NEW SYNTHETIC "TRICKS". $[Et_3NH][Sn(SPh)_3]$ AND Bu_2SnH_2, TWO USEFUL REAGENTS FOR THE REDUCTION OF AZIDES TO AMINES

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Treatment of Sn(SPh)2 with PhSH and Et3N affords a tin(II) complex, soluble in organic solvents, which is the best reducing agent for azides reported so far. Bu2SnH2, although not so reactive, also shows several advantages with regard to the standard reducing agents for azides, such as its solubility in most solvents or its scarce reactivity with water.

For a long time, the reducing agents $SnCl_2$ and Bu_3SnH and Lewis' acid $SnCl_4$ were almost the only tin-based reagents utilised in organic synthesis. Nowadays, there is a boom in this connection, owing to the interesting synthetic applications of O-stannyl enol ethers, stannoxanes, allylstannanes and vinylstannanes (among others), whose preparation requires other reagents such as R_3SnX, Bu_2SnO, etc.[1]

We describe here the properties of a new tin(II) reagent, $[Et_3NH][Sn(SPh)_3]$, arising from the known $Sn(SPh)_2$,[2] PhSH, and Et_3N, as well as those of Bu_2SnH_2,[3] with regard to the reduction of azides to amines.

The more general reagents or methods employed to perform this important reduction may be classified as follows: (i) hydrides such as $LiAlH_4$ or $NaBH_4$;[4] (ii) hydrogenolysis;[5] (iii) reducing metals or low-valence metal ions ($SnCl_2$, $CrCl_2$, $TiCl_3$...);[6] (iv) reaction with phosphines followed by hydrolysis;[7] (v) reduction with S^{2-}, thiolates, or other sulphur derivatives.[8,9] As any synthetic method, each of them has some shortcomings: azide groups and carbonyl (and carboxyl) functions are generally incompatible as far as the reduction with hydrides is concerned, so that these last functions must be normally protected or modified; catalytic hydrogenation may be inadequate if the azide to be reduced is unsaturated or contains benzyl/benzylidene/trityl protecting groups; most reducing metals or metal ions react too slowly with azides and/or tend to afford separation problems; both the reaction of phosphines with azides to give iminophosphoranes and their hydrolyses require prolonged heating when the azides are hindered; the reducing power of thiols and thiolates, in this context, is very moderate, so that competitive reactions may take place in polyfunctional azides when forcing the reaction conditions; etc.

Our results with the above-mentioned tin reagents, from 1 mmol of azide plus 1.5 mmol of reagent in 5-10 ml of benzene at ca. 15 $^\circ$C, are summarised in the Table (next page). As shown, the yields are very good within few minutes with $Sn(SPh)_3^-$ or within a few hours with Bu_2SnH_2. Heating at 40 $^\circ$C was only necessary for heterocyclic compounds **10** and **11**, whose reduction requires a previous tautomerisation to their azide forms. Instead of benzene, we have utilised other solvents —CH_2Cl_2, Et_2O, THF, THF-H_2O, MeOH—with identical results. As a working hypothesis, the reactions involved might be:
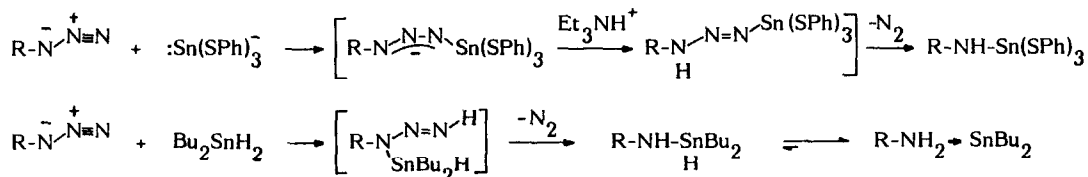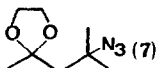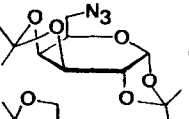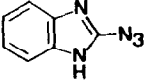
$$R-\overset{-}{N}\overset{+}{N}\equiv N \; + \; :Sn(SPh)_3^- \; \longrightarrow \; \left[R-N\overset{N-N}{\underset{-}{\diagdown}}Sn(SPh)_3 \right] \xrightarrow{Et_3NH^+} R-N\overset{N=N}{\underset{H}{\diagdown}}\overset{Sn(SPh)_3}{\diagdown} \xrightarrow{-N_2} R-NH-Sn(SPh)_3$$

