Tetrahedron Letters,Vol.24,No.26,pp 2685-2688,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

UNUSUAL BEHAVIOUR OF N-BROMOSUCCINIMIDE. CONVERSION OF N,N-DIMETHYLAMIDES TO N-METHYL,N-SUCCINIMIDOMETHYLAMIDES

C. Caristi, G. Cimino, A. Ferlazzo, M. Gattuso and M. Parisi

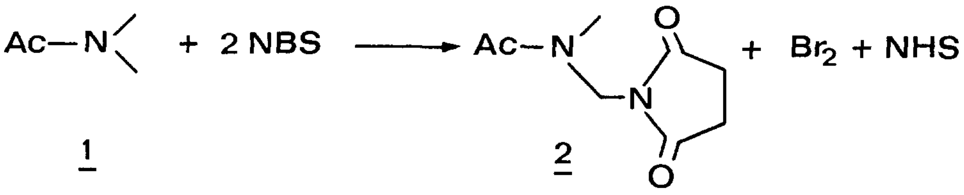
Dipartimento di Chimica Organica e Biologica - Università
Piazza S. Pugliatti, 98100 Messina (Italy)

Summary. N,N-Dimethylamides 1 are converted by NBS to the N-succinimidomethylamides 2 in an almost quantitative yield. The intermediacy of bromomethylderivatives 3 which further react with NBS to give 2 is demonstrated.

Succinimidyl derivatives were exceptionally obtained in the reactions of N-bromosuccinimide (NBS) different from the addition[1] of this reagent to the double bond, and only few examples were described.[2] Furthermore, elusive 2-succinimido-1,3-dioxolanes were recently observed as intermediates in the reaction of NBS on some bicyclic 2-aryl-1,3-dioxolanes.[3]

Although some suggestions were made in order to explain the formation of the above unusual products, the overall course of the reaction still remains obscure.

We now wish to report the results of the reaction of NBS with the N,N-dimethylamides 1 which leads to the succinimidomethylamides 2[4] in an almost quantitative yield.



a, Ac = PhCO
b, Ac = pMeO-C_6H_4CO
c, Ac = mNO$_2$-C_6H_4CO
d, Ac = $PhSO_2$
e, Ac = EtOCO
f, Ac = MeCO

The reaction, carried out in boiling carbon tetrachloride in the presence of benzoyl peroxide, requires a two to one molar ratio of NBS to amides 1. During the course of the reaction free bromine was liberated together with succinimide and a viscous reddish-brown oil. The bromine was continually distilled off while the separated oil disappeared. At the end of the reaction chloroform was added and the reaction mixture was treated with concentrated Na_2SO_3 solution. The organic layer, evaporated under vacuum, gave 2a-e in an almost quantitative yield; the succinimidyl derivative 2f was recovered in a 70% yield after column chromatography.[5]

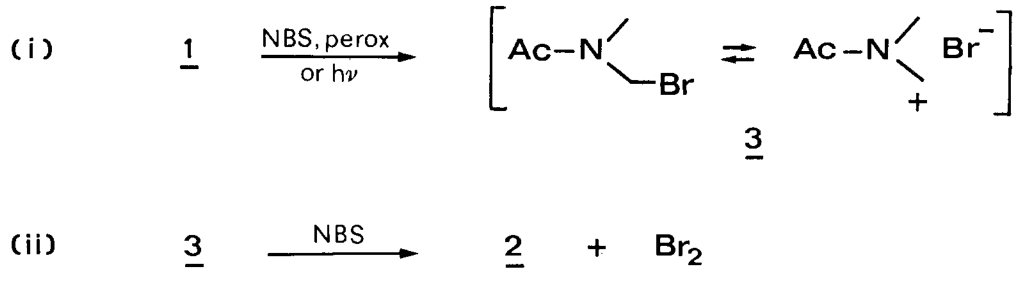
The ^1H nmr spectra[6] of 2 clearly indicate the presence of a succinimido moiety (2.66-2.82 δ) attached to an amido methyl group (4.90-5.15 δ). In addition the ir spectra[8] show a peak near 1770 cm^{-1} which well accords with an imide carbonyl absorption.

