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INTRAMOLECULAR RADICAL REACTIONS IN α-HALOMETHYL SUBSTITUTED PIPERIDINE SULFONAMIDES

by

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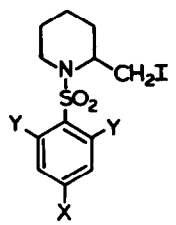
Interaction of a radical centre with systems containing π-electrons is fairly well documented[1]. Recently the 1,4 rearrangement of the p-tolyl group of a p-toluenesulfonamide to a methylene radical in certain benzo[f]quinoline derivatives was shown to belong to this reaction type[2]. We now wish to report on the remarkable efficiency and extreme versatility of this novel rearrangement in simple piperidines 1. Depending on the nature of the aryl substituent and the reaction conditions chosen the process gives rise to 1,6 addition products 2, rearranged amines 3 and some reduced material 4 in nearly quantitative yield.



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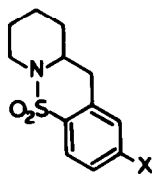

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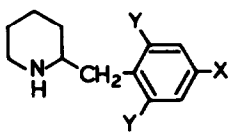

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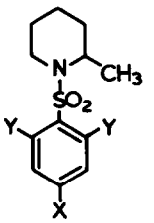

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a) X = $-CH_3$ Y = -H
b) X = -H Y = -H
c) X = $-OCH_3$ Y = -H
d) X = -Cl Y = -H
e) X = $-CH_3$ Y = $-CH_3$

Preparation of the iodides 1a - 1e was carried out via reaction of 2-hydroxymethylpiperidine and the appropriate arylsulfonyl chloride to form the N,O-disulfonyl

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derivatives. The latter compounds were reacted with NaI/acetone to afford the desired materials. According to the ^{1}H-NMR data all of the piperidine sulfonamides 1a - 1e appear to possess a chair conformation in which the iodomethyl group occupies an axial position[3] for which an average CH_2I-Ar distance of approximately 1.6 Å can be estimated.

Upon reflux of 1a - 1d in benzene with azobisisobutyronitrile (ABIN) as a radical initiator[4] in the presence of 2.7 equiv. tributylstannane[5] (SnH) a rapid reaction ensued after which three products were formed in yields as indicated in Table I. From GLC monitoring the reaction appeared to be clean and almost quantitative and upon carrying out kinetic experiments[6] in anisole at 96 ± 1°C the following apparent first order reaction constants and compositions of reaction products were obtained (Table I). The kinetic parameters were calculated with respect to the disappearance of the iodides.[7]

TABLE I

	k-obsd.	% 2	% 3	% 4
1a	$(4.48 \pm 0.10) \times 10^{-5}$ s^{-1}	45	32	23
1b	$(3.42 \pm 0.02) \times 10^{-5}$ s^{-1}	48	27	25
1c	$(5.17 \pm 0.57) \times 10^{-5}$ s^{-1}	40	37	23
1d	$(3.18 \pm 0.06) \times 10^{-5}$ s^{-1}	34	41	25

From these data it follows that the nature of the phenyl substituent does not affect greatly the course of the reaction. This fact again is best compatible with a radical process[8].

Upon increasing the ratio SnH/iodide more of the reduced compound 4 is formed. A remarkable alteration in product ratio, however, is noted upon variation of the reaction temperature (Table II, Isolated yields).

TABLE II

Compound	Solvent	Temperature	Time	% 2	% 3	% 4
1a	anisole	22°C	24 h	68	-	30
1a	anisole	86°C	7 h	46	30	23
1a	anisole	152°C	2 h	30	56	13
1a	diphenylether	190°C	0.5 h	26	64	9

Thus it appeared possible to control thermally the product compositior within considerable limits. Furthermore, the efficiency of the process at room temperature (r.t.) is to be noted.

The products formed may be tentatively explained via the mechanism indicated in Scheme I. Both 1,5 and 1,6 intramolecular radical additions[9] take place at

