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SODIUM BOROHYDRIDE REDUCTION OF SOME CARBOXYHYDRAZONES

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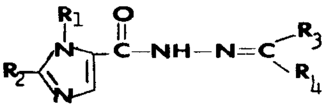
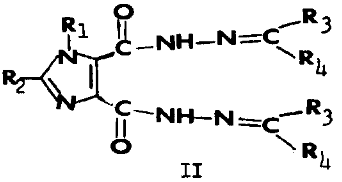
While seeking to prepare substituted imidazolecarboxyhydrazides, which have been of chemical and biological interest to us, it became necessary to explore a synthetic route which involved the reduction of imidazolecarboxyhydrazones:



I



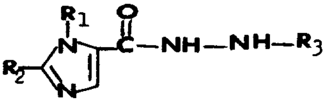
II

I & II: R_1=H ,CH_3; R_2=H , SH; R_3=H ,CH_3; R_4=CH_3 , Ph.

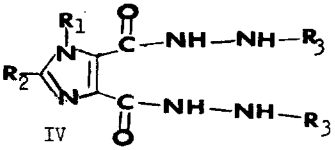
Catalytic hydrogenation using PtO_2 has been the most widely used procedure for the reduction of C=N. Although the method is known to be applicable in the reduction of oximes, it is not unambiguous with carboxyhydrazones. Moreover, catalytic hydrogenation suffers from the disadvantage in that the catalyst is quite sensitive to poisoning by sulfur or sulfur containing compounds, and in many instances, in order for such reduction to proceed, a relatively high temperature is necessary. This latter feature is particularly detrimental to the integrity of the heat-sensitive molecules.

Catalytic hydrogenation of I and II in various solvents, using PtO_2, at 60 psi H_2 gas and about 80° for 12 to 30 hr., afforded hydrazides only from those hydrazones which did not contain SH group or phenyl group. Using Raney nickel and catalysts such as Ru, Rh, and Pd on charcoal or on alumina likewise did not provide the desired hydrazides.

Attempts to reduce a few of the carboxyhydrazones by diborane in THF, either by generating B_2H_6 in situ or externally, were unsuccessful. The starting hydrazones were recovered unchanged (2). Various commonly employed metal hydrides were then evaluated for their reduction capabilities in a number of solvents. Tetrahydrofuran, ether, methanol, water, and DMF individually or in a mixture were tried. The experimental results indicated that only an aqueous solution of sodium borohydride was capable of reducing these hydrazones. The representative of a few hydrazides with their yield percent, melting point, and chemical shifts in δ are listed in Table I.



III



IV

III & IV: R_1=H,CH_3; R_2=H,SH; R_3= $CH(CH_3)_2$,CH_2Ph.

TABLE I

NMR peaks (in d6-DMSO)

	R_1	R_2	R_3	CH_3	CH_2	Ph	m.p.	% Yield
III	H	H	$CH(CH_3)_2$	1.0(d)			159-161	70
	CH_3	H	$CH(CH_3)_2$	1.05(d)			128-130	86
	H	H	CH_2Ph		3.95	7.21	157-158	90
	H	SH	CH_2Ph		3.75	7.00	120-123	67
	CH_3	H	CH_2Ph		3.97	7.25		70
IV	H	H	$CH(CH_3)_2$	1.02(d)			208-210	90
	H	H	CH_2Ph		3.86	7.28	186-189	70
	CH_3	H	$CH(CH_3)_2$	1.02(d)			58- 59	80
	CH_3	H	CH_2Ph		3.80	7.10	86- 88	76

In an effort to elucidate the mechanism of reduction of these carboxyhydrazones, reference was made to previous investigations (3,4) on the sodium borohydride reduction of C=N of 3 or 4 substituted 1-methylpyridinium iodide solution in DMF. The pyridinium salt apparently provides proper electrophilic sites in 2 and 6 positions of the ring for the hydride ion attack. The 1,2-dihydro derivative, however, could be reduced to the tetrahydro derivative by using a solution of $NaBH_4$ in water. In D_2O, this reduction was proved to proceed by an electrophilic attack of a proton on position 5 of the ring.