In principle, the N-bromomethyl derivatives 3 may be expected to be the products of a "normal" bromination of the alkylamides 1 by NBS.[2d] One may also predict that these compounds are strongly reactive intermediates and will further react very quickly.[9]

Therefore the course of the reactions of 1a,e with NBS, both in refluxing carbon tetrachloride in the presence of benzoyl peroxide and under photolysis conditions,[10] was ^1H nmr monitored. The analysis of the spectra of samples taken out from the above reaction mixtures reveals the presence in solution of the bromomethylamides 3a,e.

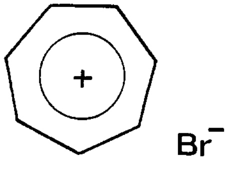
Moreover, independently synthesized[11] 3a,e easily react at room temperature with NBS, but not with succinimide, to give 2a,e and free bromine.

The above results point out that the formation of the succinimidyl derivatives 2 arises from two consecutive reactions: (i) a radical bromination[13] of 1 by NBS which leads to the bromoderivatives 3, and (ii) a fast reaction of 3 with the excess of NBS to give 2 and free bromine.



It is interesting to emphasize that bromomethylamides are effective sources of amidocarbonium ions and are therefore used as α-amidoalkylating agents towards sufficiently active substrates.[14] This suggests that the conversion of 3 to 2 may be regarded as an electrophilic substitution at the imidic nitrogen of NBS promoted by an ionic attack of 3, which seems like one of the proton in the reaction of NBS with HBr.

Although no direct evidence was presented, the elusive bromides 4 and 5 were previously claimed as intermediates in the reaction of NBS with cycloheptatriene[2a] and some alkylamides[2d] respectively, and it was suggested that these intermediates would react with NBS or succinimide to give succinimidyl derivatives.[15] Moreover the ^{1}H nmr monitored reaction of perbromide 6 with NBS showed the presence in solution of an elusive succinimidyl derivative.[3]



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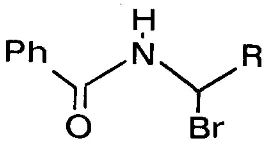

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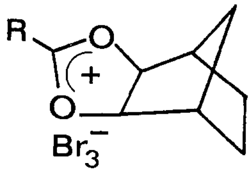
a, R = Ph

b, R = Me



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R = p-NO_2-C_6H_4

Owing to the close analogy between the conversion of 1 to 2 and the above reported succinimidyl derivatives formation, it appears that, generally, the succinimidation at saturated carbons by NBS is strictly related to the effective halogen "mobility" of the intermediate bromoderivatives.

Further investigations are currently in progress for confirmation of the above suggestion.

Acknowledgement: We are grateful to the C.N.R. (Rome) for financial support.

REFERENCES AND NOTES

1) F. Lu, Y.M.A. Naguib, M. Kitadini and Y.L. Chow, Can.J.Chem., 57, 1967 (1979), and references therein.

2) a) H.L. Dryden, jr. and B.E. Burgert, J.Am.Chem.Soc., 77, 5633 (1955); b) D.G. Markees, J.Org.Chem., 23, 1490 (1958); c) L.L. Braun and J.H. Looker, ibid., 26, 574 (1961); d) C. Caristi, G. Cimino, G. Dugo and M. Gattuso, Atti Soc. Peloritana Sci.Fis. Mat.Nat., 24, 65 (1978).

3) A. Bazbouz, H. Christol, J. Coste, F. Pietrasanta and F. Plenat, Tetrahedron, 36, 2757 (1980).

4) Melting points: 2a 116-118, 2b 149, 2d 134 °C. Compounds 2c, 2e and 2f are viscous oils. Satisfactory elemental analyses were obtained for all the compounds described.

