Dipolar 1,3-Cycloaddition of Arylnitriloxides on 1,2-Dihydroisoquinolines in a Two-phase Medium

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The 1,3-dipolar cycloaddition of arylnitriloxides on 1,2-dihydroisoquinoline derivatives led to new 3-aryl, 3a-8,9,9a-tetrahydro[5,4-*c*]-isoxazoloisoquinoline adducts. The regioselectivity of the cycloaddition reactions is discussed on the basis of ^1H and ^{13}C NMR data.

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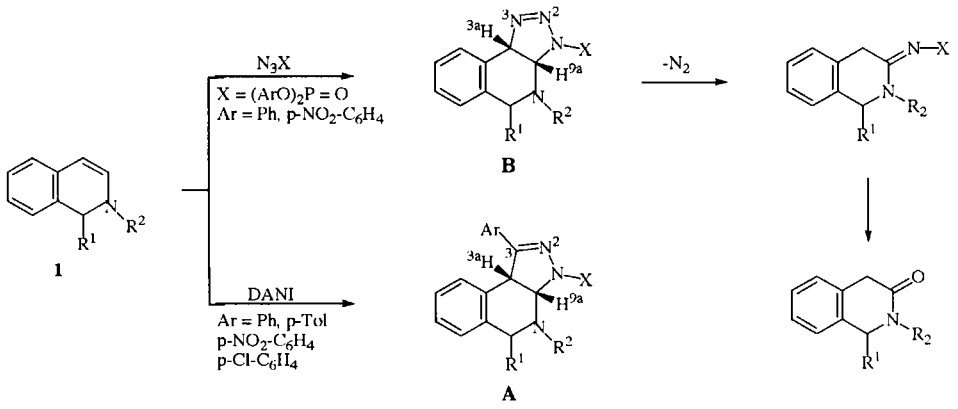
Introduction.

1,2-Dihydroisoquinolines **1** are useful starting materials for the synthesis of a large number of alkaloids [1]. As shown in Scheme 1, various cycloadditions of selected 1,2-dihydroisoquinolines with diarylnitrilimines (DANI) or azides (RN_3) to yield pyrazoloisoquinolizines [2], triazolo and iminoisoquinoline derivatives [3] as novel anti-neoplastic agents [4] were already reported by some of us.

Scheme 1



Reactions of 1,2-dihydroisoquinolines with diarylnitrilimines (DANI) or azides (RN3).

We report here about the reaction of arylnitriloxides (ANO) with substrates of general formulae **1** according to the convenient and inexpensive method proposed by Soufiaoui and coll [5].

Results and Discussion.

As outlined in Scheme 2, cycloadditions of aryl-aldoximes **2** with dipolarophiles **1** were performed at -15°C in a two-phase mixture of chloroform and aqueous sodium hypochlorite.

The use of aqueous NaClO was found to be the sole effective way for the *in situ* generation of ANO from aryl-aldoximes **2** *via* oxidative dehydrogenation without dimerization and ring chlorination as side-reactions. The regiochemistry of cycloadducts **3** was deduced from ^1H and ^{13}C NMR data which are summarised in Tables 1 & 2. For example, the proton H-9a displayed a lowfield signal near 6.1 (± 0.1) ppm according to its peculiar position between a nitrogen and an oxygen atom, while it resonated between 5.1 and 5.2 ppm in the pyrazolines **A** and triazines **B** depicted in Scheme 1. It is worth noting that the coupling constants $J_{3a\text{-}9a}$ are in fair agreement with the *cis*-addition of ANO on ethylenic double bonds [6]. Moreover, ^{13}C NMR resonance of C-9a at 95-98.5 ppm fits also with the proposed regioselectivity where the oxygen atom of the dipole binds to the α-carbon atom of the heteroatom of the six-membered ring.

Having isolated and characterised the adducts **3a-n**, we decided to check the stability of some of them (and those of 3 new adducts) towards acidic media. Either a 90 minute reflux in an ethanolic hydrochloride solution or a simple elution through a silica gel column at room temperature opened the isoxazolinic ring to yield the oximes **4** quantitatively (Scheme 3).

