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A New Method for the Synthesis of Many-membered Sulfides by Means of Thioacetamide

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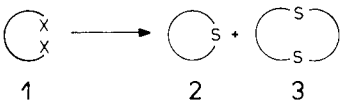
Neue Methode zur Synthese vielgliedriger Sulfide mittels Thioacetamid

Ausgehend von Brommethyl-Verbindungen und Thioacetamiden werden die Sulfide **4**–**7** durch Umsetzung in wäßrigem – oder besonders vorteilhaft – wasserfreiem Medium in Gegenwart von Basen wie Alkalihydroxiden oder *tert*-Butoxid in guten Ausbeuten erhalten. Die Vorteile der Thioacetamid-Cyclisierung gegenüber dem bisher üblichen Einsatz von $Na_2S \cdot 9H_2O$ werden herausgestellt.

The simple preparation of many-membered ring compounds by the reaction of halogeno- or tosyl compounds **1** with sodium sulfide or dithiolates has given strong stimulus to the chemistry of many-membered rings (cyclophanes, crown ethers) [1]. In particular, cyclisations involving nucleophilic substitution by Na_2S at benzylic carbon atoms, followed by elimination of sulfur *via* sulfone pyrolysis, Stevens rearrangement, etc. [2] have allowed the preparations of ring-contracted, many-membered, strained or sterically hindered cyclophane hydrocarbons.



1 2 3

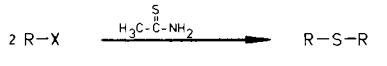
(X = halogen, tosyl)

The cyclisation **1** → **2**, **3** with $Na_2S \cdot 9H_2O$, a method which has been commonly employed, suffers from the disadvantage of having to be carried out in aqueous or aqueous-alcoholic solution to dissolve the sodium sulfide. As a result, two phases are often formed, making it difficult to work with dilution knees or dilution apparatus [3] or even necessary to resort to appropriate glass ware devices for heterogeneous azeotropes [3]. However, it is often desirable to carry out the cyclisation reaction in homogeneous phase with exclusion of water, especially when functional groups prone to hydrolysis are present. We have now used thioacetamide as a synthetic equivalent for sodium sulfide and found that it allows organic sulfides to be synthesized in non-aqueous medium.

[1] For references see: [1a] *J. Grütze* and *F. Vögtle*, Chem. Ber. **110**, 1978 (1977). – [1b] *G. Hohner* and *F. Vögtle*, ibid **110**, 3052 (1977). – [1c] *F. Vögtle* and *E. Weber*, Kontakte (Merck) **1/77**, 11.

[2] Compare herewith: *F. Vögtle* and *P. Neumann*, Synthesis **1973**, 85; *P. Neumann* and *F. Vögtle* in Themen zur Chemie des Schwefels, p. 9, (*K. Maas*, Ed.), Hüthig Verlag, Heidelberg 1975; *B. M. Trost* and *L. S. Melvin*, Sulfur Ylides, Academic Press, New York 1975; further literature is mentioned there.

[3] *F. Vögtle*, Chem.-Ztg. **96**, 396 (1972); manufacturer: Otto Fritz GmbH (Normag®), Feldstr. 1, D-6238 Hofheim/Taunus, BRD.



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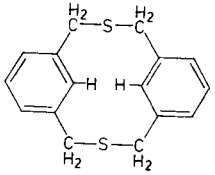
(R = $C_6H_5CH_2$-)

Thus reactions of various bromomethyl compounds with thioacetamide gave dibenzyl sulfide (**4**) as well as the many-membered sulfides **5** – **7** listed in the table. In all cases, the expected sulfides were easily obtained and yields were better or at least as good as those obtained with sodium sulfide.



