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Electrolytically Generated Nucleophiles. V. Reductive Acetylation of Some Aliphatic and Aromatic Nitro and Nitroso Compounds

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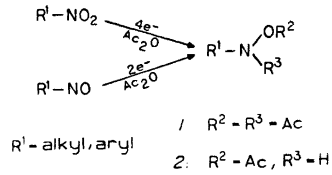
N,O-Diacetylated hydroxylamines *1* are readily synthesized by direct electrochemical reduction of both aliphatic and aromatic nitro and nitroso compounds in aprotic media in the presence of acetic anhydride (Ac_2O). Primary, secondary and tertiary nitroaliphatics produced *1* in isolated yields from 40 to 70 %. Similarly, simple nitro- and nitrosoaromatics produced *1* in yields from 45 to 85 %.

The presence of acidic impurities in the catholyte is shown to affect the yield of *1* producing *O*-acetylated hydroxylamines *2*. These products are isolable in certain cases, but can also produce a number of side products. A mechanism is suggested.

Reduction of nitro compounds to hydroxylamines has been accomplished with a variety of chemical reagents including zinc and acid, diborane and metal hydrides,[1] as well as catalytic hydrogenation [2] and electrochemical reduction.[3]

Reductive substitution of nitro compounds in the presence of an electrophile to give *N,O*-substituted hydroxylamines directly without isolation of the free base has, however, had limited success. Reduction of nitrobenzene with zinc dust in acetic anhydride (Ac_2O) gave the hydroxamic acid,[4] whereas catalytic hydrogenation of nitroaromatics in the presence of Ac_2O is reported to give *N,O*-diacetylated hydroxylamines *1* in poor yield.[5]

As previously reported [6] it was discovered that the electrochemical reduction of both aliphatic and aromatic nitro or nitroso compounds in aprotic media with Ac_2O as electrophile did produce *1* in yields from 40 to 70 %, thus constituting an efficient synthesis of these products. We now report a further investigation of this reaction.



Recently, others [7] have similarly reported the high yield formation of *N,O*-dialkylhydroxylamines in the electrochemical reduction of nitro compounds with alkyl halides present.

RESULTS

The results of reductive acetylation of some aliphatic nitro and nitroso compounds are given in Table 1. By distillation of the crude catholyte, *1* was isolated in 40–65 % yield and the reaction was found to work equally well for primary, secondary and tertiary nitroalkanes.

Column chromatography of the reaction mixture from reduction of 2-nitro-2-phenylpropane revealed the formation of the *O*-acetylated hydroxylamine (*2*, $R = C_6H_5C(CH_3)_2^-$) as a minor product. The addition of a proton donor (acetic acid or water) caused *2* to be the only product formed, thus demonstrating the effect of proton donor impurities in the medium. The by-product *2* may also be formed from other nitroaliphatics but were not isolated by the work-up procedure (distillation) employed.

The anion radicals of *t*-nitroalkanes are of limited stability,[8] decomposing into a radical

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Table 1. Results from preparative reductive acetylations of some aliphatic nitro and nitroso compounds.[a]

Substrate	Medium [c]	Working Potential [d]	Yield of R-N(OAc)Ac Isolated/%	Analyzed/%
Nitromethane	A	1.0	41	61
Nitroethane	A	1.0	69	–
1-Nitropropane	A	0.8	63	–
2-Nitropropane	A	0.8	63	–
2-Methyl-2-nitrosopropane	A	1.0	58	73
2-Methyl-2-nitropropane	A	1.0	51	63
2-Methyl-2-nitropropane	C	1.0	–	100
2-Methyl-2-nitropropane	B	1.1	65	
2-Nitro-2-phenylpropane	A	0.8	53+15 % RNHOAc	
2-Nitro-2-phenylpropane [b]	A	0.8	(75 % RNHOAc)	

[a] 12 % (by volume) of Ac_2O added. [b] 8 % of glacial acetic acid added, too. [c] A: $CH_3CN/NaClO_4$ 0.8 M; B: DMF/TBAI 0.1 M; C: $Ac_2O/NaClO_4$ 0.8 M. [d] – V *vs.* Ag/AgBr.

