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# SODIUM BOROHYDRIDE IN DIMETHYL SULFOXIDE OR SULFOLANE. CONVENIENT SYSTEMS FOR SELECTIVE REDUCTIONS OF PRIMARY, SECONDARY AND CERTAIN TERTIARY HALIDES AND TOSYLATES

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The use of various metal hydrides as selective reducing agents has attracted a considerable amount of interest in recent years (2). It occurred to us that one unexplored possibility in this area might be to employ the relatively mild reducing agent sodium borohydride in $SN_2$ rate enhancing, polar, aprotic solvents to selectively displace halogens and other good leaving groups with hydrogen without affecting other reducible functional groups.

We wish to report that, indeed, sodium borohydride in dimethyl sulfoxide (DMSO) or sulfolane provides a very versatile and convenient method for removing primary, secondary and, in certain cases, tertiary alkyl and benzylic halides and tosylates in the presence of other groups including carboxylic acids, esters and nitro groups. The conditions and yields for a variety of such reductions are shown in Table I. Several features of these reactions make the procedure particularily attractive for synthetic applications. First, yields of hydrogenolysis products are good to excellent (53-98%) for the examples studied. Furthermore, unlike corresponding reductions with lithium aluminum hydride (3), essentially no olefin or other organic soluble side products were isolated or detected with the exceptions of benzhydryl chloride and bromide as discussed below. Also, 1,2-dibromides (i.e. entries 24 and 25) are reduced to the hydrocarbons in moderately good yields in contrast to lithium aluminum hydride reductions which afford only olefins (3). Thus, the method can be utilized to hydrogenate double bonds in sensitive compounds by way of bromination and reduction. Heterogeneous reactions appear to offer no problem as illustrated by the smooth reductions of several compounds of limited solubility (i.e. dodecyl derivatives, Table I).

TABLE I

Reduction of Halides and Tosylates with Sodium Borohydride in Dimethyl Sulfoxide or Sulfolane

| Entry | Compound | Solvent | Mole Ratio $NaBH_4$/Compound | T°C. | Time (Hours) | Yield Hydrocarbon[a] |
|---|---|---|---|---|---|---|
| 1. | 1-Iododecane | DMSO | 2 | 85 | 0.25 | 93.4 |
| 2. | | Sulfolane | 2 | 100 | 0.25 | 92.6 |
| 3. | 1-Bromodecane | DMSO | 2 | 85 | 1.5 | 93.5 |
| 4. | 1-Bromododecane | DMSO | 2 | 85 | 1.5 | 95.3 |
| 5. | | Sulfolane | 2 | 100 | 1.5 | 95.6 |
| 6. | n-Dodecyl Tos. | DMSO | 2 | 85 | 2.0 | 86.5 |
| 7. | | Sulfolane | 2 | 100 | 2.0 | 88.1 |
| 8. | 1-Chlorododecane | DMSO | 2 | 85 | 4.0 | 91.0 |
| 9. | | Sulfolane | 2 | 100 | 6.0 | 85.4[b] |
| 10. | ω-Bromoundecanoic acid | DMSO | 2 | 25 | 2.5 | 98[c] |
| 11. | p-Nitrobenzyl Bromide | DMSO | 2 | 25 | 1.5 | 95[c] |
| 12. | α,2,6-Trichlorotoluene | DMSO | 2 | 25 | 2.5 | 85.4[c] |
| 13. | | Sulfolane | 6 | 100 | 2.0 | 76.3[c] |
| 14. | 2-Iodooctane | DMSO | 3 | 85 | 1.0 | 81.7 |
| 15. | | Sulfolane | 3 | 100 | 1.0 | 80.6 |
| 16. | 2-Bromooctane | DMSO | 3 | 85 | 18 | 71.5 |
| 17. | 2-Bromododecane | DMSO | 3 | 85 | 18 | 85.6 |
| 18. | | Sulfolane | 3 | 100 | 18 | 68.6 |
| 19. | 2-Chlorooctane | DMSO[d] | 6 | 85 | 48 | 67.2 |
| 20. | Ethyl-2-Bromohexanoate | DMSO | 2 | 15 | 0.75 | 85.6 |
| 21. | α-Phenylethylbromide | DMSO | 3 | 85 | 1.0 | 78.7 |
| 22. | | Sulfolane | 3 | 100 | 1.0 | 81.7 |
| 23. | Cyclododecyl Tos. | DMSO | 3 | 85 | 24 | 53.9 |
| 24. | Styrene Dibromide | DMSO | 4 | 85 | 1.5 | 64.5 |
| 25. | | Sulfolane | 4 | 100 | 1.5 | 63.6 |
| 26. | Benzhydryl Chloride | DMSO | 6 | 35 | 24 | 61.4 (32.3)[e] |

