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A novel reaction of ketone arylhydrazones with nitric oxide

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Abstract—The reaction of ketone arylhydrazone (1) with nitric oxide affords Cl'-nitro azo-compounds (2) in good yields. Products were identified by NMR, IR, MS, and X-ray crystallography. The reaction is assumed to be most likely initiated by an electrophilic addition of NO₂ to the carbon atom of the carbon–nitrogen double bond. © 2003 Elsevier Ltd. All rights reserved.

People have learned the important roles of nitric oxide (NO) in atmospheric processes¹ and in biological events.² Therefore, the intensive researches have been directed towards reactions of NO with biological molecules.³ However, its chemical mysteries have been still waiting for probing by chemists. It has led papers concerning the reactivity of NO with various organic compounds to grow at a rapid rate. Many reactions of NO were reported, such as with secondary amines,⁴ α -tocopherol,⁶ ethyl olefines,⁵ linoleate,⁷ 2'deoxyguanosime,⁸ dihydropyridines, aromatic primary amines, nucleus acid bases,⁹ amides,¹⁰ oximes,¹¹ Schiff bases,^{9a,c} arylhydrazines,¹² etc. In parallel with these, those of other oxides of nitrogen such as NO₂, N₂O₃, N₂O, etc., have been also attracted more attention from chemists. These reactions include in: nitrogen oxides with amine derivatives, nitrous and nitrate salts with hydrazines,¹³ NO₂ with olefines,^{5c} nitrosonium and nitronium with oximes, hydrazines and hydrazones,¹⁴ and so on. It is worthy pointing out that the imine double bond of hydrazones was found to be cleaved exclusively in the reaction of aldehyde or ketone hydrazones with nitrous acid, nitronium or nitrosonium, as those with NO.9c,14



Scheme 1.

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Arylhydrazones have long been utilized for analysis of carbonyl compounds.¹⁵ In recent years, some of them and their complexes with transition metal were found to have the anticancer properties.^{16,17} In particular, hydrazones have been used to build chiral configurations and certain specific skeletons.¹⁸ The reactions investigated were those with vinylsilane, azide, lithio methoxyallene, isocyanates, [60]fullerences, etc.¹⁹

Moon²⁰ studied the bromination and chlorination of hydrazones. They obtained the corresponding azo-compounds. The Cl'-halogenated hydrazones were known as unstable intermediates before they converted into the end products. The parallel conclusion was obtained by Guo,²¹ who recently reported that the halogenation was an electrophilic reaction on Cl'-atom and the conversion of halogenated hydrazones to azo-compounds underwent a prototropy.

In the present work, the reaction of ketone arylhydrazones (1) with NO was carried out at ambient temperature (Scheme 1).²² The brightly colored C1'-nitro azo-compounds (2) were obtained in good yields (Table 1).

All the products were identified by ¹H and ¹³C NMR, MS, HRMS, IR, and X-ray crystallography diffraction.²² A representative crystallographic structure is shown in Figure 1 (deposition number: CCDC-212523). It indicates that a NO₂ group in **2a** is linked on the carbon atom (C7, i.e. C1'-atom, N5–C7, 1.544(2) Å) of the carbon (C7)–nitrogen (N4) single bond (1.475(5) Å) and an azo-bond (N4–N3, 1.237(5) Å) is constructed. The presence of a nitro group was indicated by an IR band at 1549 cm^{-1.22} The imine bond of parent sub-

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 Table 1. Reaction of ketone arylhydrazones with NO

Entry	$R^1R^2C=$	R ³	R^4	ť	Yield ^b
				hr	%
1a		NO ₂	NO ₂	14	92
1b	\succ	NO ₂	NO ₂	14	90
1c		NO ₂	NO ₂	16	90
1d		Н	NO ₂	16	92
1e	O ₂ N	NO ₂	NO ₂	19	86
1f		Н	Н	17	84
1g	(C)	NO ₂	NO ₂	18	68
1h	H ₃ C	NO ₂	NO ₂	14	91
1i	H ₃ CO	NO ₂	NO ₂	12	88

^a The reaction time

^b Yields of the isolated products



Figure 1. Molecular structure of 2a.

strates was found to be not cleaved. The above reaction did not occur when the reaction systems were completely protected from air.