Table 2. Results from preparative reductive acetylation of aromatic nitro and nitroso compounds.[a]

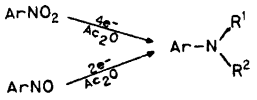
Substrate	Medium [b]	Working Potential [c]	Isolated Yields [d]/% R-N(OAc)Ac	R-N(Ac)$_2$	R-NHAc	Others
Nitrosobenzene	A	0.6	74 (85)	–	15 (15)	Azobenzene 1
Nitrosobenzene	B	0.6	70 (80)	–	3 (2)	Azobenzene 4
Pentafluoro-nitrosobenzene	A	0.0	63	–	–	Decafluoro-azoxybenzene 13
Pentafluoro-nitrosobenzene [e]	A	0.0	10	–		R-NHOAc 23; Decafluoro-azoxybenzene 8
Nitrobenzene	A	0.6	69 (76)	8 (11)	10 (11)	
Nitrobenzene	B	0.6	86 (87)	–	–	
p-Nitrotoluene	A	0.8	68 (76)	–	7 (12)	
p-Nitrotoluene	B	0.8	85 (92)	–	–	
2-Nitrosobiphenyl	A	0.0	42 (45)	35 (40)	8 (16)	Carbazole 2 2-Azobiphenyl 1 2-Azoxybiphenyl 1
2-Nitrosobiphenyl	C	0.2	32 (35)	17 (16)	8 (17)	2-Azobiphenyl 6 2-Azoxybiphenyl 5
2-Nitrobiphenyl	A	0.6	45 (50)	trace	34 (50)	Carbazole 2
2-Nitrobiphenyl	C	0.6	75 (75)	20 (22)	–	–
2-Nitrobiphenyl	D	0.7	80	6	–	–
2-Nitrobiphenyl [e]	A	0.5	17	–	45	Carbazole 3 2-Azobiphenyl 3 3-Acetoxy-2-acetyl-aminobiphenyl 10
2-Nitrofluorene	A	0.4	51	trace	12	
m-Dinitrobenzene	A	0.3	85	–	–	
2,2′-Dinitro-biphenyl	A	0.35	15 [f]	16 [g]		
2,2′-Dinitro-biphenyl	C	0.7	35 [h]			

[a] 12 % of Ac_2O added. [b] A: $CH_3CN/NaClO_4$ 0.8 M; B: DMF/$NaClO_4$ 0.8 M; C: CH_3CN/TBAI 0.1 M; D: DMF/TBAI 0.1 M. [c] – V *vs.* Ag/AgBr. [d] Analytical yields in parentheses. [e] 2 % water added too. [f] 2-(*N*-Acetoxy-*N*-acetyl)amino-2′-nitrobiphenyl. [g] 2,2′-Bis[(*N*-acetoxy-*N*-acetyl)amino]biphenyl. [h] 2-(*N*-Acetoxyamino)-2′-(*N*-acetylamino)-biphenyl.

and nitrite ion. However, only in the catholyte from reduction of 2-nitro-2-phenylpropane could traces of nitrite ion be detected (Griess' test [9]). Any products from this degradation would, therefore, be expected to be of minor importance under the employed conditions and none were detected.

Reductive acetylation of nitroaliphatics did not produce any acetylated amines as was the case in the reduction of nitroaromatics (*vide infra*).

Table 2 shows the results of reductive acetylation of some aromatic nitro and nitroso compounds. In all cases *1* was isolated as the major product. Under optimized conditions, the isolated *1* from simple nitroaromatics (nitrobenzene, nitrotoluene, 2-nitrobiphenyl, *m*-dinitrobenzene) exceeded 80 % constituting an excellent one-step synthesis of *1*. However, under less than ideal conditions several other compounds were isolated. Acetamides *3* and diacetylated amines *4* were detected in varying amounts, as well as small amounts of azo compounds.