Table 1

^{1}H NMR data of cycloadducts **3a-n** (δ in ppm relative to TMS in $CDCl_3$, J in Hz)

Adducts	R^1	R^2	R	H-8	H-3a	H-9a	ArH
3a	1.40 (d, 3 H) J_{Me-8} 7.0	2.90 (s, 3 H)		3.90 (q, 1 H) J_{8-Me} 7.0	4.70 (d, 1 H) J_{3a-9a} 10.0	5.95 (d, 1 H) J_{9a-3a} 10.0	7.4-8.0 (m, 9 H)
3b	1.40 (d, 3 H) J_{Me-8} 7.0	2.85 (s, 3 H)	2.30 (s, 3 H)	3.90 (q, 1 H) J_{8-Me} 7.0	4.70 (d, 1H) J_{3a-9a} 10.0	5.95 (d, 1H) J_{9a-3a} 10.0	7.2-7.9 (m, 8 H)
3c	0.90 (t, 3 H) J_{Me-CH2} 7.0 1.40 and 2.10 ($ABMX_3$, 2 H)	2.90 (s, 3 H)		3.60 (dd, 1 H) $J_{8-A} = J_{8-B}$ 5.0	4.80 (d, 1 H) J_{3a-9a} 10.0	6.00 (d, 1 H) J_{9a-3a} 10.0	7.1-7.8 (m, 9 H)
3d	0.85 (t, 3 H) J_{Me-CH2} 7.0 1.40 and 2.10 ($ABMX_3$, 2 H)	2.90 (s, 3 H)	2.30 (s, 3 H)	3.50 (dd, 1 H) $J_{8-A} = J_{8-B}$ 5.0	4.70 (d, 1 H) J_{3a-9a} 10.0	5.90 (d, 1 H) J_{9a-3a} 10.0	6.9-7.5 (m, 8 H)
3e	1.35 (t, 3 H) J_{Me-8} 7.0	1.15 (t, 3 H) J_{Me-CH2} 7.5 2.70 and 2.90 ($ABMX_3$, 2 H)	J_{8-Me} 7.0	3.90 (q, 1 H) J_{3a-9a} 10.0	4.80 (d, 1 H) J_{9a-3a} 10.0	6.00 (d, 1 H) (m, 9 H)	7.1-7.8
3f	1.40 (d, 3 H) J_{Me-8} 7.0	1.15 (t, 3 H) J_{Me-CH2} 7.5 2.70 and 2.95 ($ABMX_3$, 2 H)	3.85 (s, 3 H)	3.90 (q, 1 H) J_{8-Me} 7.0	4.80 (d, 1 H) J_{3a-9a} 10.0	6.05 (d, 1 H) J_{9a-3a} 10.0	7.1-7.8 (m, 9 H)
3g	0.90 (t, 3 H) J_{Me-CH2} 7.4 Hz 1.50-2.10 ($ABMX_3$, 2 H)	1.20 (t, 3 H) J_{Me-CH2} 7.2 3.10-3.30 ($ABMX_3$, 2 H)		3.67 (dd, 1 H) $J_{8-A} = J_{8-B}$ 4.0	4.85 (d, 1 H) J_{3a-9a} 10.4	6.10 (d, 1 H) J_{9a-3a} 10.0	7.05-7.65 (m, 9 H)
3h	0.90 (t, 3 H) J_{Me-CH2} 7.5 1.50-2.12 ($ABMX_3$, 2 H)	1.20 (t, 3H) J_{Me-CH2} 7.3 3.00-3.25 ($ABMX_3$, 2 H)	3.80 (s, 3 H)	3.67 (dd, 1 H) $J_{8-A} = J_{8-B}$ 4.0	4.85 (d, 1 H) J_{3a-9a} 10.2	6.10 (d, 1 H) J_{9a-3a} 10.2	7.0-7.6 (m, 8 H)
3i		2.50 (s, 3 H)		4.95 (s, 1 H)	4.80 (d, 1 H) J_{3a-9a} 8.5	6.00 (d, 1 H) J_{9a-3a} 8.5	6.55-7.8 (m, 14 H)
3j		2.50 (s, 3 H)	3.85 (s, 3 H)	5.00 (s, 1 H)	4.85 (d, 1 H) J_{3a-9a} 8.3	6.00 (d, 1 H) J_{9a-3a} 8.3	6.5-7.6 (m, 13 H)
3k		2.50 (s, 3 H)		4.95 (s, 1 H)	4.85 (d, 1 H) J_{3a-9a} 8.2	6.00 (d, 1 H) J_{9a-3a} 8.2	6.5-7.65 (m, 13 H)
3l		1.15 (t, 3 H) J_{Me-CH2} 7.0 2.70-2.95 ($ABMX_3$, 2 H)		5.20 (s, 1 H)	4.70 (d, 1 H) J_{3a-9a} 7.8	6.00 (d, 1 H) J_{9a-3a} 7.8	6.5-7.7 (m, 13 H)
3m		1.10 (t, 3 H) J_{Me-CH2} 7.0 2.70-2.90 ($ABMX_3$, 2 H)	3.90 (s, 3 H)	5.20 (s, 1 H)	4.75 (d, 1 H) J_{3a-9a} 7.8	6.00 (d, 1 H) J_{9a-3a} 7.8	6.5-7.6 (m, 13 H)
3n		1.10 (t, 3 H) J_{Me-CH2} 7.0 2.70-2.90 ($ABMX_3$, 2 H)		5.20 (s, 1 H)	4.75 (d, 1 H) J_{3a-9a} 7.8	6.00 (d, 1 H) J_{9a-3a} 7.8	6.5-7.7 (m, 13 H)