A possible mechanism is postulated to account for the results (Scheme 2). As is well-known, NO is a highly stable free radical and does not abstract a hydrogenatom nor add to an inactivated double bond.^{5d} However, it could couple with other radicals. NO₂ is appreciably more reactive than NO and reacts preferen-



Scheme 2.

tially with dienes. Brown reported that NO containing trace of NO₂ reacted readily with unsaturated bonds to give substituted and additive nitro compounds.^{5a} In the present case, it is assumed that traces of oxygen oxidizes NO to NO₂. An electrophilic addition of NO₂ to the imine double bond of a ketone arylhydrazone produces a nitrogen centered radical 3. It couples with one molecule of NO to give the nitroso adduct 4. The addition of two molecules of NO to its nitroso group yields the N-nitroso-N-nitrite 5. It rearranges to the diazonium nitrate 6, which then undergoes a heterolytic decomposition to give 2, nitric acid and N₂.^{5d,f} Except for the Cl'-nitro azo-compounds 2, one of the other products in liquid phase was identified to be nitric acid.23 Components such as N2 and NO2 in the gas phase were hard to detect due to technical difficulties.

The results listed in Table 1 seem to indicate roughly that an electron-donating substituent linked on the *para*-position of the phenyl ring would shorten the reaction time, such as in the cases of **1i**, **1h**, **1c** and **1e**. Electron-donating substituents make the C1' more electron-rich. Thus, we imagine that the key step of the reactions may be the initially electrophilic addition of NO₂ to the C1'-atom. A similar suggestion was proposed previously,^{20,21} where the neighboring NH group of hydrazone led to an attack of eletrophilic reagent to the atom of carbon–nitrogen double bond, giving a nitrogen centered radical. Kelly tested the similar mechanism for dienes.^{5d}

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- 22. Representative procedure: Stock solutions were prepared by dissolving 0.5 mmol 1a in 100 mL dry CH₂Cl₂. NO was produced by the reaction of 1 M H₂SO₄ solution with saturated NaNO₂ aqueous solution. The former was added to the latter which was stirred under an argon atmosphere. NO was carried by argon and purified by passing it through a series of scrubbing bottles containing 4 M NaOH, ditilled water and CaCl₂ in this order. Bottles were under an argon atmosphere. The purified NO was bubbled through a previously degassed stirred stock solution at room temperature for an appropriate time. After completion of the reaction, as indicated by TLC, the reaction mixture was dried with anhydrous MgSO₄, concertrated in vacuo and purified by column chromatography on silica gel (200-300 mesh, ethyl acetate-hexane), giving the pure 2a. Data for 2a: mp 125.6°C; IR (KBr): 3104, 2942, 2868, 1612, 1549, 1447, 1349, 901, 840, 740 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.60 (4H, m), 1.76 (2H, m), 2.23 (2H, m), 2.62 (2H, m), 7.46 (1H, d, J=9.0 Hz), 8.56 (1H, dd, J=9.0 Hz, J=2.1Hz), 8.89 (1H, d, J=2.1 Hz); ¹³C NMR (75 MHz, CDCl₃): *δ* 21.8, 23.9, 31.7, 113.8, 120.5, 121.0, 128.6, 144.8, 148.1, 148.3; HRESIMS m/z calcd for $C_{12}H_{17}N_6O_6$ (MNH₄⁺): 341.1204; found: 341.1204; EIMS *m*/*z* 323 (M^+) , 289, 107, 91, 79, 55. Crystal data for 2a: $C_{12}H_{13}N_5O_6$, $M_r = 323.27$, monoclinic, space group $P2(1)/c, a = 11.282(2), b = 13.033(2), c = 10.162(1) \text{ Å}, \beta =$ 98.50(1)°, V=1477.8(4) Å³, Z=4, $\rho_{calcd}=1.453$ g/cm³, $\mu = 0.119 \text{ mm}^{-1}$, F(000) = 672, $3.7 \le 2\theta \le 51.0^{\circ}$, $-13 \le h \le$ 13, $-15 \le k \le 0$, $0 \le l \le 12$, 3164 data collected, 2748 unique data ($R_{int} = 0.0113$), 1854 data with $I > 2\sigma(I)$, 228 refined parameters, GOF $(F^2) = 1.017$, $R_1 = 0.066$, $wR_2 =$ 0.112. The X-ray crystallographic structure of 2a is shown in Figure 1. The crystallographic data has been deposited at the Cambrigde Crystallographic Data Centre as Supplementary Publication No. CCDC-212523.
- 23. The solution became acidic along with reaction. After the completion of reaction, the organic phase was washed with a 10 mL aqueous solution of 0.05 M NaOH. IR indentification of compounds in the aqueous phase presented the existence of sodium nitrate (KBr, νNO_2^{-1} 1384 cm⁻¹).