1: R^1 = OAc, R^2 = Ac

2: R^1 = OAc, R^2 = H

3: R^1 = H, R^2 = Ac

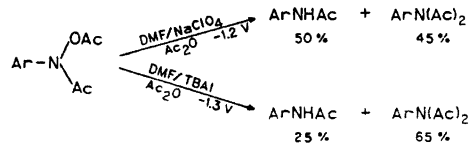
4: $R^1 = R^2$ = Ac

As indicated in Table 2 improving the aprotic conditions (changing medium from CH_3CN/$NaClO_4$ to DMF/$NaClO_4$ to DMF/TBAI), as well as keeping the excess of added Ac_2O low, increases the yield of *1*, and minimizes the formation of *3* and *4*. On the other hand, adding a proton donor (*e.g.*, water) results in the formation of *3* as the major product. In addition to these products, azoxy aryls were always formed in the reductive acetylation of nitrosoaromatics.

Reduction of both 2-nitro- and 2-nitrosobiphenyl also produced carbazole but only under conditions where the acetamide *3* was formed in larger amounts. Finally, in this case the addition of water to the catholyte resulted in the formation of an appreciable amount of 3-acetoxy-2-acetylaminobiphenyl together with the 2-biphenylacetamide main product.

Reductive acetylation of pentafluoronitrosobenzene constitutes a special case among the investigated aromatics, since addition of proton donor to the catholyte resulted in the isolation of the *O*-acetylated hydroxylamine *2* as main product, and never produced any acetamide *3* or azo compound.

The product *1* is also electroactive, but at a more negative potential than required for the reduction of the parent nitro compound, forming *3* and *4* as shown in Scheme 1 for *N*,*O*-diacetyl-2-biphenylhydroxylamine (isolated yields, no other products observed).



Ar = 2-biphenylyl

Scheme 1.

MECHANISM AND DISCUSSION

The DC-polarographic reduction waves (DME electrode) of all investigated nitro or nitroso compounds showed an increase in wave height and an anodic shift of the half-wave potential with addition of Ac_2O. This is the expected behavior for a multielectron reduction of a nitro or nitroso group to the hydroxylamine.

The cyclic voltammetric (CV) behavior of 2-nitrosobiphenyl in DMF with 0.8 M $NaClO_4$, is shown in Fig. 1. The first electron transfer forming the anion radical is reversible with $I_p^a I_p^c = 0.98$ and a constant peak potential (E_p) on varying the sweep rate (v) from 20 mV s^{-1} to 10 V s^{-1}.

Addition of less than equimolar amounts of Ac_2O gives rise to a distinct prepeak (2 on Fig. 1), the height of which is proportional to the amount of Ac_2O added. Also, a new pair of peaks (3) appears near the anodic switching potential on the anodic scan and following second cathodic scan. This couple is so far unidentified. As Ac_2O is added the peak potential of the prepeak first moves slightly cathodic then anodic. Addition of more than

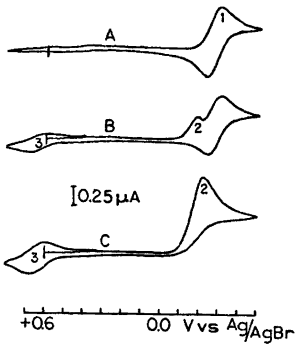


Fig. 1. Voltammetric curves of 2-nitrosobiphenyl 4.5 mM) in DMF/$NaClO_4$ 0.8 M; A: without Ac_2O; B: 1.8 mM AC_2O added; C: 8.8 mM Ac_2O added. Scan rate 100 mV s^{-1}, reference electrode Ag|AgBr|0.1 M Br^-.

