A new reaction of cyclohexanone enolate with nitroarenes

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Reaction of cyclohexanone enolate with some nitroarenes carried out at 60–80 °C proceeds *via* addition to the nitro group followed by a series of transformations giving *o*-hydroxydiarylamines.

Carbanions react with nitroarenes mainly *via* addition to electron-deficient rings, in positions *ortho*- or *para*- to the nitro group giving anionic σ adducts. Addition at positions occupied by nucleofugal substituents X give σ^x adducts rapidly converted into products of $S_N Ar$ reaction.[1] Faster and reversible addition at positions occupied by hydrogen produces σ^H adducts,[2,3] which can be converted into products of nucleophilic substitution of hydrogen on a few pathways such as oxidation,[4] vicarious nucleophilic substitution VNS,[5] formation of nitroso compounds[6] *etc*. Direct intermolecular addition of stabilized carbanions to the nitro group is almost unknown, although there are numerous examples of such addition proceeding as intramolecular processes resulting in the formation of hetero-cyclic systems.[7,8] Addition of indan-1-one enolate to the nitro group of *o*-nitrobenzaldehyde appears to be assisted by initial addition to the carbonyl group, thus being in fact an intra-molecular process.[9] Of particular interest in this respect is the observation reported by Scorrano[10] and subsequently by one of us[11] that methyl aryl ketones react with some nitroarenes giving 1,2-diaroyl-1-arylaminoethylenes. The reaction proceeds apparently *via* direct addition of the enolates to the nitro group, although redox process and nitrosoarene intermediates are suggested by Scorrano.[10]

In this communication we report that treatment of some nitroarenes **1a**–**d** with cyclohexanone **2a** and 2- and 3-methylcyclohexanones **2b,c** in presence of base results in the formation of substituted *o*-hydroxydiarylamines **3a**–**f** in reasonable yields. Since these anilines are sensitive to oxidation, particularly in basic media, some problems were encountered in isolation and purification, and thus the reaction mixtures were treated with MeI to produce stable *o*-methoxydiarylamines **4a**–**f**, which were then readily isolated and purified.† Some results are collected in Table 1.

The reaction proceeds apparently *via* direct addition of the enolate to the nitro group in nitroarenes and is undoubtedly related to reported earlier formation of 1,2-diaroyl-1-arylamino-ethylenes.[10,11] The speculative mechanistic pathway of these complicated processes, which bifurcate at the stage of further transformation of the nitrone intermediate **5**, is shown in Scheme 1.

Direct addition of the enolate to the nitro group produces the anionic adduct converted into nitrone **5**. Nitrone **5a** derived from cyclohexanone undergoes 1,3-proton shift leading to the hydroxylamine derivative, followed by 1,4-dehydration giving the imino ketone which tautomerizes in basic media to form the aromatic system of *o*-hydroxyaniline **3**. In the similar reaction of acetophenone there is no possibility for such proton shift and 1,4-dehydration in the linear nitrone intermediate **5b**, so addition of the second enolate molecule to the nitrone takes place to produce hydroxylamine **6** which upon dehydration and tautomerisation gives the final diaroylethylenes **7**.

The main problem to be clarified is the reason for the observed dichotomy of the reaction course of enolates with nitroarenes. At low temperature, enolates generated by treat-ment of ketones with base or activation of silyl enol ethers with F^- anions add at the *ortho*- or *para*-position of halonitro-benzenes.[12] Subsequent oxidation of the σ^H adducts leads to nitrobenzylic ketones—products of the oxidative substitution of hydrogen. On the other hand, as has been shown in previous papers[10,11] and in this report, at higher temperature the same enolates add to the nitro group of nitroarenes. Since it is not reasonable to assume that changing the temperature changes the mode of the initial step, one can suppose that also in the latter reaction reversible addition to the ring is a fast initial process. At low temperature the σ^H adducts produced are long lived species and are oxidized, whereas at high temperature the concentration of the σ^H adducts becomes so low that the bimolecular oxidation process does not occur and the reaction proceeds *via* addition of the enolate to the nitro group.

The possibility that the reaction, in analogy to other processes,[13,14] proceeds *via* nitrosoarenes, was excluded by experiments in which *p*-nitroso-*N,N*-dimethylaniline subjected to the reaction with cyclohexanone under the identical condi-tions gave mainly *p,p*-bis(*N,N*-dimethylamino)azoxybenzene in a fast process, whereas slow introduction of this nitrosoarene to the reaction mixture of *p*-nitrodimethylaniline and cyclohex-anone did not improve the yield of the *o*-hydroxydiarylamine, being rapidly converted into the azoxycompound. Direct

Table 1 Reaction of nitrobenzenes **1** with cyclohexanones **2**

Z	R	Conditions	Time/h	Product yield (%)[a]
1a, H	**2a**, H	KF/Al$_2$O$_3$, 80 °C	1	**4a**, 15
1b, MeO	**2a**, H	KF/Al$_2$O$_3$, 80 °C	2	**4b**, 30
1c, Me$_2$N	**2a**, H	KOH, 60 °C	3	**4c**, 50
1d, Et$_2$N	**2a**, H	KOH, 80 °C	1	**4d**, 60
1d, Et$_2$N	**2b**, 2-Me	KOH, 80 °C	3	**4e**, 63
1d, Et$_2$N	**2c**, 3-Me	KOH, 80 °C	1	**4f**, 57