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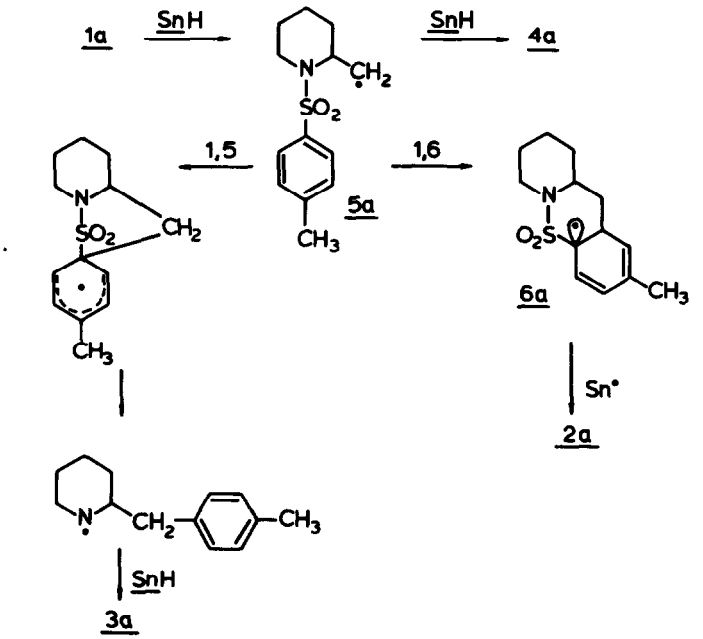
80°C. The former type of reaction is conformationally favored at higher temperature in view of the shortened average distance between the methylene radical and aromatic ring while at r.t. the transition state for 1,6 addition is more easily accommodated. After heating a solution of 2a in diphenylether for 6 h at 190°C no changes were observed, thus rendering the possibility of a final 2a → 3a rearrangement unlikely. The proposed mechanism (Scheme I) also indicates that hydrogen transfer to the initially formed methylene radical 5a to form 4a most probably takes place via reaction with the tin hydride.

SCHEME I



On the other hand once 5a is formed via halogen abstraction from 1a by the Sn-radical the rearrangement and insertion processes may well be proceeding without competitive formation of 4a. This assumption could be verified by carrying out the reaction with a different source of Sn-radicals.

Upon refluxing 1a in benzene for 21 h with hexabutylditin in presence of di-tert-butylperoxalate as an initiator the formation of 4a was completely suppressed and yields of 64% of 2a and 25% of 3a were obtained. The source of the hydrogen atoms necessary to form 3a has not been established unequivocally but they may originate in part from the phenyl intermediate 6a.

Finally, in order to determine the effect of blocking the ortho position

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of the phenylsulfonyl substituent, the SnH-reaction of the mesitylene derivative 1e was investigated. Indeed it was found that none of the corresponding 1,6-adduct was formed. The sole product, however, was the rearranged amine 3e while no trace of the also expected 4e was detected. This could tentatively be explained by assuming an interaction of the radical intermediate with the aromatic substituent in such a way that steric factors prevent effective hydride transfer by the bulky tin hydride[10].

In summary the reactivity of α-halomethylpiperidine sulfonamides constitutes a novel type of radical reaction. Further results on the influence of variations of the aryl substituent are reported in the accompanying communication

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1b) C, Rüchardt and R. Hecht, Chem.Ber., 98, 2471 (1965) and preceding papers.

2) R. Loven and W.N. Speckamp, Tetrahedron Lett., 1567 (1972).

3a) Data taken from ^{1}H-NMR analysis. Similar results were obtained in a variety of other α-substituted piperidine sulfonamides. P.P.M. Rijsenbrij, forthcoming Ph.D. thesis, University of Amsterdam. The same effect is observed in N-acetyl-2-methylpiperidines[3b].

3b) R.R. Fraser and T. Bruce Grindley, Tetrahedron Lett., 4169 (1974).

4) It was found later that the use of a radical starter like ABIN is not necessary in this type of reaction, fairly similar results being obtained by mere stirring of 1a at 40°C in benzene with 2·7 eq. of SnH. J.J. Köhler and W.N. Speckamp, results to be published.

5) L.W. Menapace and H.G. Kuivila, J.Am.Chem.Soc., 86, 3047 (1964).

6) At regular intervals 1 µl aliquots were removed from the reaction solution and determined via GLC on a Varian aerograph 2100, all-glass system, N_2. Flow 44 ml/min, gas chrom Q 80-100 M, OV-17 5% analytical column with temperature programming from 100-250°C. Relative peak areas were obtained by use of a Kip-recorder BD-12 with integrator and with phenanthrene as an internal standard. Reactions were carried out in duplicate.

7) Data were analyzed by the least square method with correlation coefficients varying from 0.9877 to 0.9967. Traces of H_2SO_4 in the reaction solution had an inhibitory effect on the rate of the reaction causing a decrease in the magnitude of the K-values, the product distribution being unaffected. Actual yields of products ranged from 93% to 100% but for presentation all have been normalized to 100% to show relative product yields.

8) W.A. Pryor, W.H. Davis Jr. and J.H. Gleaton, J.Org.Chem., 40, 2099 (1975).

9) A.L.J. Beckwith and W.B. Gara, J.Chem.Soc.Perkin Trans 2, 795 (1975).

10) In the accompanying communication the steric factors involved in hydride transfer are discussed.