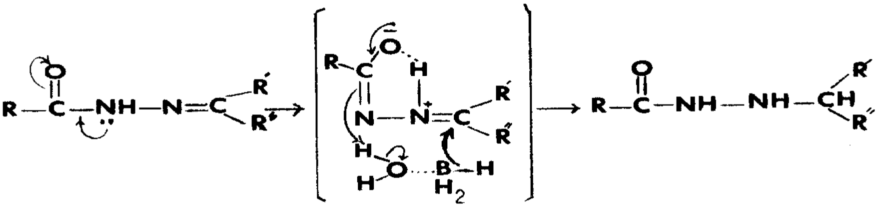
The rate of reduction of the carboxyhydrazones with various substituents (R_1=R_2=H; R_3=R_4=CH_3; R_3=H, R_4=Ph) in aqueous $NaBH_4$ solution did not seem to vary according to the electron donating or withdrawing properties of the groups. If the attacking species on C=N were hydride ions, the rate would be expected to be retarded with a methyl substituent and enhanced with a phenyl, as the latter group provides an electrophilic site by the resonance effect. This and the fact that the reductions did not proceed in DMF, prompted us to explore the possibility of involvement of water protons. Compound I (R_3=H, R_4=Ph) was subjected to reduction in a solution of $NaBH_4$ in D_2O, (excess D_2O was used to compensate for exchangeable NH hydrogens). The methylene group of the resulting product, imidazole-4-(2-benzyl)carboxyhydrazide (III: R_1=R_2=H; R_3=CH_2Ph) did not contain D as no C-D stretching frequency was detected at about 2300 cm^{-1} in its IR spectrum. This was further substantiated by observing a correct peak integral ratio of CH_2 to Ph in the NMR spectrum of the compound.

The nature of substituents in N_1 of the hydrazine moiety of the hydrazones were then evaluated for their possible effect on the C=N reduction. The compounds 1-acetyl-2-benzylidenehydrazine, CH_3-CO-NH-N=CHPh (V) and 1-benzoyl-2-benzylidenehydrazine, Ph-CO-NH-N=CHPh (VI) were found to undergo reduction to their respective benzyl derivatives by the analogous procedures used for I and II. This indicated that the reduction proceeds without a prime influence from the groups attached to C=O.

Finally, the influence of C=O group in this borohydride reduction needed to be examined. The hydrazones,1-phenyl-2-benzylidenehydrazine, Ph-NH-N=CHPh (VII) and 1-(2,4-dinitrophenyl)-2-benzylidenehydrazine, $(NO_2)_2$Ph-NH-N=CHPh (VIII) were subjected individually to the similar borohydride treatment indicated above. Neither compound was found to react and both were recovered unchanged. It was then assumed that the presence of C=O was necessary for such reduction. It should, however, be recognized that the effect of C=O on lowering electron density of C=N, due to conjugation of the lone pair of electrons on N_1, is not the major influencing factor, if any, in the reduction of carboxyhydrozones. Similar conjugation also occurs with the phenyl and 2,4-dinitrophenyl groups in VII and VIII, nevertheless, neither compound lends itself to reduction.

After observing the involvement of BH_4^-, H_2O, and C=O in the reaction, it was relevant to explore the influence of pH as the next step toward the elucidation of the mechanism of this reduction. Heating a mixture of I (R_1, R_2, R_3=H; R_4=Ph) with an aqueous solution of $NaBH_4$ at pH 5 did not provide the corresponding hydrazide. Since this was ascribed to a rapid decomposition of $NaBH_4$ in a low pH, I was treated with an aqueous solution of morpholine-borohydride adduct at pH 7.5 and pH 3.0. No reduction occurred even when the reaction mixture was subjected to a prolonged heating and the adduct was replenished from time to time. Apparently, due to the steric effect or otherwise, this adduct can not function analogous to H_2O-borohydride adduct discussed below. A similar resistance to reduction was found to be true when I was treated with an aqueous solution of $NaBH_4$ at pH 13. In this case probably the removal of H from N_1 does not favor the formation of the proposed cyclic intermediate (illustrated below) analogous to thiohydrazides reported recently (5).

Based on the results of the foregoing experiments, it is possible to envisage that the mechanism of reduction of carboxyhydrazones by an aqueous solution of $NaBH_4$ consists of the formation of H_2O-BH_3 adduct from which a proton and a hydride ion are given to the cyclic intermediate IX, as shown below:



IX

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