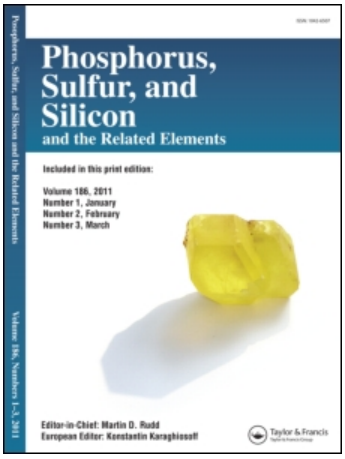


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

INTRODUCTION OF SULFUR IN COMPOUNDS WITH REACTIVE HALOGEN ATOMS VIA THE *t*-BUTYLTHIOLATE ANION

Jan Bcherr[a]; John Lundsgaard[a]
[a] Department of Chemistry, Odense University, Odense, M, Denmark

To cite this Article Bcherr, Jan and Lundsgaard, John(1983) 'INTRODUCTION OF SULFUR IN COMPOUNDS WITH REACTIVE HALOGEN ATOMS VIA THE *t*-BUTYLTHIOLATE ANION', Phosphorus, Sulfur, and Silicon and the Related Elements, 14: 2, 131 — 138
To link to this Article: DOI: 10.1080/03086648308075933
URL: http://dx.doi.org/10.1080/03086648308075933

Phosphorus and Sulfur, 1983, Vol. 14, pp. 131–138
0308-664X/83/1402-0131/$18.50/0

INTRODUCTION OF SULFUR IN COMPOUNDS WITH REACTIVE HALOGEN ATOMS VIA THE *t*-BUTYLTHIOLATE ANION

JAN BECHER and JOHN LUNDSGAARD

Department of Chemistry, Odense University, Campusvej 55, DK-5230, Odense M, Denmark

(*Received August 10, 1982*)

The preparation of *t*-butylthioethers from examples of halogen substituted heterocycles are described. *S*-Dealkylation of the *t*-butylthioethers readily takes place by pyrolyses with catalytic amounts of aluminum chloride or *p*-toluenesulfonic acid.

INTRODUCTION

A large number of different sulfur nucleophiles have been used for the replacement of reactive halogen atoms for the preparation of sulfur compounds. Meth-Cohn *et al.*[1] have demonstrated 2-(*t*-butylthio)-benzaldehyde to be a useful synthon for the unstable 2-mercaptobenzaldehyde. In a communication[2] we have shown that *t*-butyl thioethers can be prepared from examples of halogen substituted heterocycles. In the present paper we wish to report a more systematic study of the preparation of *t*-butylthioethers as well as the *S*-dealkylation of some of these *t*-butylthioethers by pyrolyses.

DISCUSSION

In many cases thiols which also contain keto or formyl groups are unstable, in these compounds it is necessary to protect[3] the thiol group, for example as a thioether. Such a protective group may be useful during a synthetic procedure. The use of a *S*-methyl group as a protective group for thiols has been suggested by Testaferri.[4]

The use of simple alkyl groups for this purpose is not always appropriate as thioethers such as **1** sometimes are cleaved at the *S*-aryl bond instead of the required *S*-alkyl bond:

aryl—S—alkyl

1

For example a 2-alkylthiopyridine will give a pyridone with aqueous base.[6]

However, as can be deduced from Meth-Cohn's[1] results a *t*-butylthio substituent on an aromatic or a heteroaromatic ring can be selectively *S*-dealkylated by acid or by pyrolyses under relatively mild conditions. This is important as a *S*-dealkylation can be expected to take place under ring closure in acetic medium. This reaction sequence has been used recently by us[7] to prepare the new 4*H*-thiopyrano[2,3-b]pyridin-4-one ring system from an appropriate *t*-butylthioether.

In order to see if *t*-butylthioethers could be prepared in general, we have investigated a number of heterocycles with reactive halogen atoms as well as a few halogenated oxo compounds in the reaction with the 2-methyl-2-propanethiolate anion, to produce compounds with a protected thione or thiol group.

