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TETRACOVALENT SULFUR INTERMEDIATES IN IMINOSULFURANE SYNTHESIS. GENESIS OF A POTENTIALLY GENERAL YLID PREPARATION[1]

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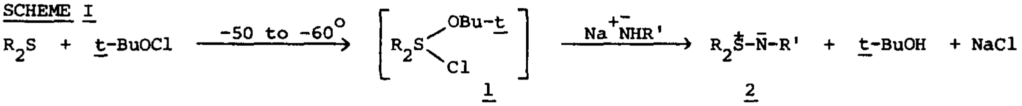
The existence of neutral, tetracovalent sulfur compounds was surmised for years on the basis of kinetic, spectroscopic and other studies,[2-5] but it has been only recently that several "sulfuranes" have been isolated and adequately characterized.[6-8] Reactions of tetracovalent sulfur compounds have received only limited study, however. We report here the *in situ* preparation of tetracovalent compounds (1) by the low temperature reaction of sulfides with *t*-butyl hypochlorite in anhydrous media, immediately followed by reaction with selected amide anions to form iminosulfuranes (2) in fair to high yields (25-80%) (Scheme I and Table 1):

SCHEME I



R = Me; R' = CN, SO_2Ph, COPh, $COCH_3$, $COCH_2Cl$, $COCHCl_2$ (25-80% yield); R = Ph; R' = CN (65% yield)

TABLE 1
IMINOSULFURANES FROM SULFIDES, *t*-BuOCl AND AMIDE ANIONS

$R_2\overset{+}{S}-\overset{-}{N}-R'$ (2)[a]	Yield, %[b]	mp, °C[b]	mp, °C (pure or literature)
R = Ph; R' = CN	65	60-62.5	62-63 (from Et_2O)[c]
R = Me; R' = CN	50	80-83	83 (from EtOAc)[9]
R = Me; R' = SO_2Ph (3)	50-80	128-130	129-130 (from EtOAc)[10]
R = Me; R' = COPh (4)	25[d]	---	108-109.5 (from C_6H_6)[11]
R = Me; R' = $COCH_3$ (5)	40	127-129(d)[e]	132-133(d) (from EtOH-Me_2CO or EtOH-Et_2O)[12]
R = Me; R' = $COCH_2Cl$	70	92-94.5	93-94.5 (from C_6H_6)
R = Me; R' = $COCHCl_2$	65	98-100.5	100.5-101.8 (from C_6H_6) (lit[13] 46°)

[a] All compounds were characterized by IR and NMR. Correct microanalyses (C,H,N,S,Cl) were obtained for new compounds. [b] Once crystallized or crude reaction product. [c] Pure product obtained by silica gel chromatography. [d] Pure compound. [e] Hydrochloride.

Amide anions are required in the second step of Scheme I as the free amides do not react with 1 under the reaction conditions. The amide anions are generated from the amides by reaction with methoxide ion in methanol or *t*-butoxide ion in *t*-butanol, the choice of base (and solvent system) being dictated by the acidity of the amide. The best yields of iminosulfuranes are obtained at the lowest temperatures, although temperatures as high as -10 to -15° have also been used but a 30% or greater decrease in yield is observed and more byproducts form (mainly sulfoxide).

A limitation exists in the choice of anions, since aniline and methylamine, e.g., are not sufficiently acidic and therefore do not provide a sufficient concentration of anions to react with 1. Although acetamide and benzamide form anions with t-butoxide, yields of iminosulfuranes are low (<50%); these amides are much weaker acids than the others employed. Also, iminosulfuranes could not be obtained from di-t-butyl sulfide or thiophene by the procedure described (cyanamide anion employed). Di-t-butyl sulfide reacts exothermically with t-butyl hypochlorite but we believe the resulting product is so sterically hindered that it is unable to undergo displacement reactions. The lone pair of electrons on sulfur in thiophene is too well delocalized into the ring to be available for reaction. On the other hand, diphenyl sulphide which is normally unsatisfactory in reactions with N-halo-amides to prepare iminosulfuranes[12] reacts readily with t-butyl hypochlorite and the intermediate (1) reacts with facility with cyanamide anion (Table 1).