$$R-\overset{-}{N}\overset{+}{N}\equiv N \; + \; Bu_2SnH_2 \; \longrightarrow \; \left[R-N\overset{N=N-H}{\underset{SnBu_2H}{\diagup}} \right] \xrightarrow{-N_2} R-NH-\overset{SnBu_2}{\underset{H}{}} \; \rightleftharpoons \; R-NH_2 + SnBu_2$$
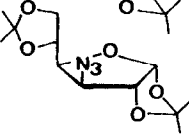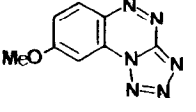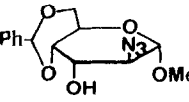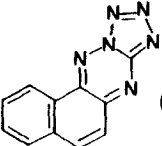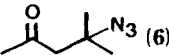
Table. Amine yields obtained by reduction of azides with $Sn(SPh)_3^-$ and with Bu_2SnH_2 in C_6H_6 at 15 $^\circ$C, unless otherwise indicated. Reaction times within parentheses.

	$Sn(SPh)_3^-$	Bu_2SnH_2			$Sn(SPh)_3^-$	Bu_2SnH_2
$PhCH_2N_3$ (1)	99% (5 min)	95% (4 h)[a]	(7)		93% (20 min)[c]	92% (7 h)
$CH_3(CH_2)_{11}N_3$ (2)	98% (5 min)	95% (3 h)	PhN_3 (8)		95% (5 min)	98% (5 h)
(3)	96% (5 min)	91% (4 h)	(9)		91% (3 min)	98% (2 h)[d]
(4)	97% (5 min)	93% (8 h)	(10)		100% (12 h)[d]	98% (4 h)[d]
(5)	95% (5 min)	93% (8 h)	(11)		100% (12 h)[d]	90% (72 h)[d]
(6)	60% (5 min)[b]	75% (8 h)[b]				

[a]The same yield was obtained after 1 h at 40 $^\circ$C or at reflux for 15 min. [b]The reduction of the azide was quantitative, the keto group being not reduced (as shown by the IR and NMR spectra of the crude), but the resulting aminoketone was partially "lost" during its isolation, as expected. [c]A 100% yield was obtained after 10 min at 40 $^\circ$C. [d]At 40 $^\circ$C.

An appropriate workup is essential to reach good yields of amines from azides, since at the end of the reactions what is usually obtained is either an ammonium salt, a $RNH\text{-}MX_n$ species, or a $RNH_2 \cdot MX_n$ complex. Therefore, some efforts have been devoted in this work to improve the workup, the following isolation methods having been tested and/or developed:

A) Strong basic medium. The final organic solution was either added to a larger volume of dichloromethane or evaporated to dryness and the residue dissolved in dichloromethane. It was then washed three times, at 0 $^\circ$C, with 0.1N NaOH to eliminate tin(II) and tin(IV) complexes as stannite and stannate anions, respectively. Drying of the organic solution and elimination of the solvent gave chromatographically and spectroscopically pure amines. This is mostly used for the reduction with $Sn(SPh)_3^-$.

B) Treatment with H_2O_2. The final organic solution, in a large volume of dichloromethane, was washed, in the case of $Sn(SPh)_3^-$, three times at 0 $^\circ$C with aqueous potassium carbonate (pH 10) containing hydrogen peroxide (2%).[10] In the case of Bu_2SnH_2, the dichloromethane solution was stirred for 1 h with an equal volume of aqueous hydrogen peroxide (5%), to oxidise $(Bu_2Sn)_n$ to insoluble $(Bu_2Sn=O)_n$. It was then partitioned in cold between dichloromethane and dilute aq. sodium carbonate, each layer being extracted three or more times. The organic extracts were mixed and dried, and the solvent was eliminated to afford pure amines.
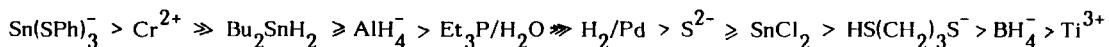
C) Al_2O_3 column. Mainly for the reduction of heterocyclic azides ($\rightleftharpoons$ tetrazoles) with $Sn(SPh)_3^-$, the direct introduction of the final reaction mixture into a short alumina column was a rapid purification method: elution with dichloromethane and then dichloromethane-methanol 98:2 or 95:5 yielded pure heterocyclic amines, the tin(II)/tin(IV) complexes being retained in the column.

