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Photooxidations of 1,1-Dialkyl-2-arylhydrazines by Single Electron Transfer

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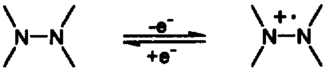
Abstract : The oxidation of substituted hydrazines through monoelectronic transfer leads regio- and stereoselectively with good yields to α-hydrazinonitriles under mild conditions.

Photocyanation by single electron transfer (SET) of tertiary amines has allowed the obtaining of α-aminonitriles with good yields, giving rise to interesting synthetic applications[1]. In the early eighties, studies by Nelsen and co-workers[2] have suggested the possibility of electron-transfer initiated photooxidations of hydrazines (Scheme 1).

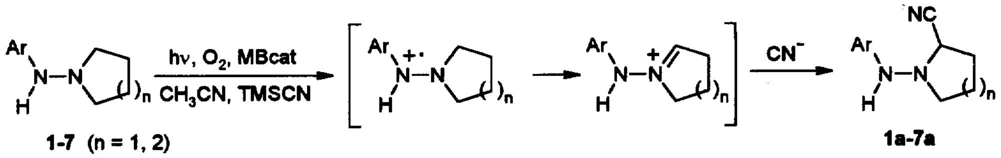


Scheme 1

The formal charge of a hydrazinium radical cation is distributed over the two nitrogen atoms, which explains the high stability observed. E° values have been measured by cyclic voltammetry for hydrazines (acetonitrile, vs. SCE). They vary between 0.2 and 0.4 V and are lower than those of tertiary amines (0.7-0.8 V). In a study of the quenching of $^1O_2$ by easily ionisable nitrogen compounds, Clennan and others[3] have shown that hydrazines are among the most potent known physical quenchers of singlet oxygen.

The usefulness of photoinduced electron transfer photosensitization has been demonstrated by several syntheses and our ongoing interest in photooxidation by visible light prompted us to investigate an extension of this method to the oxidation of 1,1-dialkyl-2-arylhydrazines.

Oxidation of *N*-arylamino-1-pyrrolidine- and *N*-arylamino-1-piperidine **1-7** by irradiation (λ>630 nm) with trimethylsilylcyanide (TMSCN) as cyanide ion source and a catalytic amount of methylene blue (MB) as sensitizer, yields α-hydrazinonitriles **1a-7a** in moderate to good yields (59-94%). As previously observed with tertiary amines, the oxidation is regio- and stereoselective (Scheme 2).



Scheme 2

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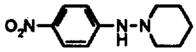
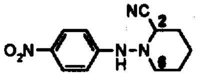
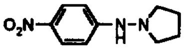
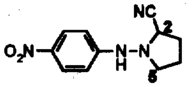
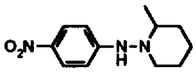
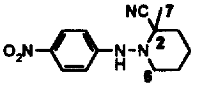
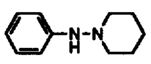
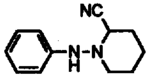
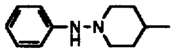
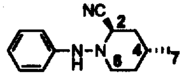
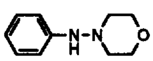
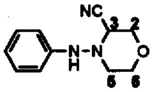
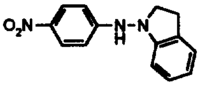
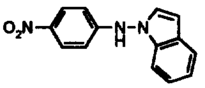
Some representative results are collected in Table I.

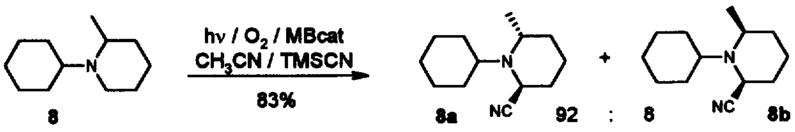
Table I

Substrate		Product $^{(iv)}$		Yield (%)
	$1^{(i)}$		±**1a**	90
	$2^{(ii)}$		±**2a**	85
	$3^{(i)}$		±**3a**	$62^{(v)}$
	$4^{(iii)}$		±**4a**	$59^{(v)}$
	$5^{(iii)}$		±**5a**	83 d.e.$^{(vi)}$ = 100%
	$6^{(iii)}$		±**6a**	75
	$7^{(iii)}$		**7a**	94

(i) prepared by reductive diamination of 4-nitrophenylhydrazine with corresponding dicarbonyl derivative[4]
(ii) synthetized by condensation of succinic anhydride with 4-nitrophenylhydrazine[5] followed by reduction with $LiAlH_4$[6]
(iii) prepared by coupling phenylhydroxylamine with the azaheterocycle[7]
(iv) the structures of the products were fully ascertained by complete spectroscopic determination (MS, IR, NMR spectra ^{1}H and ^{13}C)
(v) purified by flash chromatography on aluminium oxide
(vi) determined by ^{1}H NMR

As can be seen from Table I, a wide variety of α-hydrazinonitriles **1a**-**7a** can be smoothly and efficiently obtained according to our typical SET photocatalytic procedure[8]. The crude products[9] were pure enough for further synthetic use.