The speed and convenience of the procedure, coupled with the good yields and ready availability of the starting materials, prompted us to examine its utility for the preparation of other classes of ylids, i.e., iminophosphoranes, aminimides and carbosulfuranes. One member of each of these three classes was prepared:

$Ph_3\overset{+}{P}\text{-}\overset{-}{N}CN$, 81% yield, mp 194° (from C_6H_6),[14] from Ph_3P, t-BuOCl and $\overset{-}{N}HCN$;

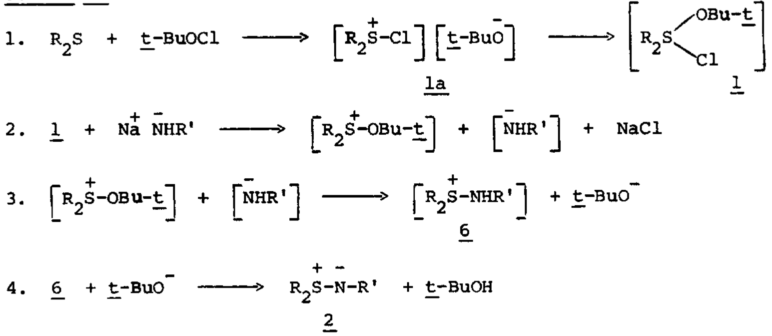
$(Me)_3\overset{+}{N}\text{-}\overset{-}{N}CN$, 75% yield, mp 175-7(d) (from i-PrOH), from Me_3N, t-BuOCl and $\overset{-}{N}HCN$;

$Me_2\overset{+}{S}\text{-}\overset{-}{C}(CN)_2$, 26% yield, mp 99-100° (by column chromatography),[15] from Me_2S, t-BuOCl and $\overset{-}{C}H(CN)_2$.

In all cases, reaction of the nucleophiles with t-butyl hypochlorite was rapid and complete at the low temperatures. In the iminophosphorane preparation, an approximately 20% yield of triphenylphosphine oxide was also isolated.

Reaction Pathways. The preparation of 2 can be rationalized as shown in Scheme II:

SCHEME II



$$1.\quad R_2S + t\text{-BuOCl} \longrightarrow \underset{1a}{[R_2\overset{+}{S}\text{-Cl}][t\text{-Bu}\overset{-}{O}]} \longrightarrow \underset{1}{\left[R_2S\begin{matrix}\text{OBu-t}\\ \text{Cl}\end{matrix}\right]}$$

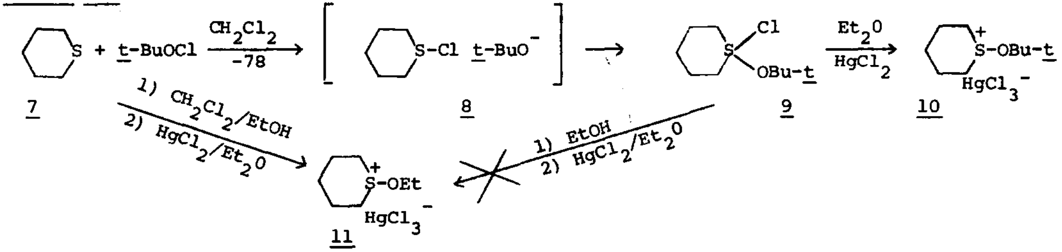
$$2.\quad 1 + \overset{+}{Na}\,\overset{-}{N}HR' \longrightarrow [R_2\overset{+}{S}\text{-OBu-t}] + [\overset{-}{N}HR'] + NaCl$$

$$3.\quad [R_2\overset{+}{S}\text{-OBu-t}] + [\overset{-}{N}HR'] \longrightarrow \underset{6}{[R_2\overset{+}{S}\text{-NHR'}]} + t\text{-Bu}\overset{-}{O}$$

$$4.\quad 6 + t\text{-Bu}\overset{-}{O} \longrightarrow \underset{2}{R_2\overset{+}{S}\text{-}\overset{-}{N}\text{-R'}} + t\text{-BuOH}$$

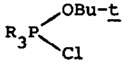
In Step 1, nucleophilic attack of the sulfide on t-butyl hypochlorite gives the chlorosulfonium salt (1a) as the initial product. This salt, an intimate ion pair, has an extremely short lifetime, and even at -60° reacts rapidly to form 1. In Step 2, the most likely pathway is reaction of 1 with the amide salt to form sodium chloride and a sulfonium salt, with the amide anion as the counter-ion. Nucleophilic attack of the amide anion at the sulfonium site (Step 3) displaces t-butoxide ion via an S_N2-like process, affording the salt of the iminosulfurane. Step 3 is really an equilibrium process with the equilibrium displaced far to the right; the position of the equilibrium depends on the relative nucleophilicity of the t-butoxide and the amide anions. Step 4 involves rapid and irreversible proton removal to yield 2 and t-butanol. The driving force for Step 4 is (a) the high basicity and low nucleophilicity of the t-butoxide anion (the reversal of Step 3 is thus disfavored) and (b) the N-H proton is highly acidic owing to electrostatic and conjugative stabilization of the resulting anion.