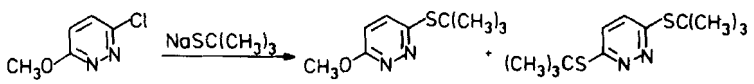
RESULTS

All *t*-butylthioethers reported in Table 1 were prepared in the usual way by addition of the halogen compound to the 2-methyl-2-propanethiolate anion in a dry solvent such as tetrahydrofurane or ethanol:

$$RCl + NaSC(CH_3)_3 \rightarrow RSC(CH_3)_3$$

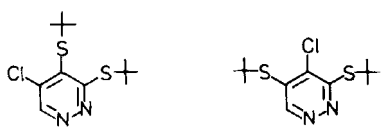
Table 1 gives the yields for analytically pure products, which were obtained either by high pressure liquid chromatography (HPLC) or by "Kugelrohr" distillation *in vacuo*.

The 2-methyl-2-propanethiolate anion is a strong nucleophile, two products can for example be obtained from 3-chloro-6-methoxypyridazine, 3-(*t*-butylthio)-6-methoxypyridazine as well as 3,6-bis-(*t*-butylthio)-pyridazine:



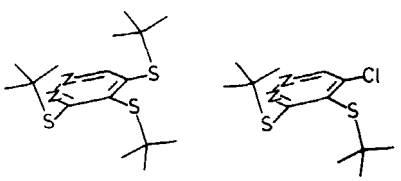
It is important to note that all *t*-butylthioethers (Table 1) distils easily, however, in some cases these products were thermally unstable. This was specially noted for the 3,4,5-tris-(*t*-butylthio)-pyridazine, which had to be stored in the cold. The thermal instability was also noted in the mass spectra, in most cases the pyrolyses to produce isobutene took place in the inlet system.

Structures of the *t*-butylthioethers in Table 1 were assigned on basis on the analytical and spectroscopic data. Compound **5** was isolated together with **6** from the reaction of 3,4,5-trichloropyridazine. Compound **5** can be ascribed structure **5a** or **5b**:



5a **5b**

Structure **5a** could be assigned from the following evidence. The bulky *t*-butylthio groups in compounds **5** or **6** must be situated on opposite sides of the pyridazine ring (as seen from a "Dreiding model"):



