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DECOMPOSITION OF ARILAZIDES AND p-TOSYLAZIDE BY THF/n-BUTYLLITHIUM. A NEW SOURCE OF DIAZOMETHANE

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Abstract - Variously substituted arylazides, as well as p-tosylazide, when allowed to react at room temperature with THF previously treated with n-butyllithium, undergo a rapid decomposition affording the corresponding amines and formamides, together with diazomethane. This diazo transfer (with deformylation) reaction is thought to involve the enolate of the acetaldehyde generated by the known cycloreversion of THF in the presence on n-butyllithium.

Decomposition of arenesulphonylazides by compounds containing an active methylene group (e.g., 1,3-dicarbonyl-, 1,3-disulphonyl-derivatives, etc.) in the presence of a base is well known.[1] This reaction, which involves the enolate ions of the above cited compounds, is called the diazo transfer reaction and represents a useful method for the preparation of the corresponding diazo-compounds.

When a single carbonyl group is present (mono-ketones), this procedure cannot be utilized, a further activation being required, unless this is provided by the presence of an aromatic residue. Otherwise, the additional activation can be obtained by converting the ketone into an α-formyl ketone before treating it with tosylazide. In this case the diazo transfer reaction is accompanied by deformylation, so that α-diazoketones are obtained.

In the case of simple aldehydes such as acetaldehyde, however, no experiments have been reported, very likely because of further complications (base-catalyzed aldol condensation and polymerization) arising when the synthesis of the corresponding enolate ions is attempted.

Since more recently Bates,[2] Tomboulian,[3] and then Jung[4] have shown that lithium enolate of acetaldehyde can be generated without aldol condensation and polymerization by cycloreversion of tetrahydrofuran (THF) in the presence of n-butyllithium, we undertaken an investigation on the behaviour of arylazides and p-tosylazide under these new conditions. Thus a number of arylazides, as well as p-tosylazide, have been allowed to react at room temperature with tetrahydrofuran previously treated with n-butyllithium under a nitrogen atmosphere for ca. 16 hrs. Under these conditions all the n-butyllithium would be converted into lithium enolate of the acetaldehyde and ethylene.[4] Except for the azides having no electron-withdrawing groups, the decomposition goes rapidly to completion (within ca. 0.5 hr), and, after quenching the reaction solution with aqueous NH_4Cl (gas evolution was observed at this stage), formamides corresponding to the starting azides, together

with variable amounts of the amines, can be isolated (Table).

TABLE

Isolated yields of amines, formamides, and methyl benzoate* in reactions of organic azides with THF/n-butyllithium at room temperature.

Y in Y-N_3	Y-NH_2%	Y-NH-CHO%	$C_6H_5COOCH_3$%
C_6H_5	none	33	25
p-$CH_3C_6H_4$	none	22	18
o-$MeSO_2C_6H_4$	10	87	70
o-$EtSO_2C_6H_4$	9	86	70
p-$NO_2C_6H_4$	15	little	little
o-$NO_2C_6H_4$	24	60	48
p-Ts	5†	65†	40**

* Reactions quenched with benzoic acid.

** In this case both methyl benzoate and N-methyl-N-formyl-p-toluenesulphonamide were isolated by quenching directly the reaction solution with benzoic acid. The reported value refers to the overall trapped diazomethane (both the above compounds) expressed as methyl benzoate.

† See Experimental.

The formamides are the only or the main isolable products (>85% yields in the case of o-$MeSO_2$- and o-$EtSO_2$-$C_6H_4N_3$).

However, when the same arylazides are dissolved in THF, and then n-butyllithium (in n-hexane) added, no appreciable formation of the formamides is detected (TLC) even after longer reaction times, confirming that the reactive species for the formamide formation is not n-butyllithium, but a different species generated by a preliminary interaction of n-butyllithium with THF.

By treating o-nitroformanilide with THF/n-butyllithium and then with aqueous NH_4Cl in conditions identical to those used in the reaction of o-nitrophenylazide, a mixture of the starting o-nitroformanilide and of o-nitroaniline in relative amounts similar to those isolated from the reaction of o-nitrophenylazide was recovered.

However, the other formamides (o-methylsulfonyl- and o-ethylsulphonyl-formanilide, as well as N-formyl p-toluenesulphonamide) were not appreciably affected by a similar treatment.

