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METHYLENATION OF OPEN N-CHLOROAMIDES

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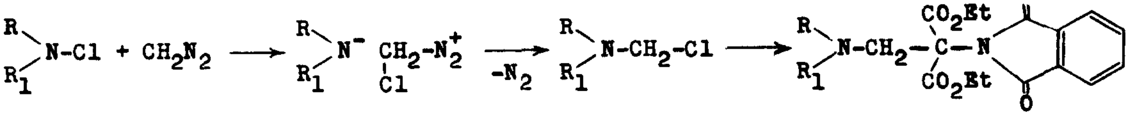
We have previously described the reaction of N-haloderivatives of cyclic amides or imides (hydantoins and succinimide) with diazomethane resulting in the insertion of a methylene group between the N-X linkage; the proposed reaction mechanism suggested that this methylenation might also occur with related types of compounds in which, like N-haloamides, the atom supporting the positive halogen lacks of orbitals for coördination with the donor diazomethane(1).

Subsequent experimentation showed that some organic hypohalites (e. g. t-butyl hypochlorite) can be successfully methylenated under appropriate conditions(2,3,4) while N-chloroamines failed to react(2).

We now report on the application of this reaction to N-chloroderivatives of N-substituted open-amides(5,6) and some results on the effect of the solvent and the behaviour of N-chloroamides containing the N-H group.

The methylenations were performed according to the directions already published(1). After addition of diazomethane (in benzene) to the N-chloroamide (I; in dioxane at 5-10º) until persistent yellow colour of the solution, diethyl sodium phthalimidomalonate (in N,N-dimethylformamide) was added to convert the N-chloromethyl-derivative (III) into the compound (IV) of easier isolation; after 12 hr at room temperature, compound (IV) was isolated and characterized by analytical and NMR data.



(I) (II) (III) (IV)

TABLE I. Methylenation of N-substituted-N-chloroamides

N-Chloroamides (I)		Product (IV)	
R	R_1	% Yield	M.p. ºC
acetyl	methyl	53	151.5-152
idem	benzyl	84	129-129.5
idem	cyclohexyl	37	165-166
benzoyl	methyl	80	181.5-182.5
p-tosyl	idem	51	159-159.5
idem	ethyl	68	161-161.5
idem	isopropyl	70	171-172
idem	t-butyl	22	146.5-147.5
idem	cyclohexyl	60	165-166
idem	benzyl	57	149-150.5

The previous results with cyclic N-halo-amides or imides(1) and the now reported using open N-substituted-N-chloroamides (Table I) point out the wide applicability and the preparative usefulness of this methylenation reaction.

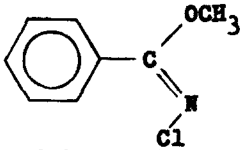
Methylenation experiments with N-chloro-N-methyl-p-tosylamide in different solvents (with diazomethane in benzene solution) showed that the consumption of positive halogen is rapid and complete in all cases but the yield of compound (IV) is strongly influenced by the nature of the solvent. Dioxane (Table I), diethyl ether and benzene furnish similar good yields while hydroxylic (t-butanol) or high polar solvents (N,N-dimethylformamide or nitrobenzene) lead to negligible yields (0-8 %).

An interesting situation is presented by unsubstituted N-haloamides in which methylenation may occur at the N-X, N-H or O-H (tautomer) linkages.

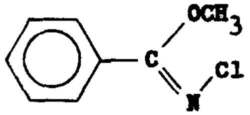
Stieglitz(7) examined the reaction of N-chlorobenzamide (and its m-nitroderivative) with diazomethane and, using classical methods, concluded that it leads to the methyl N-chloroimidobenzoate and that no methylenation of the N-H bond takes place.