6 **5a**

TABLE 1

Preparation of *S-tert*-butylthioethers

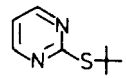
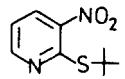
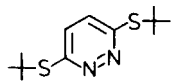
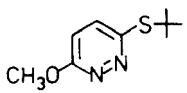
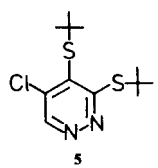
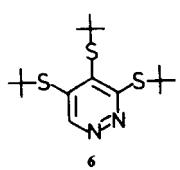
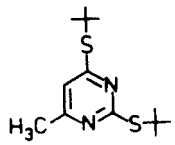
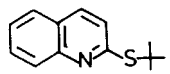
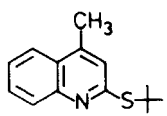
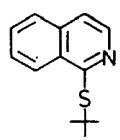
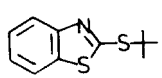
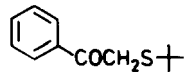
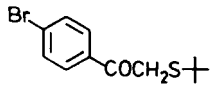
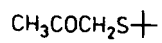
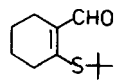
Reagent[a]	Product	Method reaction conditions	Yield[b] [%]	m.p. or b.p./torr[°C]	Molecular formula	Mass spectrum m/e	^{1}H-NMR ($CDCl_3$/TMS)δ[ppm] *J* in Hz	Analyses
2-Chloropyrimidine	 **1**	A, 1,3 h reflux	58	60°/0.6	$C_8H_{12}N_2S$ [168.27]	168(M^+,28%) 112(M-56,100%)	8.60(d,2H,*J* = 5) 6.87(t,1H,*J* = 5) 1.67(s,9H)	calc. C 57.13 H 7.19 N 16.68 found C 57.25 H 7.27 N 16.66
2-Chloro-3-nitropyridine	 **2**	B, 0.5 h 20°	32	33–34°	$C_9H_{12}N_2O_2S$ [212.28]	212(M^+,41%) 156(M-56,100%)	8.64(dd,1H,*J* = 1 and 4) 8.33(dd,1H,*J* = 1 and 8) 7.13(dd,1H,*J* = 4 and 8) 1.67(s,9H)	calc. C 50.92 H 5.70 N 13.20 found C 51.10 H 5.80 N 12.84
3-Chloro-6-methoxypyridazine	 **3**	A, 23 h reflux	21[c]	104–107°	$C_{12}H_{20}N_2S_2$ [256.43]	256(M^+,3%) 200(M-56,20%) 144(M-112,100%)	7.25(s,2H) 1.67(s,9H)	calc. C 56.20 H 7.86 N 10.93 found C 56.62 H 7.99 N 10.67
3-Chloro-6-methoxypyridazine	 **4**	A, 3.3 h reflux	56[d]	oil	$C_9H_{14}N_2OS$ [198.29]	198(M^+,2%) 142(M-56,100%)	7.30(d,1H,*J* = 8) 6.84(d,1H,*J* = 8) 4.16(s,3H) 1.60(s,9H)	calc. C 54.51 H 7.16 N 14.13 found C 54.81 H 7.16 N 12.98
3,4,5-Trichloropyridazine	 **5**	A, 0.1 h 20°	16	87–89° e	$C_{12}H_{19}ClN_2S_2$ [290.07]	290(M^+,9%) 234(M-56,15%) 178(M-112,100%)	9.30(s,1H) 1.60(s,9H) 1.39(s,9H)	M.S. found 290.0697 calc. 290.0678
3,4,5-Trichloropyridazine	 **6**	A, 0.1 h	34	99–101° f,h	$C_{16}H_{28}N_2S_3$ [344.14]	344(M^+,2%) 288(M-56,16%) 232(M-112,18%) 176(M-168,100%)	9.00(s,1H) 1.67(s,9H) 1.52(s,9H) 1.38(s,9H)	M.S. found 344.1423 calc. 344.1414

TABLE 1 (*continued*)

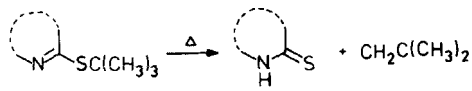
Reagent[a]	Product	Method reaction conditions	Yield[b] [%]	m.p. or b.p./torr[°C]	Molecular formula	Mass spectrum m/e	^{1}H-NMR ($CDCl_3$/TMS)δ[ppm] J in Hz	Analyses
2,4-Dichloro-6-methylpyrimidine	 7	A, 20 h reflux	70	31–34° e	$C_{13}H_{22}N_2S_2$ [270.12]	270(M^+,2%) 214(M-56,32%) 158(M-112,100%)	6.67(s,1H) 2.35(s,3H) 1.67(s,9H)	M.S. found 270.1201 calc. 270.1224
2-Chloroquinoline	 8	A, 18 h reflux	58	36–38° 119–121°/0.1	$C_{13}H_{15}NS$ [217.09]	217(M^+,8%) 161(M-56,100%)	8.2-7.1(m,6H) 1.61(s,9H)	M.S. found 217.0952 calc. 217.0925
2-Chloro-4-methylquinoline	 9	A, 3 h reflux	23	76–78°	$C_{14}H_{17}NS$ [231.35]	231(M^+,8%) 175(M-56,100%)	8.0-7.0(m,5H) 2.60(s,3H) 1.67(s,9H)	calc. C 72.68 H 7.41 N 6.05 found C 73.18 H 7.65 N 5.79
1-Chloroisoquinoline	 10	A, 0.1 h 20°	86	85–87°/0.05	$C_{13}H_{15}NS$ [217.32]	217(M^+,7%) 161(M-56,100%)	8.45-7.2(m,6H) 1.68(s,9H)	calc. C 71.84 H 6.96 N 6.45 found C 71.98 H 6.83 N 6.87
2-Chlorobenzothiazole	 11	A, 2.5 h reflux	70	165–170°/5	$C_{11}H_{13}NS_2$ [223.35]	223(M^+,13%) 167(M-56,100%)	8.03-7.32(m,4H) 1.60(s,9H)	calc. C 59.15 H 5.87 N 6.26 found C 59.64 H 5.65 N 6.90