5) Purification was carried out on a Merck silica gel 60 column, eluent EtOAc/Et_2O.

6) ^{1}H nmr in CDCl$_3$: 2a δ 7.47(bs, 5H), 5.15(s, 2H), 2.97(s, 3H), 2.70(s, 4H); 2b δ 7.9-6.8 (m, 4H), 5.13(s, 2H), 3.92(s, 3H), 2.97(s, 3H), 2.73(s, 4H); 2c δ 8.5-7.3(m, 4H), 5.17(s, 2H), 3.03(s, 3H), 2.80(s, 4H); 2d δ 7.4-8.0(m, 5H), 4.90(s, 2H), 2.98(s, 3H), 2.66(s, 4H); 2e δ 5.08(s, 2H), 4.20(q, J=7.4, 2H), 3.00(s, 3H), 2.77(s, 4H), 1.28(t, J=7.4, 3H); 2f[7] δ 5.13 (s, 0.9H), 5.08(s, 1.1H), 3.12(s, 1.35H), 2.93(s, 1.65H), 2.82(s, 2.2H), 2.77(s, 1.8H), 2.42 (s, 1.65H), 2.12(s, 1.35H).

7) The nmr spectrum of 2f shows a doubling up of signals due to the restricted rotation around to the C-N bond of the amide group.

8) Ir ν (cm^{-1}): 2a 1779(w), 1718, 1647; 2b 1774(w), 1695); 2c (in CHCl$_3$) 1780, 1705, 1635; 2d 1763(sh), 1715; 2e 1778(w), 1695; 2f 1775(w), 1695, 1638.

9) G.A. Olah and P.R. Schleyer, "Carbonium Ions", vol. IV, p. 1670, in "Reactive Intermediates in Organic Chemistry", Wiley-Interscience, 1973.

10) The reaction was carried out in a Hanovia photochemical reactor at 10 °C, under nitrogen atmosphere, using a Pyrex glassware with a medium pressure arc tube emitting predominantly at 254-366 nm.

11) Compounds 3a,e were prepared analogously to the reported synthesis of S-ethyl, N-bromomethyl, N-methylthiocarbamate.[12] They are very reactive oils and their purification is difficult to obtain. The yield (nmr-based) was ca. 70% and 90% for 3a and 3e respectively. ^{1}H nmr in CCl$_4$: 3a δ 7.4(bs, 5H), 5.33(s, 2H), 3.05(s, 3H); 3e δ 5.33(s, 2H), 4.08 (q, J=7.0, 2H), 2.88(s, 3H), 1.40(t, J=7.0, 3H).

12) W. Wierenga and J. Woltersom, *J. Org. Chem.*, 43, 529 (1978).

13) The reaction (i) proceeds by a radical chain mechanism in which the succinimidyl radical acts as chain carrier. This arises from the following observations: a) the reaction is greatly accelerated by the presence of a catalytic amount of benzoyl peroxide and also takes place under photolysis conditions; b) during the conversion of 1 into 2 insoluble 1:1 dimethylamides:Br$_2$ complexes separate as reddish viscous oils; these complexes are formed when hot solutions of 1 in CCl$_4$ are allowed to react with bromine: they are quite stable and do not evolve into bromination products even under prolonged refluxing with an excess of free bromine in the presence of benzoyl peroxide; however they react with NBS to afford 3; c) no variation in the yield of succinimidyl derivative 2a is observed if the reaction of 1a with NBS is carried out in the presence of ethylene or ethylene oxide as Br$_2$ and HBr scavengers respectively.

14) H.E. Zaugg, *Synthesis*, 49 (1970).

15) By contrast, a direct attack on the imidic nitrogen of NBS by a benzyl radical was proposed to justify the formation of the succinimidyl derivative in the reaction of p-bromophenylbenzyl ether[2c] with NBS.

(Received in UK 14 April 1983)