SCHEME III



Evidence supporting Step 1 in our proposed reaction pathway for synthesis of iminosulfuranes has already been provided by Johnson and Rigau[4] (Scheme III). Reaction of t-butyl hypochlorite with thiane (7) in methylene chloride at -78° yields the tetracovalent, neutral sulfur species (9), via the initially formed intimate ion pair 8. Addition of mercuric chloride and ether precipitates the t-butoxysulfonium trichloromercurate (10) which was isolated and characterized. However, if ethanol is present initially at the time of reaction of 7 with t-butyl hypochlorite, the intimate ion pair 8 reacts with ethanol rapidly, and the principal product on treatment of the reaction mixture with mercuric chloride and ether is the ethoxysulfonium trichloromercurate (11). In contrast, if ethanol is added to the reaction mixture after reaction of 7 with t-butyl hypochlorite is complete the only salt obtained is the t-butoxy salt (10). These experiments provide convincing evidence for the rapid, irreversible formation of 9. This species undergoes negligible ionization to the intimate ion-pair 8 and it is unaffected by weak nucleophiles. However, chloride ion can be removed by addition of a suitable electron-deficient species ($HgCl_2$, Na^+). The NMR spectrum of the compound formed from phenyl methyl sulfide and t-butyl hypochlorite in methylene chloride at low temperature provides further confirmation for the existence of neutral, tetracovalent sulfur species.[2a,4a] The possibility that ionic species (1a) are involved in Step 2 cannot be entirely discounted.[4b]

It is appealing to suggest that triphenyl phosphine reacts similarly with t-butyl hypochlorite to form the neutral pentacovalent phosphorus species (12) although we have no direct evidence to support this conclusion, and 12 behaves like 9, its sulfur counterpart. There is ample precedent for such an intermediate in the phosphorus field.[7] With trimethylamine, however, the initial ion pair 13 is the probable reactive species.



12

$\left[R_3\overset{+}{N}\text{-Cl}\right]\left[t\text{-BuO}^-\right]$

13

The balance between the acidity of the amide and the nucleophilicity of its conjugate base (the anion) must play an important role in determining the success and generality of the ylid syntheses. To date, the best yields have been obtained with relatively acidic amides (benzenesulfonamide, cyanamide) which produce sizeable concentrations of anions with sodium methoxide. On the other hand, the delocalization of the negative charge does not reduce the nucleophilicity of the anion below the level at which it can perform a displacement reaction. Malonitrile is also a relatively strong acid but, in the only case studied, the yield of carbosulfurane was only fair (26%). We believe the more extensive charge delocalization to be expected in the anion $[\bar{C}H(CN)_2]$ militates strongly against a successful nucleophilic displacement. Furthermore, acetamide and benzamide, two amides of intermediate acidity, give only moderate yields of iminosulfuranes. Amides themselves do not react; they must first be converted to their conjugate bases (anions) with alkoxides. This experimental observation is in accord with our interpretation of the reaction pathway (Scheme II).

REFERENCES

1. Iminosulfuranes. VIII. Work supported in part by Grants CA-07803, 07174 and 98793 of the National Cancer Institute.
2. (a) J.C. Martin and R.J. Arhart, J. Amer. Chem. Soc., 93, 2339 (1971) and references cited therein; (b) E.N. Givens and H. Kwart, ibid., 90, 378,386 (1968).
3. W.A. Sheppard, J. Amer. Chem. Soc., 93, 5597 (1971).
4. (a) C.R. Johnson and J.J. Rigau, J. Amer. Chem. Soc., 91, 5398 (1969); (b) C.R. Johnson, C.C. Bacon, and W.D. Kingsbury, Tetrahedron Lett., 5011 (1972).
5. G.E. Wilson, Jr. and M.M.Y. Chang, Tetrahedron Lett., 875 (1971).
6. J.C. Martin and R.J. Arhart, J. Amer. Chem. Soc., 93, 2341 (1971).
7. E.L. Muetterties and R.A. Schunn, Quart. Rev. Chem. Soc., 20, 245 (1966).
8. N.C. Baenziger, R.E. Buckles, R.J. Maner and T.D. Simpson, J. Amer. Chem. Soc., 91, 5749 (1969).
9. F.D. Marsh, U.S. Patent 3,505,401 (1970).
10. M.V. Likhosherstov, Zhur. Obshchei Khim., 17, 1478 (1947).
11. J.G. Moffatt and U. Lerch, J. Org. Chem., 36, 3391 (1971).
12. H. Kise, G.F. Whitfield and D. Swern, Tetrahedron Lett., 1761 (1971); J. Org. Chem., 37, 1121(1972).
13. R. Neidlein and E. Heukelbach, Arkiv. Pharm., 299, 64 (1966).
14. A.S. Shetepanek, E.N. Tkachenko, and A.V. Kirsanov, J. Gen. Chem., USSR, 39, 1445 (1969).
15. A.F. Cook and J.G. Moffatt, J. Amer. Chem. Soc., 90, 740 (1968).