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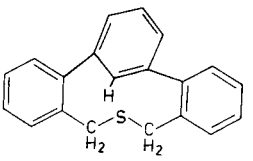

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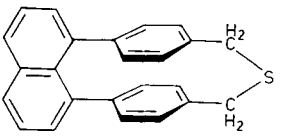

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The thioacetamide method possesses the following advantages over the sodium sulfide method:

a) Thioacetamide is neither hygroscopic nor sensitive to air-oxidation, as opposed to $Na_2S \cdot 9\,H_2O$, and can thus be used stoichiometrically without any difficulty.

b) In common organic solvents thioacetamide is soluble enough for use in high dilution reactions. It shows good solubility in polar, organic solvents. Moreover, it is possible to utilize simple dilution knees or dilution apparatus.

c) Reaction in non-aqueous media is thus possible in the following way: potassium *tert*-butoxide, e.g., may serve as base. In contrast, the use of $Na_2S \cdot 9\,H_2O$, which is insoluble in pure alcohol, requires that a certain amount of water be added, thereby leading to the formation of heterogenous azeotropes, if solvents such as benzene are used in the reaction.

Table. Comparison of the thioacetamide and the $Na_2S \cdot 9\,H_2O$ method

Nr.	thioacetamide method % yield, not optimized (reaction conditions)	$Na_2S \cdot 9\,H_2O$ method % yield
4	97 (benzene/ethanol 1:1, KOH) 96 (abs. benzene/abs. ethanol 1:2, K-t-butoxide)	[4] (abs. conditions not possible)
5	11 (benzene/ethanol 1:2, KOH)	8 – 10 [5]
6	19 (benzene/ethanol 2:1, KOH)	11 [6]
7	48 (*tert*-butyl alcohol/benzene 20:1, KOH)	68 [7]

[4] *C. Märcker*, Liebigs Ann. Chem. **136**, 88 (1865); yields are not mentioned there.

[5] [5a] *T. Sato, M. Wakabayashi*, and *M. Kainosho*, Tetrahedron Lett. **1968**, 4188. – [5b] *F. Vögtle* and *L. Schunder*, Chem. Ber. **102**, 2682 (1969).

[6] *F. Vögtle* and *L. Schunder*, Liebigs Ann. Chem. **721**, 132 (1969).

[7] *W. Bieber* and *F. Vögtle*, Angew. Chem. **89**, 199 (1977); Angew. Chem., Int. Ed. Engl. **16**, 175 (1977).

The new cyclisation method offers an efficient, elegant alternative to the Na_2S method, enabling simplifications and improvement of yield. Undoubtedly, it is also transferable to other molecular skeletons, leaving groups, bases, and solvents.

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Experimental Part

Dibenzyl sulfide (**4**): A mixture of 1.71 g (10.0 mmol) of benzyl bromide, 0.38 g (5.00 mmol) of thioacetamide, and 0.60 g (10.7 mmol) of KOH or 1.12 g (10.0 mmol) of potassium *tert*-butoxide in 100 ml of benzene/ethanol (1:1) or 100 ml anhydrous benzene/anhydrous ethanol (1:2) is refluxed with stirring for 3–4 h. After concentrating the yellow solution is evaporated to dryness, the residue is taken up in diethyl ether, the solution filtered from insoluble products, and the clear filtrate concentrated again. The product which crystallises on cooling is purified by recrystallization from chloroform. Yield 1.04 or 1.03 g (97 or 96%), m.p. 49 °C (49–50 °C [8]).

General method for the preparation of thiaphanes **5**–**7** *by cyclization of dihalides with thioacetamide*: A solution of 2.00 mmol of the bis(bromomethyl) compounds and 2.00 mmol of thioacetamide in 150 ml of solvent (e.g. benzene/ethanol) and a solution of 4.50 mmol of KOH in 150 ml of solvent (e.g. ethanol/water 20:1) are simultaneously dropped from two precision dropping funnels over a period of 7 h into 1200 ml of solvent (e.g. benzene/ethanol), boiling under reflux and stirred vigorously in a 2-l flask. After 8 h, the reaction mixture is evaporated to dryness and worked up as described in lit. [5–7].

[8] *L. N. Levin*, J. Prakt. Chem. [2] **118**, 286 (1928).

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