Phenacylbromide	 **12**	C 6.5 h reflux	45	85–87°/0.05	$C_{12}H_{16}OS$ [208.32]	208(M^+,25%) 152(M-56,49%)	8.05-7.33(m,5H) 3.83(s,2H) 1.33(s,9H)	calc. C 69.18 H 7.74 S 15.39 found C 68.90 H 7.62 S 15.61
p-Bromophenacylbromide	 **13**	C, 3 h reflux	84	27–29°	$C_{12}H_{15}BrOS$ [286.31]	286(M^+,2%) 230(M-56,6%)	7.85(d,2H,J = 8) 7.65(d,2H,J = 8) 3.83(s,2H) 1.33(s,9H)	calc. C 50.18 H 5.26 S 11.16 found C 50.12 H 5.27 S 11.41
	 **14**	C, 2 h reflux	65	85–87°/10 Ref. 8 has 103.5–104°/48	$C_7H_{14}OS$ [146.25]	146(M^+,22%) 90(M-56,9%) 57(M-89,100%)	3.33(s,2H) 2.30(s,3H) 1.33(s,9H)	see ref. 8
1-Chlor-2-formylcyclohexene	 **15**	A 2.5 h reflux	61	78–83°/0.5	$C_{11}H_{18}OS$ [198.11]	198(M^+,15%) 142(M-56),78% 141(M-57),100%	10.46(s,1H) 2.7-1.33(M,8H) 1.40(s,9H)	M.S. found 198.1058 calc. 198.1078

[a] Commercially available. 1-Chloro-2-formylcyclohexene was prepared according to ref. 10.
[b] Yield of purified product.
[c] From the reaction was also obtained 10% of compound **4**.
[d] From the reaction was also obtained 10% of compound **3**.
[e] Unstable.
[f] Very unstable.
[g] Analyses for the thermally unstable products were obtained by peak matching in the MS, however satisfactory elementary analyses could be obtained after careful combustion of the sample.
[h] Light sensitive.

This is reflected in the ^{13}C-NMR spectrum (see Table 2) of **6** with the values for the *t*-carbons in the 3 and 5 substituents at 48.96 – 48.50 ppm, while that at the 4-position is found at 53.20 ppm. This shift in compound **4** is found at 48.24 ppm. This corresponds to the 48.70 ppm found for the *t*-carbon in the 3-position of **5**. The 3-chloro atom in the starting 3,4,5-trichloropyridazine is chemically the most reactive one and therefore it is first substituted. The other *t*-carbon in compound **5** is found at 54.20 ppm, and therefore assigned the sterically hindered 4-position, which means that structure **5a** is the correct one.

Table 3 gives the results for the pyrolyses of some of the *t*-butylthioethers by refluxing in 1,2-dichlorobenzene, with *p*-toluenesulfonic acid as catalyst or at a lower temperature in refluxing benzene with anhydrous aluminum chloride as catalyst, in these cases the expected thiones were isolated; in some cases in quantitative yields:



In other cases, such as for example compound **2**, a number of products were formed by pyrolyses, therefore, this reaction mixture was not investigated further. Without any catalyst elimination of isobutene only takes place very slowly.

