A NEW SYNTHESIS OF 1-HYDROXYISOINDOLES

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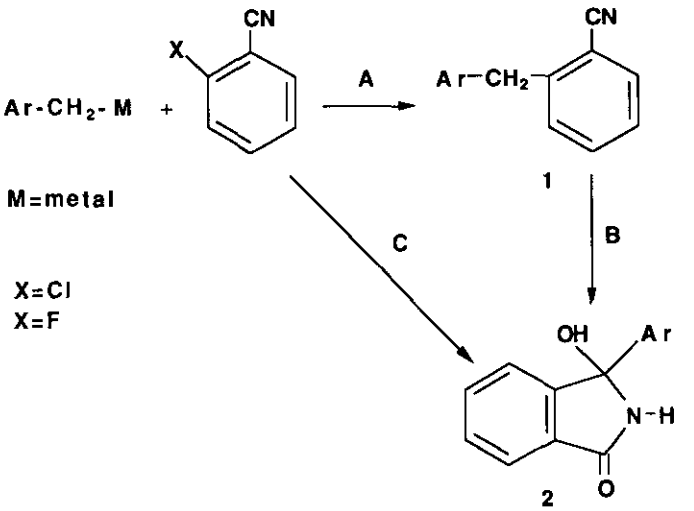
Abstract - Heteroarylmethylation of halogenobenzonitriles in the presence of air (O_2) gives 1-hydroxy-3-oxo-1-aryl-1*H*,3*H*-isoindoles in liquid ammonia. A *"one-pot" or two- step* synthesis is described and a mechanism is proposed.

Due to the importance of 1-hydroxy-3-oxo-1*H*,3*H*-isoindoles in the synthesis of various molecules of biological interest [1-3], we have studied a new route to this type of compounds and we propose a "one-pot" (C) or two-step (A.B) synthesis. We have previously reported an arylmethylation of benzonitrile and, initially we improved the yields of the reaction A (Scheme 1).[4]



Scheme 1

The use of *o*-fluorobenzonitrile(OFBN) in place of *o*-chlorobenzonitrile (OCBN) clearly showed an increase of the yields for compounds (**1**) (Table I) .

Table I

	Ar	O.C.B.N.	O.F.B.N.
1a	2-pyrazyl	70%	92%
1b	2-quinoxalyl	47%	57%
1c	4-pyridyl	40%	96%
1d	2-quinolyl	23%	42%

In the second step of the synthesis, nitriles (**1**) were dissolved in liquid ammonia, treated with $NaNH_2$ to generate the carbanion, and dry air was bubbled into the solution. After 2 h, water was added and compounds (**2 a-d**) were isolated in satisfactory yields (Table II). This way requires two steps and a "one-pot" synthesis, without isolation of compounds (**1**), could be performed (C). When **Ar** was monocyclic (**2a** and **2c**) yields were good, while if **Ar** was bicyclic (**2b** and **2d**) yields were lowered and the separation was more difficult (Table II).

Table II

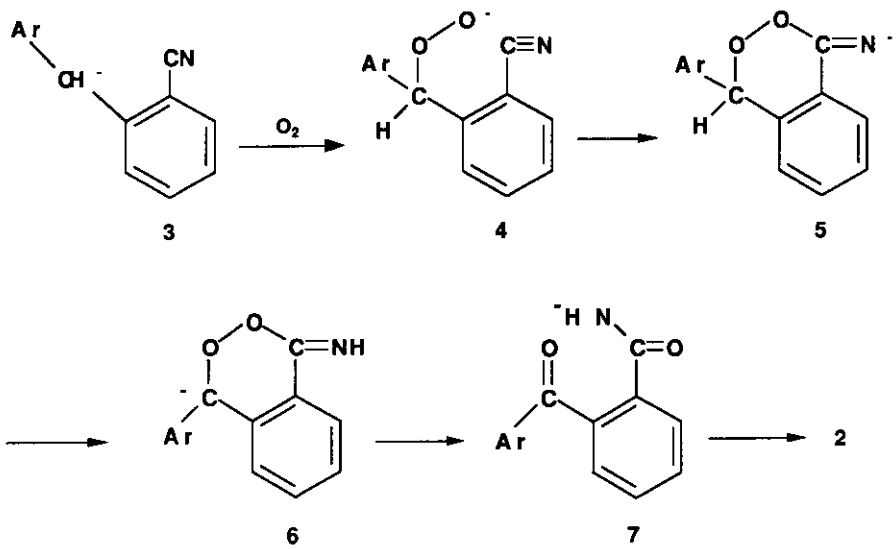
	Ar	**2** Yield (%) reaction **B**	**2** Yield (%) reaction **A+B**	**2** Yield (%) reaction **C**
2a	2-pyrazyl	55	51	63
2b	2-quinoxalyl	48	27	3
2c	4-pyridyl	61	58	71
2d	2-quinolyl	53	22	13

The structure of compound (**2a**) was studied by mass spectroscopy, ^{1}H and ^{13}C nmr, and unambiguously established by X ray cristallography .[5]

The formation of **2** occurred in liquid ammonia with high concentration of reagents and without air. But the yields of oxidation were increased when air was bubbled through the reaction mixture. Dimerisation products supporting a radical mechanism could never be isolated. The following ionic sequence may be proposed: the air oxygen is trapped by the carbanion (**3**) to give an endo-peroxyde (**4**), which forms intermediates (**5**) and (**6**) leading to the amidoketone (**7**) which cyclises easily to **2** (Scheme 2).