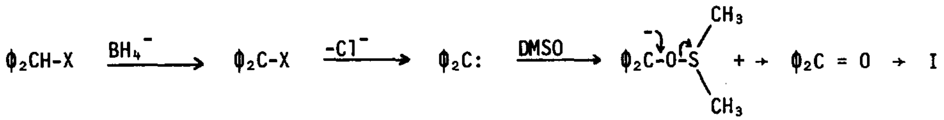
TABLE I (Cont.)

| Entry | Compound | Solvent | Mole Ratio $NaBH_4$/Compound | T°C. | Time (Hours) | Yield Hydrocarbon[a] |
|---|---|---|---|---|---|---|
| 27. | | Sulfolane | 3 | 100 | 1.0 | 94.4 |
| 28. | Benzhydryl Bromide | DMSO | 3 | 25 | 24 | 62.4 (33.1)[e] |
| 29. | | Sulfolane | 3 | 100 | 1.0 | 93.7 |
| 30. | Triphenylmethyl Chloride | DMSO | 6 | 85 | 1.5 | 90.4[c] |
| 31. | Cumyl Chloride | DMSO | 6 | 85 | 2.0 | 9.5 |
| 32. | | Sulfolane | 6 | 100 | 2.0 | 9.5 |
| 33. | | Sulfolane[f] | 1·1 | 100 | 2.0 | 32.4 (42.3)[h] |
| 34. | | Sulfolane[g] | 1·1 | 100 | 2.0 | 78.0 |

[a] yields determined by glpc analysis using standard solutions of the product (average of five determinations). [b] 9.7% starting material also recovered. [c] yield determined by isolation. [d] sealed tube reaction. [e] yield of benzhydrol. [f] oxidized with alkaline hydrogen peroxide prior to workup. [g] refluxed with valeric acid prior to workup. [h] yield of 2-phenyl-1-propanol.

After some initial experimentation, the conditions listed in Table I were chosen to minimize reaction times and maximize yields. When other reducible groups are present, it appears advisable to conduct the reactions at lower temperatures (i.e. 15-25°) to prevent undersirable side reductions. For example, while nitro groups are not reduced at 25°, nitrobenzene in dimethylsulfoxide at 85° is reduced to aniline and azobenzene (4). Primary iodides and benzylic bromides and chlorides often reacted quite vigorously even at 25° and it was sometimes necessary to provide cooling and to add the compound slowly (10-20 min.) to the borohydride solution. The reaction mixtures were worked up by diluting with water and extracting with cyclohexane or ether; yields were determined by gas-liquid chromatography and/or by isolation.

The reductions of benzhydryl chloride and bromide in dimethyl sulfoxide afforded substantial quantities of benzhydrol (I) along with expected diphenylmethane. Treatment of benzhydryl chloride with dimethyl sulfoxide under the same conditions resulted in recovery of starting material indicating that borohydride was implicated in formation of the alcohol. The probable pathway to I involves initial formation of diphenyl carbene which is oxidized to benzophenone (5) followed by reduction to benzhydrol. The corresponding reductions in sulfolane occurred readily to the hydrocarbon (entries 27 and 29).



$$\phi_2CH\text{-}X \xrightarrow{BH_4^-} \phi_2C\text{-}X \xrightarrow{-Cl^-} \phi_2C: \xrightarrow{DMSO} \phi_2\bar{C}\text{-}O\text{-}\overset{+}{S}(CH_3)_2 \rightarrow \phi_2C=O \rightarrow I$$

The reduction of cumyl chloride afforded only 9.5% cumene and no other cyclohexane or ether soluble products, including starting material or α-methyl styrene. We envision the initial reaction to be β-elimination of hydrogen chloride to form α-methylstyrene (and borane) which was subsequently hydroborated. To test this possibility, the reduction in sulfolane was repeated but the reaction mixture was oxidized with alkaline hydrogen peroxide prior to work up. In this case there was obtained 32.4% cumene and 42.3% 2-phenyl-1-propanol, the product expected from initial hydroboration of α-methylstyrene (1a). In view of this result, overall reduction of cumyl chloride to cumene in 78% yield was effected by refluxing the reaction mixture with valeric acid. We are exploring the scope of this procedure as a possible convenient method of reducing tertiary halides to hydrocarbons (i.e. by elimination, hydroboration and protonolysis in one step).

In conclusion, the reductions reported here provide alternative convenient procedures for selective and clean removal of halogens and tosylates and compliments well the method of Brown and Bell which uses sodium borohydride in aqueous diglyme to reduce halides capable of forming stable carbonium ions (1b). We are currently investigating the reducing capabilities of other metal hydrides in polar aprotic solvents.

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