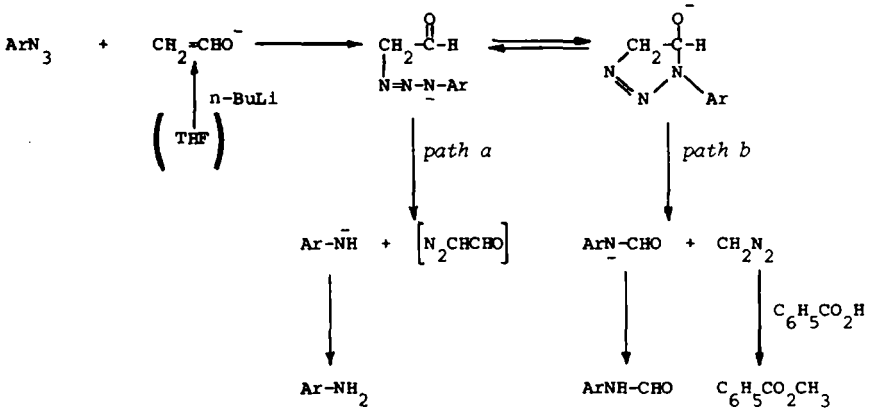
On the other hand, when the reactions of azides are quenched with benzoic acid (ca. 2.5 moles compared to the starting n-butyllithium) again gas evolution is observed (N_2) and methyl benzoate can be isolated together with the cited amines and formamides, thus revealing the simultaneous formation of diazomethane. Besides, an additional formation of methyl benzoate is also obtained by using a final trap containing benzoic acid in THF (the reactions are carried out under a nitrogen steam).

In a different procedure, the reaction mixture was warmed at ca. 50°C (bath), once again u-

sing a nitrogen steam, and the volatile fraction entirely collected into a trap containing benzoic acid in THF, as described above. Lower yields of methyl benzoate were isolated in these cases, presumably because a not proper apparatus[5] was used (see Experimental).

In our view, a possible mechanism of reaction accounting for the above results is that reported in the Scheme.

Scheme



Only one of the possible electromeric structures is indicated in each case.

The enolate of the acetaldehyde would attack the azido-group affording the triazene and/or the triazoline salt intermediate, from which formamides, diazomethane and amines would form.

The route (b) would afford diazomethane and the formamide, and would correspond to the scheme previously proposed for ß-oxoaldehydes and some other cases[1] in order to explain a similar kind of azide decomposition (diazo transfer with deformylation).

On the other hand the isolated amines, except for some cases (e.g., o-nitroaniline: see above), could arise entirely or mainly from a similar interaction of the azide with the enolate of the acetaldehyde [route (a)], as in the more usual scheme of the diazo transfer reaction.[1]

If so, diazoacetaldehyde would form together with the amine, but we were not able to isolate or trap it (through benzoic acid). This, however, could also be due to the known instability of diazoacetaldehyde both in alkaline and acidic medium.[6]

The relative percentages of formamides (and diazomethane) compared to the amines are clearly depending on the substituent in arylazide.

Although the presence of electron-withdrawing groups enhances the rate of decomposition of the azides (as required by the electrophilic role of the azide in such a reaction), as well as (generally) the overall yields of the isolable products, when such groups are present, however, appreciable amounts of amines are also formed. The optimum yields of the formamides, as well as of diazomethane, are observed in the case of o-$MeSO_2$-, and o-$EtSO_2$-$C_6H_4N_3$.

Further mechanistic investigations are in progress in order to ascertain the effective role of the route a in the amine formation, as well as its dependence on the effect of the substituents in arylazide.

However, besides the mechanistic aspects, this reaction seems to be worthy of consideration also from a synthetic point of view. In fact, by choosing suitable starting azides, diazomethane can be obtained in satisfactory yields (70% from both o-$MeSO_2$- and o-$EtSO_2$-$C_6H_4N_3$). Such yields are

of comparable order of magnitude with respect to those generally obtained from various N-nitroso-N-methyl compounds (or other precursors) utilized to this aim.[7]

Thus, the reaction described here may constitute a new valid approach to the synthesis of diazomethane. Furthermore, the same procedure could in principle also be extended to the synthesis of other diazoalkanes by generating the appropriate enolates from suitably substituted starting tetrahydrofurans and n-butyllithium,[2] or from other sources (e.g., from trialkylsilyl enol ethers[8]).