We have studied this reaction using equimolecular amounts of N-chlorobenzamide and diazomethane in benzene as solvent. The NMR spectrometry directly applied to the reaction solution and after treatment with aqueous sodium thiosulphate in acid medium (removal of positive halogen and hydrolysis of the imidoester to the ester) demonstrated that methylenation of the N-H and O-H bonds (approx. ratio 1:2) takesplace, with formation of N-chloro-N-methylbenzamide and methyl N-chloro-imidobenzoate respectively. On the other hand, no reaction at N-X bond occurs since the spectrum lacks of signals in the N-CH_2-Cl region.

The NMR spectrum recorded immediately after the end of the reaction shows a peak at δ 3.20 ppm (O-CH_3) which is gradually replaced (often incompletely) by another one at 3.60 ppm. This change is interpreted in terms of conversion of the initially formed methyl N-chloro-imidobenzoate (a) into its geometrical isomer (b). The shown configurations are assigned on the basis of the chemical shifts of the methoxyl group; closer spatial proximity of the chlorine atom in (b) must produce a deshielding effect. Stereomodels indicate that this is the more stable isomer due to conjugation of the benzene ring with the double bond; this conjugation is sterically inhibited in isomer (a)$^{(8)}$.



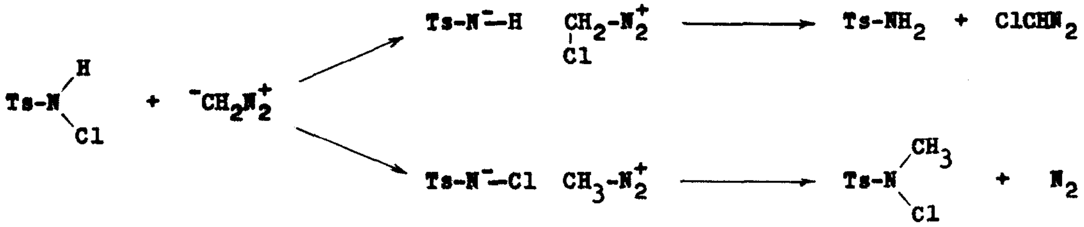
(a)



(b)

Fractional distillation of the reaction mixture furnished an oil b.p. 64-67° at 0.3 mm; the NMR spectra (in CCl_4 or C_6H_6) indicate that it is the compound (b) but still containing 15 % of (a) according to the relative areas of the O-CH_3 signals.

The reaction of N-chloro-p-tosylamide under similar conditions gives a complex mixture of products. From the reaction medium crystallizes out a compound identified as p-tosylamide (ca. 30 %) by mixed m.p. and infrared spectra; furthermore, NMR spectrum of the filtrate reveals the presence of a small amount of N-chloro-N-methyl-p-tosylamide. The formation of these products is interpreted as follows:



Ts= p-tosyl

REFERENCES

(1) R. A. Corral and O.O. Orazi, Tetrahedron Letters, 1693 (1964).

(2) R. A. Corral, O. O. Orazi and L. Trippetta, Anales asoc. quím. Argentina, 54, 221 (1966).

(3) H. Baganz and H. J. May, Angew. Chem., 78, 448 (1966); Chem. Ber., 99, 3766 (1966).

(4) G. L. Closs and J. J. Coyle, J. Amer. Chem. Soc., 87, 4270 (1965); working at -100º obtained good yields of halodiazomethanes.

(5) These results were taken from the Doctoral thesis of H. S. (National University of La Plata, 1967).

(6) Very recently, A. Schönberg and E. Singer, Chem. Ber., 101, 3445 (1968), obtained the N-diphenylmethylen-derivatives of phenyl- and p-tolyl-sulphonamide reacting the corresponding N,N-dichloro-sulphonamide with diphenyldiazomethane; according to the authors these reactions probably take place through methylenations of the type described in ref. (1).

(7) J. Stieglitz, Amer. Chem. J., 29, 49 (1903); J. Stieglitz and R. B. Earle, ibid. 30, 399 (1903).

(8) L. Birkofer and H. Dickopp, Chem. Ber., 101, 2585 (1968), have used the same arguments for similar cases.