The ^{1}H NMR spectrum of **4** displayed a singlet between 3.0 and 3.4 ppm, which disappeared by addition of D_2O and was assigned to the OH group. Also, in the ^{13}C-NMR spectrum, a peak around 160 ppm, is observed and assigned to the oxime carbon C-9 (Table 3). These results altogether are in good agreement with those of the literature in the field and especially with the observations of Caramella *et al.* relative to adducts of benzonitriloxide with *N*-methylindole [7].

Conclusion.

In presence of aqueous sodium hypochlorite, the dihydroisoquinolines **1** undergo rapid (within 1 hour)

Table 2

Selected ^{13}C NMR data of cycloadducts **3g**, **3i**, and **3k-n** (δ in ppm relative to TMS in $CDCl_3$ at 50 MHz)

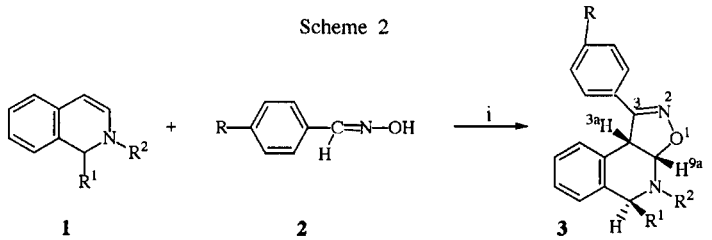
Adducts	R^1	R^2	R	C-8	C-9a	C-3a	C-3
3g	CH_2-CH_3 12.3 CH_2-CH_3 25.4	N-CH_2-CH_3 13.5 N-CH_2-CH_3 48.2		61.7	95.0	45.6	159.0
3i		N-CH_3 40.4		61.8	98.0	46.2	159.4
3k		N-CH_3 40.4		61.9	98.6	46.3	159.9
3l		N-CH_2-CH_3 12.5 N-CH_2-CH_3 45.6		60.4	96.2	45.5	159.2
3m	- - - -	N-CH_2-CH_3 12.5 N-CH_2-CH_3 45.6	OCH_3 55.2	60.4	95.8	45.5	160.8
3n	- - - -	N-CH_2-CH_3 12.5 N-CH_2-CH_3 45.5	- - - -	60.3	96.5	45.4	160.3

Table 3

Selected ^1H- and ^{13}C NMR data of oximes **4** (δ in ppm relative to TMS in $CDCl_3$, J in Hz)

Oximes	H-1	H-2	OH	C-1	C-3	C-4	C-9
4c	3.62, dd $J_{1\text{-}A}$ 6.8 $J_{1\text{-}B}$ 3.6	5.50 s	3.45 s	63.8	104.0	82.2	160.1
4e	4.15, q $J_{1\text{-}Me}$ 6.8	5.60 s	3.10 s	52.5	102.5	81.6	160.1
4f	4.15, q $J_{1\text{-}Me}$ 6.8	5.70 s	3.00 s	54.0	102.2	81.6	160.1
4o	3.35 d, $J_{1\text{-}A}$ 6.6	5.55 s	3.25 s	69.9	105.3	80.9	160.3
4p	3.40 d, $J_{1\text{-}A}$ 6.0	5.50 s	3.25 s	69.2	104.9	80.6	160.1
4q	3.40 d, $J_{1\text{-}A}$ 6.4	5.65 s	3.00 s	67.7	104.5	80.3	160.2

Scheme 2



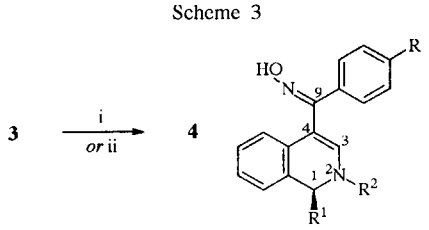
1 **2** **3**

3a: $R^1 = R^2 = Me$, R = H
3b: $R^1 = R^2 = R = Me$
3c: $R^1 = Et$, $R^2 = Me$, R = H
3d: $R^1 = Et$, $R^2 = R = Me$
3e: $R^1 = Me$, $R^2 = Et$, R = H
3f: $R^1 = Me$, $R^2 = Et$, $R^3 = OMe$
3g: $R^1 = R^2 = Et$, R = H

3h: $R^1 = R^2 = Et$, R = OMe
3i: $R^1 = Ph$, $R^2 = Me$, R= H
3j: $R^1 = Ph$, $R^2 = Me$, R = OMe
3k: $R^1 = Ph$, $R^2 = Me$, R = Cl
3l: $R^1 = Ph$, $R^2 = Et$, R = H
3m: $R^1 = Ph$, $R^2 = Et$, R = OMe
3n: $R^1 = Ph$, $R^2 = Et$, R = Cl

(i) CHCl3/NaClO, -15°C, 1 hour.