[a] Isolated products.
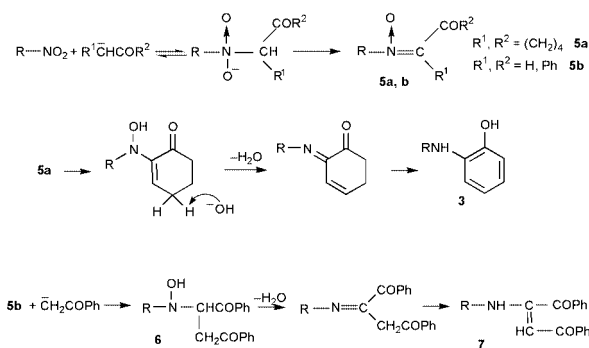
Scheme 1 The reaction pathways of nitroarenes R = Ar with enolates of cyclohexanone R′, R^2 = (CH$_2$)$_4$ and acetophenone R′ = H, R^2 = Ph.

intermolecular addition of carbanions to the NO$_2$ group is a common process when it is connected with oxygen used as a preparative method for nitration of enolates with alkyl nitrates.[15] Such reaction can occur with nitroalkanes provided they are not C–H acids. Thus we found that when *tert*-nitrobutane was allowed to react with cyclohexanone in the presence of KOH in DMSO at 80 °C, *N-tert*-butyl-2-hydroxy-aniline **3g** was isolated in moderate yield 12%.‡

It is worth stressing that the presented reaction is a useful one-pot alternative to only a few methods designed for the synthesis of diarylamines containing electron-donating substituents in both rings.[16,17]

Notes and references

† Typical procedure: to a stirred solution of **1** (5 mmol) and **2** (5–15 mmol) in DMSO (10 ml) under argon, powdered KOH (30 mmol) or KF/Al$_2$O$_3$ was added in one portion. The mixture was treated as shown in Table 1, cooled to rt and MeI (10 mmol) was added. After stirring for 5 min the mixture was poured into aq. NH$_4$Cl, the product was extracted with EtOAc and chromatographed on silica gel (hexane–toluene 1 : 3). **3a**: mp 68–70 °C, lit. 71 °C.[18] **4a**: bp 158–162 °C/5 mm, lit. 151–156 °C/5 mm.[19] **4b**: mp 69–70 °C, lit. 71–72 °C.[16] *Selected spectral data for compounds not reported earlier:* **4c**: mp 44–45 °C; ^{1}H NMR (200 MHz, CDCl$_3$, TMS); δ = 2.92 (s, 6 H, N(CH$_3$)$_2$), 3.89 (s, 3 H, OCH$_3$), 5.90 (br s, 1 H, NH), 6.74 (d, *J* = 9 Hz, 2 H, arom H), 6.80–7.01 (m, 4 H, arom H), 7.10 (d, *J* = 9 Hz, 2 H, arom H); **4d**: oil; ^{1}H NMR (CDCl$_3$): δ = 1.15 (t, *J* = 7 Hz, 6 H, (CH$_3$)$_2$), 3.32 (q, *J* = 7 Hz, 4 H, N(CH$_2$)$_2$), 3.89 (s, 3 H, OCH$_3$), 5.88 (br s, 1 H, NH) 6.68 (d, *J* = 9 Hz, 2 H, arom H), 6.70–6.98 (m, 4 H, arom H), 7.07 (d, *J* = 9 Hz, 2 H, arom H); **4e**: mp 59–60 °C; ^{1}H NMR (CDCl$_3$): δ = 1.15 (t, *J* = 7 Hz, 6 H, (CH$_3$)$_2$), 2.30 (s, 3 H, CH$_3$), 3.32 (q, *J* = 7 Hz, 4 H, N(CH$_2$)$_2$), 3.78 (s, 3 H, OCH$_3$), 5.87 (br s, 1 H, NH), 6.58 (m, 1 H, arom H), 6.68 (d, *J* = 9 Hz, 2 H, arom H), 6.83 (m, 2H, arom H), 7.07 (d, *J* = 9 Hz, 2 H, arom H); **4f**: mp 80–82 °C, ^{1}H NMR (CDCl$_3$); δ = 1.14 (t, *J* = 7 Hz, 6 H, (CH$_3$)$_2$), 2.28 (s, 3 H, CH$_3$), 3.30 (q, *J* = 7 Hz, 4 H, (CH$_2$)$_2$), 3.86 (s, 3 H, OCH$_3$), 5.70 br s, 1 H, NH), 6.60 (m, 2 H, arom H), 6.68 (d, *J* = 9 Hz, 2 H, arom H), 6.87 (d, *J* = 8 Hz, 1 H), 7.05 (d, *J* = 9 Hz, 2 H, arom H).

‡ **3g**: mp 76–77 °C; ^{1}H NMR (CDCl$_3$): δ = 1.2 (s. 9 H, *tert*-C$_4$H$_9$), 4.40 (br s, 2 H, NH, OH) 6.60–7.10 (m, 4 H, arom H).

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