-(1-propynylthio)phenylhydrazono]acetate (**10**).

Compound **10** was obtained in a crude state from aniline **7** (0.85 g.) by the same procedure described for compound **4**. Column chromatography on silica gel by eluting with benzene gave pure **10** (0.7 g., 45%), m.p. 58°; ir (nujol): 3270 and 1720 cm^{-1} ; nmr: δ 1.40 (3H, t), 1.93 (3H, s), 4.38 (2H, q), 6.8-7.7 (4H, m), 9.25 (1H, broad s).

Anal. Calcd. for $\text{C}_{13}\text{H}_{13}\text{ClN}_2\text{O}_2\text{S}$: C, 52.61; H, 4.39; N, 9.45. Found: C, 52.46; H, 4.47; N, 9.20.

2-Carbethoxy-4*H*-pyrazolo[5,1-*c*][1,4]benzothiazine (**6**).

A solution of **4** (0.50 g.) and triethylamine (0.85 g.) in dry

benzene (50 ml.) was refluxed for 72 hours. The mixture was then washed with aqueous hydrochloric acid, dried and evaporated. The residue was chromatographed on silica gel column (40 g.) by eluting with petroleum ether/diethyl ether 4/1. After some amounts of by-products, pyrazole **6** was obtained (0.185 g., 42%), m.p. 110° (from diisopropyl ether); ir (nujol): 1720 cm^{-1} ; nmr: δ 1.41 (3H, t), 4.03 (2H, s), 4.43 (2H, q), 6.67 (1H, s), 7.1-7.5 (3H, m), 8.0-8.2 (1H, m).

Anal. Calcd. for $\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}_2\text{S}$: C, 59.99; H, 4.65; N, 10.77. Found: C, 60.21; H, 4.75; N, 10.50.

2-Carboethoxy-3-methylpyrazolo[5,1-*b*]benzothiazole (**12**).

A solution of **10** (0.50 g.) and triethylamine (0.85 g.) in dry benzene (50 ml.) was refluxed for 96 hours. The mixture was washed with aqueous hydrochloric acid, dried and evaporated. The residue was chromatographed on silica gel column (50 g.) by eluting with petroleum ether/diethyl ether, 1/1. Beside some

amounts of starting hydrazone **10** and side products, pyrazole **12** was isolated (0.056 g., 12%), m.p. 89-90° (*n*-pentane); ir (nujol): 1700 cm^{-1} ; nmr: δ 1.45 (3H, t), 2.45 (3H, s), 4.50 (2H, q), 7.3-7.8 (3H, m), 8.1-8.2 (1H, m).

Anal. Calcd. for $\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}_2\text{S}$: C, 59.99; H, 4.65; N, 10.77. Found: C, 59.68; H, 4.50; N, 10.61.

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