EXPERIMENTAL

The starting materials were all obtained from Aldrich, except 1-chloro-2-formylcyclohexene which was prepared according to ref. 10. Microanalyses were carried out at NOVO A/S, Bagsvaerd, Denmark. Instrumentation ^{13}C and ^{1}H-NMR: Jeol JNM-PMX 60; M.S.: Varian MAT CH7A; m.p. Büchi apparatus

TABLE 2

^{13}C NMR shift values for the *t*-butyl groups in the pyrimidines **4**, **5** and **6**

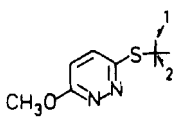
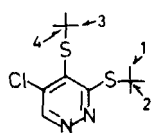
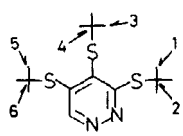
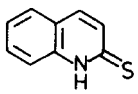
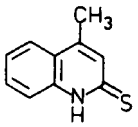
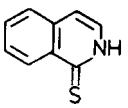
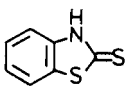
Compound	carbon no. (δ in ppm from TMS in $CDCl_3$)					
	1	2	3	4	5	6
 **4**	30.79	48.24	—	—	—	—
 **5**	31.02	48.70	32.02	54.20	—	—
 **6**	30.11	48.50	31.40	53.62	32.38	48.96

TABLE 3

Pyrolyses of *S-tert*-butylthioethers

Starting compound	Product[a]	m.p. °C found[b]	m.p. °C (reported)	Method and yield
1		210–215°d	(218–219°d)[5]	D 95%
8		174–176°	(178–179°)[7]	E 57%
9		261–263°	(266°)[6]	D 95%
10		169–170°	(171°)[7]	E 65%
11		176–178°	(178–181°)[8]	E 91%

[a] Yields of crude product is quantitative. Method D and E gives the yields of recrystallized product.
[b] m.p. of products after washing with hexane or recrystallization. The products were characterized by ^{1}H-NMR and mass spectra.

(uncorrected); distillations were carried out in a Kugelrohr apparatus (Büchi); boiling points are oven temperatures; HPLC on a Waters Prep. LC, 500A, 5 cm prep. pak 500 silica columns, microporacil 63, eluent, benzin (70–90°) with 5–15% ethylacetate. All reactions must be carried out in an efficient hood due to the smell of *t*-butylmercaptane. With great care, these reactions can be carried out without smell, it is important to have a small excess of base.

***t*-Butylthioethers; General procedure:** *Method A.* (Compounds 1, 3–11 and 15). Sodiumhydride (2,1 g, 60% suspension in oil, 0.055 mol) is stirred in dry tetrahydrofurane (50 ml) whereupon *t*-butylmercaptane (4.0 g, 0.044 mol) is slowly added with cooling. The white suspension is heated to room temperature and stirred at this temperature for one hour. Now the halogen compound (dissolved in tetrahydrofurane 10 ml) is slowly added and the mixture refluxed according to Table 1. The reaction mixture is then cooled, filtered and concentrated *in vacuo*, whereupon the product was purified according to Table 1.

Method B. (Compound 2). The sodium *t*-butylthiolate suspension is prepared as described above and diluted with dry tetrahydrofurane (60 ml). This suspension is transferred to an addition funnel and kept homogeneous by percolation with dry nitrogen. This suspension of the anion (0.055 mol) is slowly added to a solution of the halogen compound (0.055 mol) in dry tetrahydrofurane (10 ml) and treated as described above.

Method C. (Compounds 12–14). Sodium (1.1 g, 0.048 mol) is dissolved in dry ethanol (30 ml) and *t*-butylmercaptane is slowly added with cooling and stirring. After stirring for one hour the halogen compound (0.044 mol) is added and the mixture refluxed and worked up as described above.

Pyrolyses of compounds 1, 8, 9, 10 and 11 (Table 3). *General procedures*: *Method D.* Pyrolyses is carried out by simply heating the dry material in a test tube.

Method E. The appropriate *t*-butylether is dissolved in 1,2-dichlorobenzene (1 g in 3 ml) with *p*-toluenesulfonic acid (1 mg). This solution is heated to reflux for 20 min. Cooling or concentration *in vacuo* yields the crystalline products which are filtered, washed with benzine and recrystallized from abs. ethanol. (Usually this method gives a better product than by method D). Under milder conditions the elimination of isobutene can also be carried out with benzene as solvent and anhydrous aluminum chloride as catalyst to give similar yields of the products from starting compounds **8**, **9**, **10** and **11**.

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