D) Addition of PhSSPh. Mainly for the reduction of heterocyclic azides ($\rightleftharpoons$ tetrazoles) with Bu_2SnH_2, the final reaction mixture was treated for 1 h at 40 $^\circ$C with 2 equiv. of PhSSPh, to convert $RNH_2 \cdot SnBu_2$ (or related compounds) into RNH_2 plus $Bu_2Sn(SPh)_2$. Column chromatography on alumina afforded pure amines (the tin(IV) derivatives were eluted with dichloromethane; the amines with dichloromethane-methanol 98:2 or 95:5).

At last, we have established **a scale of reducing power** as far as the conversion of RN_3 to RNH_2 at room temperature is concerned, in the following way: the apparently better reducing agents were checked against tertiary azide **7** (100 mg of **7** in 10 ml of a suitable solvent in each case) and the slower reducing agents were checked against **1** (100 mg of **1** in 10 ml of solvent too); 1.5 molar equiv. of the reducing agent were added at once and the relative reaction rates were monitored independently by volumetry (nitrogen evolved), IR (disappearance of the azide band) and ^{1}H NMR.

Thus, reduction of **7** with $Sn(SPh)_3^-$ was accomplished in 20 min (93% of amine), with Cr^{2+} (from Cr^{3+} plus Zn in acetone-water) it takes 40 min, but only a 45% yield of amine could be obtained due to isolation problems, with Bu_2SnH_2 it was complete in 6-7 h (after 6 h, the amine was isolated in 85% yield; after 7 h, in 92% yield), with $LiAlH_4$ in ether in 6 h (81% of amine using 1.5 mmol of LAH per mol of azide, but only a 45% yield using 0.7 mmol of LAH per mol), with Et_3P in acetonitril-water in 10 h (91% yield).[11] The remaining reagents studied in this work do not reduce **7** at all after 24 h at r.t.

However, they reduce slowly **1**: after 24 h at r.t., catalytic hydrogenation (1 atm, Pd/C, MeOH, HCl) gave quantitatively benzylamine, $Na_2S \cdot 9H_2O$ in MeOH afforded 68% of amine (32% of azide being recovered), $SnCl_2$ in MeOH yielded 64% of conversion, propanedithiol and Et_3N in MeOH 32%, $NaBH_4$ in THF plus MeOH 15%, and $TiCl_3$ in H_3O^+/EtOH do not react at all. In other words, the following qualitative order results:

$$Sn(SPh)_3^- > Cr^{2+} \gg Bu_2SnH_2 \geqslant AlH_4^- > Et_3P/H_2O \ggg H_2/Pd > S^{2-} \geqslant SnCl_2 > HS(CH_2)_3S^- > BH_4^- > Ti^{3+}$$

In summary, $Sn(SPh)_3^-$ is the best reducing agent for azides reported so far, being active in a large variety of solvents, including $THF-H_2O$ and acetone.[12] Bu_2SnH_2 is not so strong, but it has some advantages with respect to its scale neighbours: (i) it works in the most common solvents, even in the presence of water, whereas Cr^{2+} and $LiAlH_4$ are very limited in this connection; (ii) it is much more selective than $LiAlH_4$, at least when the azide reduction is compared to that of a keto group[12] since, in fact, only the azide group of **6** was reduced; (iii) isolation of the amine requires milder conditions and/or less cumbersome workup than its competitors (in the Cr^{2+} method it is necessary to precipitate the resulting $Cr(OH)_3$, to evaporate the aq. soln to dryness, to extract the amine hydrochloride, etc.; no strong basic medium is needed as in the $LiAlH_4$ case or even in the $Sn(SPh)_3^-$ case), which is relevant in polyfunctional molecules to avoid undesired reactions.

We expect that these two reagents will find wide application in the field of the natural products, especially for the reduction of hindered azides.

References and Footnotes

1. (a) "Fieser and Fieser's Reagents for Organic Synthesis", Vols. 1-12, Wiley, New York, 1967-86; (b) "Theilheimer's Synthetic Methods of Organic Chemistry", Vols. 36-40, Karger, Basel, 1982-86; (c) "Organotin Compounds: New Chemistry and Applications", Adv. Chem. Ser. 157, J. J. Zuckerman, Ed.; ACS, Washington D. C., 1976; (d) H. G. Kuivila, Synthesis, 499 (1970); (e) S. David and S. Hanessian, Tetrahedron, 41, 643 (1985) (TR 180); (f) J. K. Stille, Angew. Chem. Int. Ed., 25, 508 (1986).