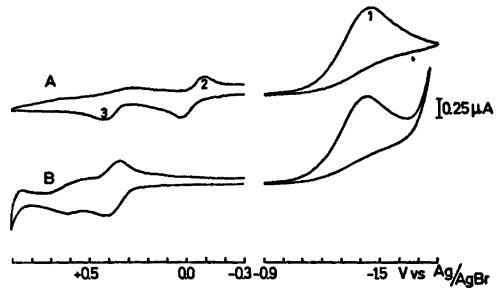


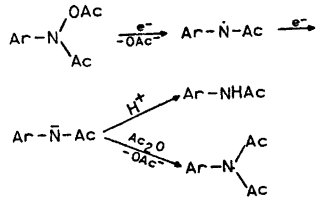
Fig. 2. Voltammetric curves of *N,O*-diacetyl-2-diphenylhydroxylamine (3.1 mM) in DMF/TEAP 0.1 M; A: without Ac_2O; B: with 0.7 M Ac_2O added. Scan rate 100 mV s^{-1}, reference electrode Ag|AgBr|0.1 M Br^-.

equimolar amounts of Ac_2O causes the prepeak to grow to the height of a two-electron irreversible peak, with the simultaneous disappearance of the one-electron reversible peak system (1).

The observation of a prepeak is often believed to indicate the formation of a complex (*i.e.*, between Ac_2O and R-NO) prior to electron transfer. However, since the characteristic UV absorptions at 745 nm in CH_3CN of nitrosobenzene (which shows the exact same behavior in CV) is unaltered by addition of 10 % Ac_2O, this is not the case. In fact, it has been shown that a prepeak of the observed kind is in agreement with an ECE mechanism.[11] Furthermore, we found a slope of E_p^2 *vs.* log *v* of 38 mV/decade (0.17 M Ac_2O added, no compensation for iR drop) not too far from the theoretical value of 29.1 mV ($t = 20$ °C) for an ECE or DISP 1 process.[12] (DISP 1: rate-determining acetylation of the anion radical followed by disproportionation of the formed radical). Also, the peak height was proportional to the concentration of substrate indicating a first-order rate-determining reaction.[13] Finally, $I_p/v^{\frac{1}{2}}$ was a slightly decreasing function of increasing scan rate.

CV of 2-nitrobiphenyl shows a perfectly reversible one-electron peak system in DMF containing tetraethylammonium perchlorate (TEAP) as electrolyte. Addition of Ac_2O causes irreversibility and an increase in the cathodic wave height as expected for a multielectroreduction with more easily reduced intermediates. No distinct prepeak is observed, probably due to a slower reaction of Ac_2O with the nitroanion radical, than with the nitroso anion radical.

Fig. 2 shows the voltammogram of *N,O*-diacetyl-2-biphenylhydroxylamine (*1*, Ar = 2-biphenylyl) in DMF/TEAP. A 2-electron (as compared to the peak height of added 2-nitrobiphenyl) irreversible peak is found on the cathodic scan, giving two new pairs of peaks (2) and (3) on the anodic and following cathodic scan. By addition of Ac_2O the couple (2) disappears, whereas the irreversible peak (1) is unaltered and (3) (unidentified) is nearly so. The observed voltammogram is consistent with the ECE mechanism visualized in Scheme 2.

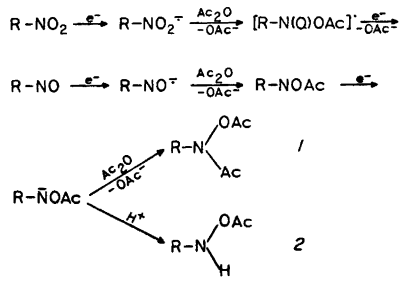


Scheme 2.

The acceptance of one electron causes the immediate loss of an acetate ion giving a radical which is further reduced to the anion at the applied cathodic potential. Without any electrophiles present, this anion is reoxidized on the anodic scan and again reduced in the second cycle giving rise to peak system (2). With Ac_2O

added or proton doner present (*e.g.*, residual water) the anion is acetylated or protonated.

