# Thiophenols via the Newman-Kwart Rearrangement

**Dr Dirk Kusch**, head of development at **SF-Chem**, introduces a protocol for thiophenols

The benzothiophene structure is an important skeleton in different pharmaceuticals and agrochemicals, such as Raloxifene (an oestrogen receptor modulator) and Bethoxazin (a fungicide and algaecide). A general synthetic route for the preparation of substituted benzothiophenes starts from substituted thiophenols, which are condensed with substituted α-halogenoketones under basic conditions and finally cyclised by means of polyphosphoric acid[1] or under Lewis acid conditions.[2]

Access to substituted thiophenols is possible by different routes. Substituted anilines can be transformed into the corresponding diazonium salts by reaction with sodium nitrite, which can be converted to thiophenols by substitution with different S-nucleophiles.[3] Another approach to thiophenols is using a Grignard-reaction with substituted halogenobenzenes and sulphur.[4] The direct substitution of halogenobenzenes by S-nucleophiles is usually performed at high temperatures and yield the desired thiols.[5] Most of the described routes lead to substituted thiophenols in either low yield or poor quality. In some cases, the reactions are not scalable due to safety hazards (Figure 1).

A promising pathway for the conversion of phenols to thiophenols involves a Newman-Kwart rearrangement reaction as a key step.[6,7] Substituted phenols were reacted under basic conditions with N,N-dimethyl thiocarbamoyl chloride. The resulting O-aryl dimethyl thiocarbamates undergo the Newman-Kwart rearrangement at temperatures in the range of 200-300°C (depending on the substituents) to the corresponding S-aryl dimethyl thiocarbamates.

Hydrolysis of the S-aryl dimethyl thiocarbamates either under acid or alkaline conditions yields the substituted thiophenols. The S-aryl dimethyl thiocarbamates may also be transformed into arene sulphonic acids by oxidation with hydrogen peroxide and formic acid or into the arene sulphonyl chlorides by oxidation with chlorine and acetic acid (Figure 2).[8]

Since the Newman-Kwart rearrangement occurs almost without by-products in high yields, the reaction is one of the most important methods for the preparation of aryl-sulphur compounds. One major advantage is the possibility of performing the reactions in substance without any solvent. A recent publication by a development group at Pfizer described a procedure for carrying out a continuous Newman-Kwart rearrangement reaction. This method provides a convenient, economical approach to the thiocarbamate rearrangement products and their thiol derivatives.[9]

SF-Chem produces the reagent N,N-dimethyl thiocarbamoyl chloride at large scale in volumes up to 50 tonnes/year. It has experience in the use of N,N-dimethyl thiocarbamoyl chloride in Newman-Kwart rearrangement reactions and in the synthesis of substituted thiophenols and benzothiophenes. N,N-dimethyl thiocarbamoyl chloride is a solid with a melting point of 42-44°C and a boiling point of 90-95°C (0.5 mm Hg).

The formation of N,N-dimethyl thiocarbamoyl chloride starting from commercially available tetramethyl thiuram disulphide is performed in liquid sulphur at 80°C by the addition of chlorine.[10] N,N-dimethyl thiocarbamoyl chloride is purified by vacuum distillation (Figure 3). The literature contains further information about the use of N,N-dimethyl thiocarbamoyl chloride as a reagent in organic synthesis.[8]

