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SUBSTITUTION VS. REDUCTION OF BENZYL HALIDES WITH THIOL AND SELENOL NUCLEOPHILES.

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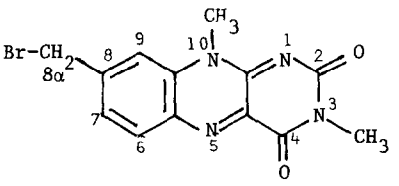
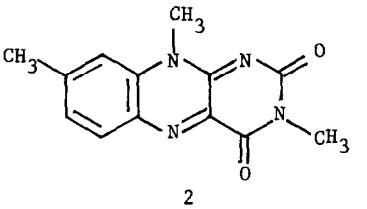
This work was induced by observations made during our research on isoalloxazines[1]. For comparison purposes we wanted to prepare 8α-cysteinyl 3,10-dimethylisoalloxazine by treating 8α-bromo 3,10 dimethylisoalloxazine 1 with L-cysteine hydrochloride in DMF (room temperature, 70h)[2]. We were surprised to find that, besides unreacted 1, the only isolable product was 3,8,10-trimethylisoalloxazine 2 : *no appreciable if any substitution occured on the benzylic carbon.*



1



2

Similarly, 1 gave 2 in high yield on reaction with two equivalents of ethylmercaptan in DMF and in the presence of two equivalents of triethylamine (room temperature, 1hr). *Again, no significant amount of substitution product could be detected.*

Since 8-bromomethylisoalloxazine 1 is a quite elaborated electron-deficient[3] benzyl bromide we decided to investigate the generality of such reduction reactions on different, more simple benzyl halides.

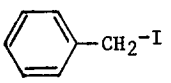
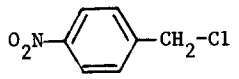
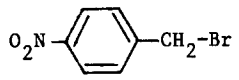
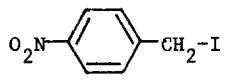
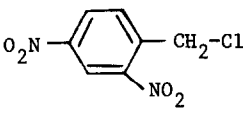
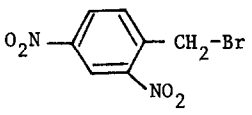
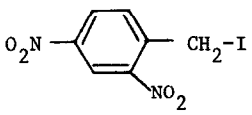
We report here our preliminary results which are shown in the Table.

In a typical experiment ethanethiol or thiophenol or selenomethanol (10^{-3} mole) and triethylamine (10^{-3}M) in anhydrous, degassed DMF (1-2 ml) are added to a degassed DMF (1-2 ml) solution of benzyl halide (10^{-3}M). A transient deep green or purple colour is observed in some cases, as well as formation of a colorless precipitate. The mixture is stirred under argon at room temperature for 1-2hrs, taken up with ether and 10% hydrochloric acid, washed and dried. After removal of the solvent, the crude product is purified by chromatography (SiO_2-Pentane/Ether).

Generally the overall yields are good to excellent, showing that the reactions proceed cleanly. Depending on the nature of the halogen atom, of the substitution pattern in the benzene ring and of the nucleophilic reagent, the reactions lead exclusively to the expected substitution product 3 (Table, entries 2a,2b,3a and 5b), to the reduction product 4 (Table, entries 5c,7a,7b and 7c) or to a mixture of the two (Table, entries 1c,3c,4a,4c,5a,5c,6a and 6c).

As a trend, we observe that 2,4-dinitrobenzyl halides give more reduction than do p-nitro derivatives. Even more striking is the effect of the halogen atom : iodides undergo reduction

Table : Overall yield in % and percentage ratios of (substitution / reduction, i.e. 3/4) products of benzyl halides with thiol-Et_3N and selenol-Et_3N nucleophiles.