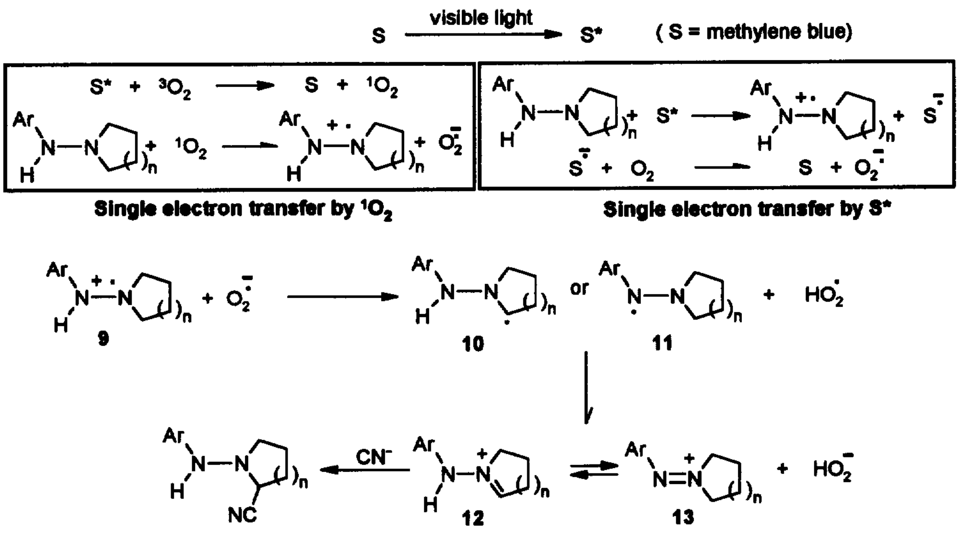
Especially surprising was the selectivity obtained during the cyanation of 2-methyl-*N*-(4-nitrophenyl)amino-1-piperidine **3**. The α-hydrazinonitrile obtained corresponds to the attack of the more substituted α-C–H bond. This result is opposite to what is expected on the basis of stereoelectronic control described by Lewis and co-workers[10] in which the order of selectivity for α-alkylated amines is Me>Et>>*i*-Pr. As shown in Scheme 3 for the photocyanation of the corresponding nonsymmetrically substituted tertiary amine **8**, the result is there in agreement with the selectivity proposed by Lewis.



Scheme 3

The photooxidation of 4-methyl-*N*-phenylamino-1-piperidine **5** gives diasteroeselectively **5a** where the substituents adopt a *trans* relationship with the CN group in the axial plane and the methyl group in the equatorial position. The regio- and stereospecificity of this reaction was in accordance with the results obtained by Hurvois and co-workers during the electrochemical oxidation of N-phenylpiperidines[11]. Also noteworthy is the selective obtaining of α-cyanated morpholinic ring **6a** ; such a regioselectivity has been only previously reported by Barton and co-workers by oxidation with phenylseleninic anhydride[12].

These photooxidations presumably proceed by an initial electron transfer (either by the photosensitizer or by singlet oxygen) along the following sequence (Scheme 4). The photooxygenation may involve energy transfer between excited triplet methylene blue and molecular oxygen. The triplet sensitizer converts ground-state oxygen into a short-lived and highly reactive species. A non-ambiguous singlet oxygen oxidation of some tertiary amines has been previously reported from such species[13]. However, photoxygenation could also proceed via a first electron transfer from the electron donor to the excited methylene blue. The radical anion $BM^{-\cdot}$ should be re-oxidized by molecular oxygen to produce the superoxide anion $O_2^{-\cdot}$.The combination between the hydrazinium radical cation and the superoxide anion could lead to oxidation products. Deprotonation of the radical cation **9** by $O_2^{-\cdot}$ should yield the α-hydrazino radical **10** or the hydrazyl radical **11** which should be rapidly oxidized in the hydrazinium alkylidene cation **12**, in tautomeric equilibrium with the 1,1-dialkyl-2-phenyldiazenium **13**.