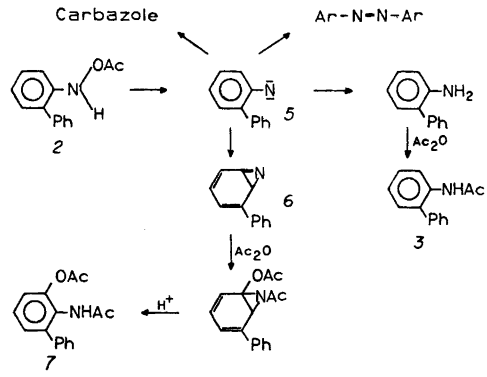
Based on the voltammetric results we favor an ECE mechanism for the reductive acetylation of nitroso compounds. Since nitro compounds are believed to go through the nitroso state during reduction we propose the general mechanism shown in Scheme 3. In the last step



Scheme 3.

protonation by impurity or purposely added proton donor may effectively take part forming *2*.

Whereas the aliphatic *O*-acetylated hydroxylamines are reasonably stable at room temperature,[14] all attempts to isolate any *O*-acetylated arylhydroxylamine *2* have failed,[15–17] except [18] in the case of *N*-(2,4-dinitrophenyl)-*O*-acetylhydroxylamine with a highly electron deficient aromatic core. They have, however, been proposed as intermediates,[15–17] believed to react further through a nitrenium ion or nitrene intermediate. To investigate this 2-nitrosobiphenyl was employed, known to form carbazole through a nitrene intermediate.[19] Table 2 shows that carbazole was indeed isolated. The generally observed by-products are thus readily explained as shown in Scheme 4 for the reduction of



Scheme 4.

2-nitrosobiphenyl. Compound *2* is formed through reaction with any proton donor and, if stable, is isolated as in the reductive acetylation of 2-nitro-2-phenylpropane (giving aliphatic *2*) or nitrosopentafluorobenzene (electron deficient aromatic core) and no degradation products are observed. If unstable *2* might form a nitrene *5*, which, through known nitrene chemistry, reacts to form carbazole through intramolecular insertion, anilines through hydrogen atom abstraction and further acetylation to give *3*, internal stabilization to form the aziridine *6* followed by addition of Ac_2O and ring opening to give 3-acetoxy-2-acetylaminobiphenyl *7*.

Formation of azo compounds is readily explained by the dimerization of nitrenes whereas the formation of azoxy compounds, only observed in reductive acetylation of aromatic nitroso compounds, is the result of dimerization of the nitroso anion radical.[10]

Even though *1* is electroactive forming *3* and *4* by reductive acetylation (*vide supra*), this is not a very likely explanation for the observed formation of these products considering the potential differences between reduction of 2-nitrosobiphenyl (0.0 V *vs.* Ag/AgBr in $CH_3CN/NaClO_4$) and *N*,*O*-diacetyl-2-biphenylhydroxylamine (-1.2 V *vs.* Ag/AgBr). It is known that *N*,*O*-diacylarylhydroxylamines rearrange to disubstituted *o*-aminophenols upon heating.[20] It has also been stated [21] that chromatography on silica gel, our method of workup, could cause the same rearrangement. However, the fact that 3-acetoxy-2-biphenylacetamide *7* is only found from reduction of 2-nitrobiphenyl under conditions where the 2-biphenylacetamide *3* was the main product rules out these two possibilities.

In summary, the reductive acetylation of nitro and nitroso compounds produces *1* in good yields in aprotic media. However, the presence of acidic impurities in the catholyte will decrease the yield of *1* and cause the formation of various by-products.

EXPERIMENTAL

Materials. The nitro and nitroso compounds were either commercial products or synthesized by published methods. They were purified by distillation or recrystallization. Solvents were commercial and used without purification

after long time storage over molecular sieves (A4). $NaClO_4$ was dried at 150 °C for 24 h before use. TEAP (dried in desiccator over P_2O_5) and TBAI were polarographic grade. The Ac_2O was distilled before use, and the purity greater than 99 % (GLC).