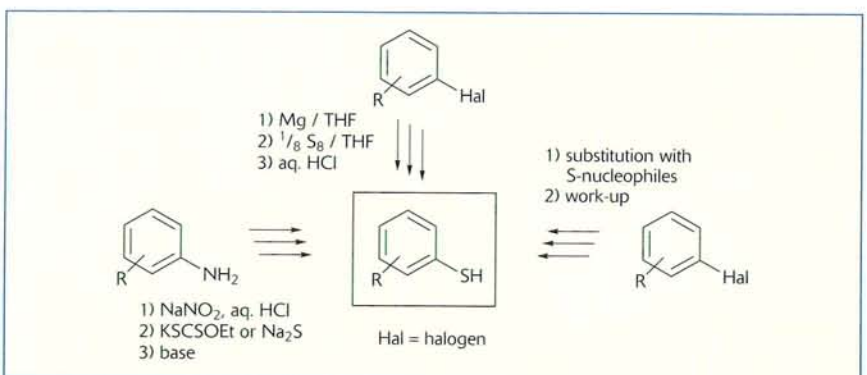


**Figure 1 - Synthetic route to thiophenols**

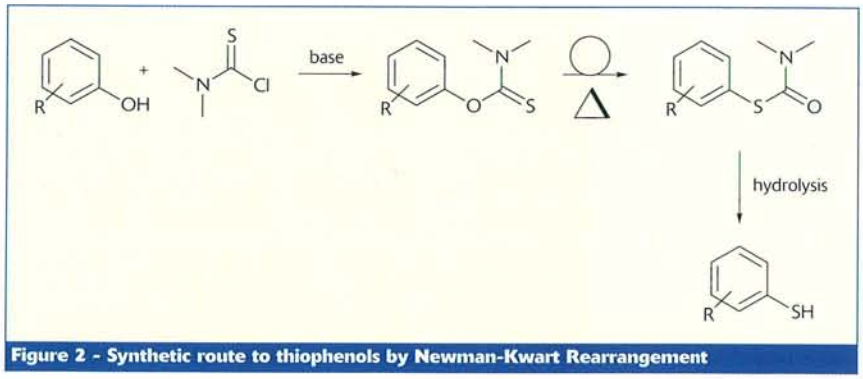


**Figure 2 - Synthetic route to thiophenols by Newman-Kwart Rearrangement**

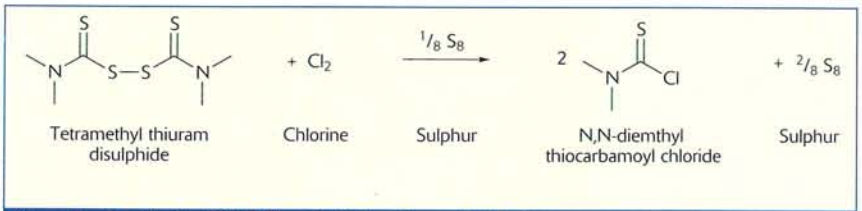


**Figure 3 - Synthesis of N,N-dimethylthiocarbamoyl chloride**

For more information, please contact:
Dr Dirk Kusch
Head of Development
SF-Chem
CH-4133 Pratteln 1
Tel: +41 61 825 32 12
Fax: +41 61 825 35 65
E-mail: dirk.kusch@sf-chem.com

**References:**

**1.** A.N. Kort *et al., Zh. Org. Khim.*, 1970, *6*, 1516
**2.** S. Kim *et al., Tetrahedron Lett.*, 1999, *40*, 2909
**3.** H.C. Godt *et al., J. Org. Chem.*, 1961, *26*, 4047
**4.** M. Zhang *et al., Synthesis*, 2003, *1*, 112
**5.** T. Kamiyama *et al., Chem. Pharm. Bull.*, 1985, *33 (12)*, 5184
**6.** H. Kwart & E.R. Evans, *J. Am. Chem. Soc.*, 1966, *31*, 410
**7.** M.S. Newman & H.A. Karnes, *J. Am. Chem. Soc.*, 1966, *31*, 3980
**8.** A.A. Ponaras, Ö. Zaim in L.A. Paquette (ed.) Enzyclopedia of Reagents for Organic Synthesis, John Wiley & Sons, 1995, 2174
**9.** S. Lin *et al., Organic Preparations and Procedures Int.*, 2000, *32 (6)*, 547
**10.** M.S. Newman & F.W. Hetzel, *J. Org. Chem.*, 1969, *34*, 3604

Reprinted from **Speciality Chemicals Magazine November 2003**