EXPERIMENTAL

MPS taken on an Electrothermal apparatus were uncorrected. ^{1}H NMR spectra were recorded on a Varian EM 360A or a Varian EM 390 spectrometer and chemical shifts are reported in parts per million (δ) from internal Me_4Si. IR spectra were recorded on a Perkin-Elmer 681 spectrometer. Mass spectra were taken on a Kratos MS 80 spectrometer. Thin-layer chromatography (TLC) was performed on silica gel sheets with fluorescent indicator (stratocrom SIF, Carlo Erba). Column chromatography was carried out by using 70-230 mesh silica gel from Merck.

Materials. Tetrahydrofuran (THF) from commercial source (RS, Carlo Erba) was purified by distillation (twice) from sodium wire in a N_2 atmosphere. Standardized (1.3 M) n-butyllithium in hexane was from Aldrich Chemical Co.. All other chemicals were commercial grade and were purified by distillation or crystallization prior to use.

Organic azides. Except for p-tosylazide, which was synthesized from p-tosyl chloride by halogen-azide exchange,[9] the other organic azides were all synthesized from the arylamines through their diazonium salts.[10] For o-methylsulphonyl- and o-ethylsulphonyl-phenylazide the following procedure was used: o-aminothiophenol was converted into the corresponding o-methylthio- and o-ethylthio-aniline by treating it with sodium ethylate in ethanol and then with methyl iodide and ethyl bromide, respectively. The alkylthioanilines so obtained were first converted into the corresponding o-methylthio- and o-ethylthio-phenylazide by the procedure described above, and then into o-methylsulphonyl- and o-ethylsulphonyl-phenylazide respectively, by oxidation with m-chloroperbenzoic acid (85%; molar ratio substrate/m-chloroperbenzoic acid ca. 1:2,5) in CH_2Cl_2, in the presence of sodium bicarbonate (in excess compared to MCPBA), by extension of the method reported for the synthesis of α-azidobenzyl phenyl sulphoxides.[11]

Phenylazide,[10] p-nitrophenylazide,[10] o-nitrophenylazide,[10] and p-tosylazide,[9] were prepared according to the reported procedures.

p-Tolylazide, oil (lit[12] kp_{32} 93°); IR (CH_2Cl_2): ν_{N_3} = 2125 cm^{-1}; ^{1}H NMR ($CDCl_3$, δ) : 2.3 (s, 3H); 6.8 (d, 2H); 7.05 (d, 2H).

o-Methylsulphonylphenylazide, mp 95-96°C (lit[13] 93-94°) (ethanol); IR (CH_2Cl_2) : ν_{N_3} = 2125 cm^{-1}; ^{1}H NMR ($CDCl_3$, δ) : 3.2 (s, 3H), 7.0-8.1 (m, 4H). (Found: C, 43.0; H, 3.7%; M^+, 197. Calc for $C_7H_7N_3O_2S$: C, 42.64; H, 3.58%; M, 197).

o-Ethylsulphonylphenylazide, mp 55-56°C (ethanol); IR (CH_2Cl_2) : ν_{N_3} = 2125 cm^{-1}; ^{1}H NMR ($CDCl_3$, δ): 1.25 (t, 3H); 3.45 (q, 2H); 7.1-8.15(m, 4H). (Found: C, 45.7; H, 4.3%; M^+, 211. Calc for $C_8H_9N_3O_2S$: C, 45.50; H, 4.30%; M, 211).

Reactions: general procedure.

Standardized (1.3 M) n-butyllithium in hexane (8 mmole) was added to anhydrous THF (20 ml) in a dropping funnel at room temperature and under a nitrogen atmosphere. The mixture was kept at this temperature for ca. 16 h and then added dropwise to a solution of the organic azide (5 mmole) in anhydrous THF (20 ml), using a nitrogen flushed, 100 ml, three necked flask equipped with a magnetic stirrer, a nitrogen inlet, and an outlet connected with an end trap containing benzoic acid in