Scheme 4

These α-cyano-1,1-dialkylhydrazines can be used for further alkylation or further oxidation.

In summary, these results clearly show that the mild and efficient synthesis of α-aminonitriles previously developed by photosensitization of amines can be successfully applied to hydrazines. In contrast to the results previously obtained with tertiary amines, the regioselective cyanation observed with hydrazines takes place on the more substituted carbon atom. These results offer a remarkable potential for the regiofunctionalisation of substituted α-amino carbon atom by using respectively amines or the corresponding hydrazines.

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8 A solution of substituted hydrazines **1-7** (0.5mmole) with trimethylsilylcyanide (TMSCN) (2mmole, 2 eq.), in acetonitrile (10mL), in presence of catalytic amounts (5%) of methylen blue was irradiated under oxygen bubbling, with a 1800W Xenon lamp through a UV cut-off glass filter (λ>630nm) at room temperature. After complete disappearance of the starting hydrazines (TLC monitoring), the resulting mixture was evaporated under reduced pressure. The crude product was dissolved in methylene chloride (20mL) and neutralized by addition of aqueous Na_2CO_3 10% (15mL). The aqueous phase layer was extracted three times with methylene chloride. The combined organic layers were dried over sodium sulfate and concentrated. The crude products were pure enough for further synthetic use.

9 Selected data for products ±**1a** : m.p ; 148°C (CH_2Cl_2) ; M^++1, 247 (23%, $C_{12}H_{14}N_4O_2$), 264 ; IR ($CHCl_3$, cm^{-1}) 3280, 2940, 2220, 1600 ; ^{1}H NMR 300MHz ($CDCl_3$, δ) 2.76 (1H, ddd, H_{6ax}), 3.03 (1H, dm, H_{6eq}), 4.11 (1H, m, H_{2eq}), 5.64 (1H, s, NH) ; ^{13}C NMR 52.42 (C6), 56.10 (C2), 116.40 (CN) ; ±**2a** : M^++1, 233 (20%, $C_{11}H_{12}N_4O_2$), 250 ; IR ($CHCl_3$, cm^{-1}) 3280, 2960, 2240, 1600 ; ^{1}H NMR 300MHz ($CDCl_3$, δ) 4.08 (1H, m, H_2), 5.67 (1H, s, NH) ; ^{13}C NMR 52.69 (C5), 53.01 (C2), 117.41 (CN) ; ±**3a** : IR ($CHCl_3$, cm^{-1}) 3280, 2940, 2230, 1600 ; ^{1}H NMR 300MHz ($CDCl_3$, δ) 1.52 (3H, s, H_7), 2.70 (1H, ddd, H_{6ax}), 3.08 (1H, m, H_{6eq}), 5.39 (1H, s, NH) ; ^{13}C NMR 25.26 (C7), 53.81 (C6), 61.75 (C2), 118.65 (CN) ; ±**5a** : $M^{+\cdot}$ 215 (100%, $C_{13}H_{17}N_3$), 188, 133, 107, 93, 77 ; IR ($CHCl_3$, cm^{-1}) 3260, 2930, 2220, 1610 ; ^{1}H NMR 300MHz ($CDCl_3$, δ) 1.0 (3H, d, H_7), 1.39 (1H, m, H_{4ax}), 2.63 (1H, ddd, H_{6ax}), 3.10 (1H, dddd, H_{6eq}), 4.17 (1H, m, H_{2eq}), 4.80 (1H, s, NH) ; ^{13}C NMR 21.01 (C7), 26.52 (C4), 51.51 (C6), 55.75 (C2), 116.81 (CN) ; ±**6a** : $M^{+\cdot}$ 203 (100%, $C_{11}H_{13}N_3O$), 120, 105, 92, 77, 65 ; IR ($CHCl_3$, cm^{-1}) 3260, 2920, 2230, 1600 ; ^{1}H NMR 300MHz ($CDCl_3$, δ) 2.89 (1H, ddd, H_{5ax}), 2.97 (1H, m, H_{5eq}), 3.72 (1H, ddd, H_{6ax}), 3.85 (1H, dd, H_{2ax}), 3.97 (1H, m, H_{6eq}), 4.00 (1H, m, H_{3eq}), 4.09 (1H, ddd, H_{2eq}), 4.89 (1H, s, NH) ; ^{13}C NMR 51.54 (C5), 55.67 (C3), 67.10 (C6), 67.77 (C2), 115.41 (CN).

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