Polarography and voltammetry. Two electrode polarograms were recorded on a Radiometer PO4 polarograph using 25 ml of DMF/TBAI solutions of the depolarizer deaerated by a dry N_2 flow and using an Ag/AgI wire directly immersed into the solution as the auxiliary electrode.

Voltammograms were recorded using a three-electrode cell with a hanging mercury drop as the working electrode. The reference electrode was an Ag/AgBr wire in a 0.1 M solution of $(Bu)_4NBr$ (polarographic grade) in the appropriate solvent and separated from the cell solution by a G4 frit. A Pt-wire as counter electrode was used. The solutions were 50 mg of depolarizer in 60 ml of solvent carefully deaerated by an N_2 flow. Recording was obtained by a Hewlett-Packard X – Y recorder or a storage oscilloscope. The sweep rates were changed from 20 mV s^{-1} to 10 V s^{-1}, no compensation for the iR-drop was performed.

Large scale reductions. Two H-type 3-electrode glass cells were used, one of *ca.* 65 ml catholyte volume for reduction of 0.5 – 1.0 g of substrate and one of *ca.* 250 ml catholyte volume for reduction of 2 – 4 g of substrate. The cathode was a mercury pool, the anode a Pt-gauge, and the reference electrode an Ag/AgBr wire in 0.1 M $(Bu)_4NBr$ solution. The cell was filled with the medium used and 12 % Ac_2O (by volume) except where otherwise stated in Tables 1 and 2. The catholyte was deaerated with N_2 and the substrate added. A slow stream of N_2 was maintained during reduction either in or just above the solution. The cell was immersed in a water bath (22 °C) and connected to a Juul Electronic 100 V (or 300 V)/1 A potentiostat.

Coulometric measurements were done by means of an electromechanical integrator. The electricity consumption corresponded to 4 F/mol for the reductions giving a high yield of *1* and somewhat more in the other cases.

The catholyte from reduction in CH_3CN/$NaClO_4$ was worked up by evaporation *in vacuo* (10 mmHg) on a bath not exceeding 40 °C and extraction of the semi-solid residue with dichloromethane. The CH_2Cl_2 solution was then evaporated *in vacuo* (1 mmHg) leaving a colored oil, free of most Ac_2O. The catholyte from reduction of CH_3CN/TBAI or DMF was poured into water and extracted 3 times with benzene or diethyl ether. The combined organic solutions were then washed 5 times with water and dried over anh. magnesium sulfate. Evaporation *in vacuo* (10 mmHg) gave the crude product.

The reduction mixture from reduction of nitromethane and 2-methyl-2-nitropropane was analyzed by GLC (HP 5700 A) using internal standard (durene and diphenyl) and an electronic integrator (HP 3370 B). The column was a 2 m SS 15 % SE 30 on 80 – 100 mesh Chromosorb W AW. Analyses of the reduction mixture from reduction of nitrobenzene, nitrosobenzene, *p*-nitrotoluene, 2-nitrobiphenyl and 2-nitrosobiphenyl were performed by NMR (in $CDCl_3$) using *t*-BuOH as internal standard. This method, however, had a poorer reproducibility.

The further work up was performed by distillation, prep. GLC (using Perkin-Elmer F21), or column chromatography on silica gel using a 3 × 60 cm water-cooled column and diethyl ether light petroleum mixtures as eluent.

Products were all identified from their spectra and/or physical data in comparison with already published results.

Spectral data. Spectra were recorded on a Varian A60 or Varian XL 100 NMR spectrometer, a Perkin-Elmer Infracord or a Beckmann IR-A spectrophotometer, a Perkin-Elmer 402 UV spectrophotometer, and a CEC 21-104 mass spectrometer.

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