THF. The reactions were carried out in all cases at room temperature and were generally completed within 0.5 h. In the only cases of phenylazide and p-tolylazide some unreacted starting azide was recovered even after 1 h. The reaction mixtures were quenched by adding aqueous NH_4Cl (HCl 6 N in the case of p-tosylazide) or benzoic acid in THF (gas evolution was observed in both cases) and the reaction products separated (except for p-toluenesulphonamide and N-formyl-p-toluenesulphonamide from the reaction of tosylazide) by column chromatography (silica gel; eluent: ether in the case of o-methylsulphonyl- and o-ethylsulphonyl-phenylazide; ether-petrol 7:3 in the other cases), after the elimination of excess benzoic acid by treatment with aqueous $NaHCO_3$ (for reactions quenched with $C_6H_5CO_2H$), separation of the organic from the aqueous layer, and removal of the solvent. In the case of p-tosylazide, the separation of p-toluenesulphonamide from N-formyl-p-toluenesulphonamide could not be accomplished by column chromatography. However, their separation could be made by extracting with ether the reaction mixture quenched with HCl 6 N (by a first extraction mainly N-formyl-p-toluenesulphonamide was removed), and then recovering p-toluenesulphonamide from the aqueous layer. Because of the procedure used, the reported values (Table) are rather rough in this case.

On the other hand, as far as diazomethane is concerned, a different trapping procedure was also used instead of direct quenching of the reaction mixture with benzoic acid. After the reaction was completed, the reaction flask was warmed at ca. 50°C (bath) and the diazomethane entirely collected into the final trap containing benzoic acid in THF (as described above). Probably because a common laboratory apparatus was used instead of that previously recommended to this aim,[5] the yields of trapped diazomethane in the latter case resulted lower compared to the former procedure. Thus the yields of methyl benzoate reported in the Table are referred to the reaction mixture "directly" quenched with benzoic acid.

Reaction products.

Formanilide, mp 46-47° (lit[14] 47°) (ether-petrol) and N-formyl-p toluidine, mp 51-52° (lit[15] 52°) (ether-petrol), were identical to authentic samples (mixed mp.s and IR spectra).

N-formyl-o-methylsulphonylaniline, mp 117-119° (ethanol); IR (CH_2Cl_2) ν_{N-H} = 3340 cm^{-1}; $\nu_{C=O}$ = 1710 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 3.1 (s, 3H); 7.1-8.7 (m, 5H : four aromatic and one formyl proton); 9.5 (bs, 1H; exchange with D_2O). (Found: C, 47.4; H, 4.4; N, 6.9%; M^+, 199. Calc for $C_8H_9NO_3S$: C, 48.24; H, 4.56; N, 7.03%; M, 199).

N-formyl-o-ethylsulphonylaniline, mp 73-74° (ethanol); IR (CH_2Cl_2): ν_{N-H} = 3340 cm^{-1} $\nu_{C=O}$ = 1710 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 1.3 (t, 3H); 3.15 (q, 2H); 7.1-8.7 (m, 5H : four aromatic and one formyl proton); 9.5 (bs, 1H; exchange with D_2O). (Found: C, 50.9; H, 5.5; N, 6.8%; M^+, 213. Calc for $C_9H_{11}NO_3S$: C, 50.70; H, 5.20; N, 6.57%; M, 213).

N-formyl-p-nitroaniline, Since very low amounts were isolated, it could not be purified (lit[16], mp 194-195°). However, the assignment was made by comparison (IR) with an authentic sample: typical IR absorptions (CH_2Cl_2: ν_{N-H} = 3420 cm^{-1}; $\nu_{C=O}$ = 1705 cm^{-1}).

N-formyl-o-nitroaniline, mp 121-122° (lit[17] 122°) (ethanol); IR (CH_2Cl_2): ν_{N-H} = 3370 cm^{-1}; $\nu_{C=O}$ = 1715 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 7.0-9.0 (m, 5H : four aromatic and one formyl proton); 10.2 (bs, 1H; exchange with D_2O).

N-formyl-p-toluenesulphonamide, mp 102-103° (lit[18] 102-103°) (EtOH/H_2O); IR (CH_2Cl_2): ν_{N-H} = 3360 cm^{-1}; $\nu_{C=O}$ = 1725 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 2.4 (s, 3H); 7.3 (d, 2H); 7.8 (d, 2H); 8.6 (s, 1H); 9.1 (broad signal, 1H; exchange with D_2O).