	Benzyl halide	Nucleophile a $C_2H_5SH/(C_2H_5)_3N$	Nucleophile b $C_6H_5SH/(C_2H_5)_3N$	Nucleophile c $CH_3SeH/(C_2H_5)_3N$
1				87 (82:18)
2		86 (100:0)	85 (100:0)	
3		85 (100:0)		89 (57:43)
4		69 (20:80)		97 (20:80)
5		94 (97:3)	90 (100:0)	98 (5:95) (0:100) [10]
6		83 (55:45) (trace:0) [11] (65:35) [12]		72 (30:70) (38:62) [13]
7		73 (0:100)	55 (0:100)	75 (0:100)

much more efficiently than do bromides or chlorides. The nucleophilic reagent system also strongly influences the outcome of the reaction. For instance, on reaction with ethylmercaptan-triethylamine, p-nitrobenzyl bromide gives exclusively p-nitrobenzyl ethyl sulfide (substitution / reduction = 100 : 0), while the reaction with selenomethanol - triethylamine leads to a mixture of p-nitrobenzyl methyl selenide and p-nitrotoluene (substitution / reduction = 57 : 43).

The case of benzyl iodide (Table, entry 1c) is particularly interesting since reduction is observed even in the absence of a nitro substituent on the benzene ring.

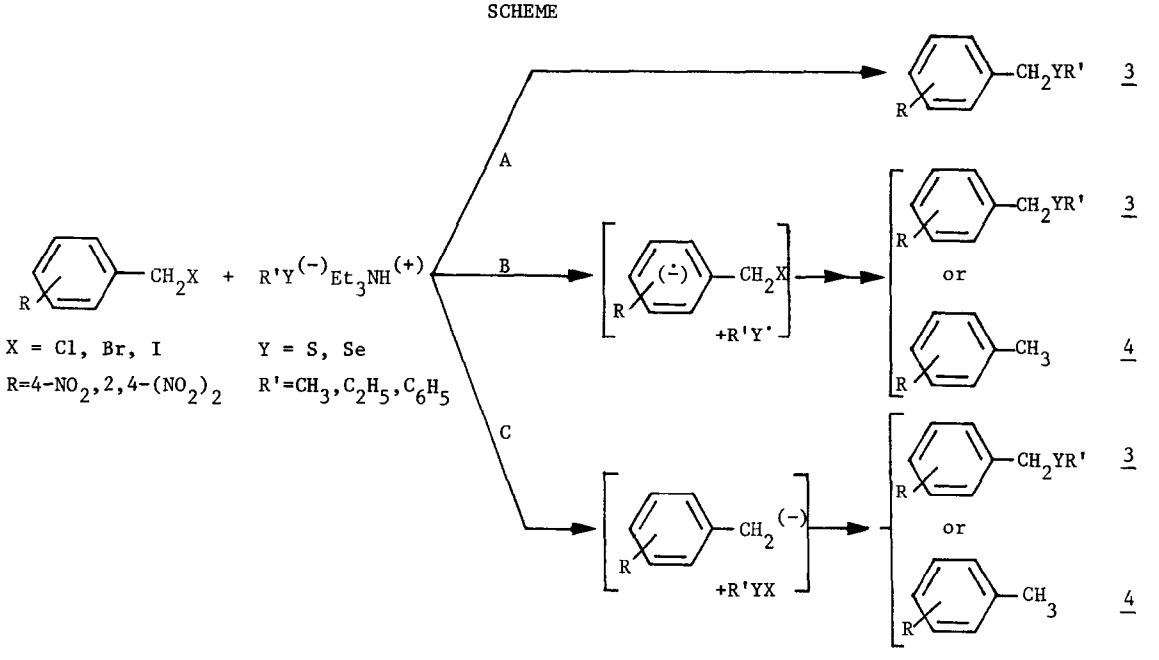
Our results show thus clearly that substitution is not the only reaction benzyl halides (especially electron-deficient ones) can undergo when opposed to good nucleophiles such as those used here. Replacement of an halogen atom by hydrogen occurs frequently and may even be the unique route followed in the most favourable cases.