2. D. E. Fenton et al., Inorg. Chim. Acta, 4, 235 (1970); P. G. Harrison and S. R. Stobart, Ibid., 7, 306 (1973).

3. A. K. Sawyer and H. G. Kuivila, J. Org. Chem., 27, 610 (1962).

4. L. A. Spurlock and R. J. Schultz, J. Am. Chem. Soc., 92, 6302 (1970); M. Hedayatullah and A. Guy, Tetrahedron Letters, 2455 (1975); F. Rolla, J. Org. Chem., 47, 4327 (1982); K. Soai, S. Yokoyama, and A. Ookawa, Synthesis, 48 (1987). Also see references therein.

5. W. S. Mungall, G. L. Greene, G. A. Heavner, and R. L. Letsinger, J. Org. Chem., 40, 1659 (1975); E. J. Corey, K. C. Nicolaou, R. D. Balanson, and Y. Machida, Synthesis, 590 (1975). Also see references therein.

6. D. N. Kirk and M. A. Wilson, J. Chem. Soc. (C), 414 (1971); T. Kondo, H. Nakai, and T. Goto, Tetrahedron, 29, 1801 (1973); T. L. Ho, M. Henninger, and G. A. Olah, Synthesis, 815 (1976); B. Stanovnik, M. Tisler, S. Polanc, and M. Gracner, Ibid., 65 (1978); S. Polanc, B. Stanovnik, and M. Tisler, Ibid., 830 (1980); S. N. Maiti, M. P. Singh, and R. G. Micetich, Tetrahedron Letters, 27, 1423 (1986).

7. J. B. Hendrickson, K. W. Bair, and P. M. Keehn, J. Org. Chem., 42, 2935 (1977); N. Knouzi, M. Vaultier, and R. Carrie, Tetrahedron Letters, 763 (1983) and Bull. Soc. Chim. Fr., 815 (1985).

8. T. Adachi, Y. Yamada, I. Inoue, and M. Saneyoshi, Synthesis, 45 (1977); B. Stanovnik, M. Tisler, S. Polanc, and J. Zitnik, Ibid., 491 (1977), and former papers of these authors; H. Bayley, D. N. Standring, and J. R. Knowles, Tetrahedron Letters, 3633 (1978); B. A. Belinka and A. Hassner, J. Org. Chem., 44, 4712 (1979). Also see H. Suzuki and K. Takaoka, Chem. Lett., 1733 (1984).

9. For other, less general approaches and for earlier papers, see Knouzi et al.[7] A interesting reagent is the pentane-2,4-dione anion (acac/Et$_3$N) which, as reported by Stanovnik et al.,[8] is very appropriate for the reduction of heterocyclic azides: since a diazo-group transfer is involved the heterocyclic rings remain untouched, in contrast to what happens with LAH and NaBH$_4$. We have observed that acac/Et$_3$N does react with 9 to give a 67% yield of the amine after 24h at r.t. (without undesirable reactions, as 30% of 9 was recovered). However, acac/Et$_3$N does not react at all with either 1 or 7 under the conditions reported here, so that from the present, general point of view it should be put close to the end of our reducing-power scale.

10. Excesses of Sn^{II} and PhSH are oxidised in situ to Sn^{IV} and PhSSPh, respectively; Sn^{IV} complexes are readily converted to stannates (soluble at pH 10). Formation of emulsions are avoided, as K$^+$PhS$^-$ disappears rapidly by oxidn (PhSSPh may be then separated by filtration through Al$_2$O$_3$).

11. After 6 h, the azide had disappeared but the iminophosphorane was not hydrolysed yet (the hydrolysis of the iminophosphorane is the slow step). Ph$_3$P cannot be compared to Et$_3$P in this connection, since Ph$_3$P does not significantly react with 7 at r.t.; as a matter of fact, Ph$_3$P has been utilised in former works,[7] but 78 h in refluxing toluene are required for a complete reaction with tertiary azide 7.

12. At present we have only evaluated the azide-vs.-ketone reactivity of the title reagents but a comprehensive study of their chemoselectivity is in project.