N-formyl-N-methyl-p-toluenesulphonamide, mp 57-58° (ether-petrol); IR (CH_2Cl_2): $\nu_{C=O}$ = 1705 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 2.45 (s, 3H); 2.95 (s, 3H); 7.35 (d, 2H); 7.75 (d, 2H); 9.1 (s, 1H). (Found: C, 49.9; H, 5.3; N, 6.3%. Calc for $C_9H_{11}NO_3S$: C, 50.70; H, 5.20; N, 6.57%).

p-Nitroaniline, mp 148-149°, o-nitroaniline, mp 71-72°, and p-toluenesulphonamide, mp 137-138°, were identical to authenthic samples (mixed mp.s and IR spectra).

o-Methylsulphonylaniline, mp 83-84° (lit[19] 65-66°, 84-85°[20], 53.5-54.5°[21]) (EtOH/H_2O); IR (CH_2Cl_2): ν_{NH_2} =3490 and 3390 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 3.05 (s, 3H); 5.0 (bs, 2H; exchange with D_2O); 6.6-6.9 (m, 2H); 7.15-7.45 (m, 1H); 7.7 (q, 1H). (Found: C, 48.6; H, 5.5; N, 8.1%; M^+ 171. Calc for $C_7H_9NO_2S$: C, 49.12; H, 5.30; N, 8.18%; M, 171).

o-Ethylsulphonylaniline, mp 71-72° (lit[20] 74-75°) (EtOH/H_2O); IR (CH_2Cl_2): ν_{NH_2} = 3490 and 3390 cm^{-1}; ^1H NMR ($CDCl_3$, δ) : 1.25 (t, 3H); 3.15 (q, 2H); 5.05 (bs, 2H; exchange with D_2O); 6.6-6.9 (m, 2H); 7.2-7.5 (m, 1H); 7.65 (q, 1H). (Found: C, 51.4; H, 6.2; N, 7.5%; M^+, 185. Calc for $C_8H_{11}NO_2S$: C, 51.88; H, 5.99; N, 7.56%; M, 185).

Methyl benzoate, oil, identical to an authentic sample (IR spectrum).

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References

1) M. Regitz, Angew.Chem.Internat.Edit., 6, 733 (1967); M. Regitz and W. Anschütz, Liebigs Ann. Chem., 730, 194 (1969).
2) R.B. Bates, L.M. Kroposki, and D.E. Potter, J.Org.Chem., 37, 560 (1972).
3) P. Tomboulian, D. Amick, S. Beare, K. Dumke, D. Hart, R. Hites, A. Metzger, and R. Nowak, J. Org.Chem., 38, 322 (1973).
4) M.E. Jung and R.B. Blum, Tetrahedron Lett., 3791 (1977).
5) J. De Boer and H.J. Backer, Org.Synth., Coll. Vol. IV, p. 250 (1963).
6) Z. Arnold, Chem.Comm., 299 (1967); J. Kucera, Z. Janouzec, and Z. Arnold, Coll.Czec.Chem.Comm., 35, 3618 (1970).
7) G.W. Cowell and A. Ledwith, Quart.Rev., 24, 119 (1970).
8) H.O. House, L.J. Czuba, M. Gall, and H.D. Olmstead, J.Org.Chem., 34, 2324 (1969).
9) M. Regitz, J. Hocker, and A. Liedhegener, Org.Synth., Coll. Vol. V, p. 179 (1973).
10) E. Noelting, O. Michel, Chem.Ber., 26, 86 (1893); see also R.O. Lindsay and C.F.H. Allen, Org. Synth., 22, 96 (1948).
11) B.B. Jarvis, P.E. Nicholas, and J.O. Midiwo, J.Am.Chem.Soc., 103, 3878 (1981).
12) P.K. Dutt, H.R. Whitehead, and A. Wormall, J.Chem.Soc., 119, 2088 (1921).
13) R.A. Abramovitch, G.N. Knaus, and R.W. Stowe, J.Org.Chem., 39, 2513 (1974).
14) O. Schmidt, Chem.Ber., 36, 2459 (1903).
15) G. Tobias, Chem.Ber., 15, 2443 (1882).
16) G.T. Morgan, F.M.G. Micklethwait, J.Chem.Soc., 87, 921 (1905).
17) H. Hübner, Liebigs Ann.Chem., 209, 369 (1881).
18) M. Regitz, J. Rüter, Chem.Ber., 101, 1263 (1968).
19) T. Zincke and G. Siebert, Chem.Ber., 48, 1242 (1915).
20) I.G. Farbenind. A.-G. Fr. 746,410, May 29, 1933 [Chem.Abstr., 27, 4685[2] (1933)].
21) M.P. Cava and C.E. Blake, J.Am.Chem.Soc., 78, 5444 (1956).