This procedure may be compared to that one observed in the Von Richter reaction [6] studied by Rosenblum [7] or in the known synthesis of azetidones .[8]

When ammonia, the reaction solvent, was replaced by THF, DMF or DMSO the 1-hydroxyisoindoles (**2**) were isolated but only in low yields (15%).



Scheme 2

EXPERIMENTAL

Melting points were measured by using a Köfler type melting point apparatus and are uncorrected. ^{1}H Nmr spectra were obtained on a Varian EM 360 and a Bruker 200 A C spectrometers. ^{13}C Nmr spectra were realised on a Bruker 200 A C spectrometer. Mass spectral data were obtained on a VG 70-70F spectrometer. Elemental analyses were performed on a Perkin Elmer 240 apparatus.

1-Hydroxy-3-oxo-1-(2-pyrazyl)-1H,3H- isoindole (**2a**):

General procedure:

To 400 ml of liquid ammonia containing a catalytic amount of ferric nitrate was added 0.50g (0.022 mol) of Na to form $NaNH_2$. Then 2-pyrazylmethylbenzonitrile (3.9g, 0.02 mol) in THF (20 ml) was slowly added with stirring. After 30 min, anhydrous air was bubbled through the solution (about 1 liter per min) during 1 h . A mixture of THF-water (20 ml-20 ml) was then added and ammonia was evaporated. The residue was dissolved in $CHCl_3$ (100 ml). The organic layer was evaporated and chromatographed on silica gel with ethyl acetate as eluent to give 2.90g (63%) of a white powder (**2a**) (mp 238 °C, EtOH). ^{1}H Nmr (DMSO-d_6) δ 9.15 (s, 1H, NH) ; 9.05 (s, 1H, H3'); 8.60-8.40 (m, 2H, H5' and H6'); 7.80-7.35 (m, 4H, H4, H5, H6, H7); 7.25 (s, 1H, OH). ^{13}C Nmr (DMSO-d_6) δ 169.6 (s, CO); 156.0 (s, C2); 149.7 (s, C3a); 144.7; 144.3; 142.6 (3d, C3',C5',C6'); 131.7 (s, C7a); 133.1; 129.9; 123.5; 123.2 (4d, C4, C5, C6, C7); 87.9 (s, C-OH). Ms m/z (relative intensity) : 228 (M+1, 1); 227 (M^+, 2); 226 (M-1, 2); 211 (4); 210 (4) 209 (4); 181 (3); 148 (30); 130 (58); 102 (26). Anal. Calcd for $C_{12}H_9N_3O_2$: C, 63.43; H, 3.99; N, 18.49. Found: C,62.90; H, 4.24; N, 18.72.

1-Hydroxy-3-oxo-1-(2-quinoxalyl)-1H,3H- isoindole (**2b**)

White powder, 2.67g (48%) (two step); mp 236°C (EtOH). ^{1}H Nmr (DMSO-d_6) δ 9.50 (s, 2H,NH); 8.10 (m, 1H); 7.90 (m, 1H); 7.80-7.70 (m, 3H); 7.65 (s, 1H, OH); 7.60-7.45 (m, 3H). ^{13}C Nmr (DMSO-d_6) δ 169.3 (s, CO); 155.6 (s); 149.3 (s); 144.1 (d); 141.7 (s); 137.7 (s); 132.8 (d) ; 131.7 (s); 130.8; 130.6; 129.8; 129.2; 129.1 (5d); 123.7; 123.2 (2d); 88.2 (s, C-OH). Anal. Calcd for $C_{16}H_{11}N_3O_2$: C,69.34; H, 4.00; N, 15.15. Found: C, 69.09; H, 4.09; N, 14.98.

1-Hydroxy-3oxo-1-(4-pyridyl)-1H,3H- isoindole (**2c**)

White powder, 3.21g (71%) (one pot); mp 272°C (EtOH). ^{1}H Nmr (DMSO-d_6) δ 9.45 (s, NH); 8.50 (m, 2H); 7.70 (m, 1H); 7.55-7.40 (m, 4H); 7.30 (m, 1H); 7.20 (s, 1H, OH). ^{13}C Nmr (DMSO-d_6) δ 168.1 (s, CO); 150.6 (s); 149.5 (2d); 149.3 (s); 132.3 (d); 130.3 (s); 129.1 (d); 122.5 (2d); 120.3 (2d); 86.1 (s, C-OH). Anal. Calcd for $C_{13}H_{10}N_2O_2$: C, 69.02; H,4.46; N,12.38. Found: C, 69.18; H, 4.48; N, 12.21.

1-Hydroxy-3oxo-1-(2-quinolyl) isoindole (**2d**)

White powder, 2.92g (53%) (two step); mp 191°C (EtOH). ^{1}H Nmr (DMSO-d_6) δ 9.40 (s, 1H, NH); 8.45 (m, 1H); 8.0-7.85 (m, 3H); 7.75-7.40 (m, 6H); 7.30 (s, 1H, OH). ^{13}C Nmr (DMSO-d_6) δ 168.7 (s, CO); 159.6 (s); 149.2 (s); 145.8 (s); 137.0 (d); 131.9 (d); 130.9 (s); 129.4; 128.7; 128.3; 127.3 (4d); 126.8 (s); 126.3; 122.7; 122.3; 118.3 (4d); 87.8 (s, C-OH). Anal. Calcd for $C_{17}H_{12}N_2O_2$): C, 73.90; H,4.38; N, 10.14. Found: C, 73.69; H, 4.44; N, 9.97.

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