This finding not only provides a general context for our observations in the isoalloxazine

series, but demonstrates also a new aspect of the reactivity of benzyl halides : these reduction reactions take place under very mild conditions, often desired in organic synthesis.

The above results can be rationalized in one of the three ways outlined in the Scheme. Path A represents most probably an S_N2 type displacement (carbenium ions implied by an S_N1 reaction would not be stabilized by electron-deficient phenyl rings).
Route B corresponds to a radical anion-free radical chain mechanism[4] initiated,as shown on the Scheme, by electron transfer from the nucleophile to the benzylic moiety:similar mechanism was recently proposed[5] for the replacement by hydrogen of tertiary nitro groups in various tertiary nitro compounds,observed under similar reaction conditions[6].
The third mechanism (Scheme, Path C) implies attack of a soft nucleophile on a soft halogen atom[7]. The resulting well stabilized carbanion can further react in two ways to give the observed products. Such a mechanism has been proposed for the reaction of α-haloketones with triphenylphosphine[8]. While α-chloroketones give α-ketophosphonium chlorides by usual nucleophilic displacement, α-bromoketones undergo debromination (reduction)[9] by attack of triphenylphosphine on the bromine atom.

SCHEME



Work is in progress in order to determine the scope of the reduction reaction[14] as well as to decide which one of mechanisms B or C (Scheme) or both are operative for this reaction.

References and notes.

1. a) L. Hevesi, Tetrahedron Letters, 1389 (1976)
   b) G. Bernard, Action du Sulfite sur la diméthyl-3,10, cyanomethyl-8 isoalloxazine, Mémoire de Licence (1976).
2. S. Ghisla and P. Hemmerich, FEBS Letters, 16, 229 (1971). The reaction of 8α-bromo tetraacetylriboflavin with cystein hydrochloride is described as giving the substitution product, i.e. 8α-cysteinyl tetraacetylviboflavin. However, no yield is reported and we suspect this was very low.
3. For a review, see T.C. Bruice, Models and Flavin Catalysis in "Progress in Bioorganic Chemistry" Eds. E.T. Kaiser and F.J. Kézdy, Wiley Interscience, Vol. 4, p1-87 (1976)
4. N. Kornblum, Angew. Chem. Int. Ed., 14, 734 (1975) and references cited therein.
5. N. Kornblum, S.C. Carlson, R.G. Smith, J. Amer. Chem. Soc., 100, 289 (1978)
6. For example, α,p-dinitrocumene was transformed to p-nitrocumene on treatment with sodium methanethiolate in DMSO at room temperature, see ref. 5.
7. G. Klopman in "Chemical Reactivity and Reaction Paths" G. Klopman Ed., Wiley Interscience, N.Y., 1974, pp.55.
8. I.J. Borowitz, P.E. Rusek and R. Virkhaus, J. Org. Chem., 34, 1595 (1969)
9. H.O. House, "Modern Synthetic Reactions" pp.698-700, W.A. Benjamin Inc., Menlo Park, California, 1972.
10. Obtained by using an excess of CH_3SeH. Therefore the 5:95 ratio should be regarded with caution. This abnormally high percentage of reduction (as compared to that of 2,4-dinitrobenzyl bromide with selenomethanol/triethylamine) might arise from reduction of the 2,4-dinitrobenzyl selenide first formed by the excess of nucleophile.
11. When the reaction is performed for 4hrs in the absence of triethylamine.
12. In a complex product mixture resulting from the use of C_2H_5SNa as nucleophile.
13. Halide and triethylamine mixed first, then CH_3SeH added.
14. For example, we think that the reaction of 9-bromo, 10-azidophenantrene with $LiAlH_4$ yielding phenantrene is closely related to those reported here (J.N. Denis and A. Krief, submitted for publication).
    Similarly, the reaction of 1,3-propanediselenolate with dibromomethane or diiodomethane does not produce the cyclic selenoacetal of formaldehyde, but rather , methylselenide derivatives in a complex mixture of products (L. Hevesi, results to be published).

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