Scheme 3



4c: R^1 = Et, R^2 = Me, R = H
4e: R^1 = Me, R^2 = Et, R = H
4f: R^1 = Me, R^2 = Et, R = OMe
4o: R^1 = *i*-Pr, R^2 = Me, R = H
4p: R^1 = *i*-Pr, R^2 = Me, R = OMe
4q: R^1 = *i*-Pr, R^2 = Et, R = H

(i) SiO2, rt ; ii, H3O+, ref. EtOH, 90 minutes.

and regioselective 1,3-dipolar cycloadditions with aryl-aldoximes **2** in 72-86% yields. These cycloadditions are predominantly *anti* in respect to the substituent R^1 which control the π-facial selection of the new cycloadducts **3**. In the presence of hydrochloric acid or silica gel, they are quantitatively hydrolysed to the corresponding oximes **4**.

EXPERIMENTAL

General.

Chemicals were purchased from Aldrich Chem Co and solvents from Prolabo (France). Ethanol was distilled over magnesium and chloroform over diphosphorus pentaoxide and stored in the dark. All chemical reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Merck silica gel plates (60 F_{254}). Visualisation was achieved under a UV-lamp at 254 nm and development with iodine vapour. Sodium sulfate was used to dry the organic solutions during work-up. Yields refer to pure isolated compounds after preparative crystallisation. Hydrolysis were performed on silica gel from E. Merck (ref. 109385), particle size 40-63 μM at room temperature. Melting points were taken in open capillary tubes on a Büchi apparatus (model 510) and are uncorrected. Unless otherwise stated, ^{1}H- and ^{13}C NMR spectra were recorded on a Bruker AC200 spectrometer in deuteriochloroform or deuteriumoxide at 200 and 50 MHz respectively at 298 K. IR spectra were recorded on a Beckman IFS-45 spectrometer at room temperature in KBr pellets. Elemental analyses were performed by Service Central de Microanalyse of the CNRS (Vernaison, France).

Cycloaddition of Arylnitriloxides With Dihydroisoquinolines **1**.

Onto a magnetically stirred solution of dipolarophile **1** (10.0 mmol) and arylaldoxime **2** (1.2 eq) in chloroform (20 mL) cooled at -15°C were dropped 10 mL of aqueous sodium hypochlorate (24°Cl = 23% NaClO w/w) over 15 minutes. The resulting two-phase system was then stirred vigorously for 1 hour at the same temperature, the organic phase separated, washed with water (3 (10 mL), dried and finally concentrated to a gum which solidified on standing in the dark at room temperature. Crystallisation from ethanol afforded pure cycloadducts **3**.

Compound **3a** was obtained in 72% yield, mp 120-122°C; ^{1}H- and ^{13}C-NMR see Table 1 and 2.

Anal. Calcd. for $C_{18}H_{18}N_2O$: C, 77.69; H, 6.47. Found: C, 77.71; H, 6.46.

Compound **3b** was obtained in 74% yield, mp 103-105°C; ^{1}H- and ^{13}C-NMR see Table 1 and 2.

Anal. Calcd. for $C_{19}H_{20}N_2O$: C, 78.08; H, 6.84. Found: C, 78.07; H6.83.

Compound **3c** was obtained in 83% yield, mp 130-132°C; ^{1}H- and ^{13}C-NMR see Table 1 and 2.

Anal. Calcd. for $C_{19}H_{20}N_2O$: C, 78.08; H, 6.84. Found: C, 78.04; H, 6.85.

Compoud **3d** was obtained in 77% yield, mp 126-128°C; ^{1}H- and ^{13}C-NMR see Table 1 and 2.

Anal. Calcd. for $C_{20}H_{22}N_{2O}$: C, 78.43; H, 7.18. Found: C,78.40; H, 7.18.

Compound **3e** was obtained in 78% yield, mp 140-142°C; ^{1}H- and ^{13}C-NMR see Table 1 and 2.

Anal. Calcd. for $C_{19}H_{20}N_2O$: C, 78.08; H, 6.84. Found: C, 78.10; H, 6.85.

Compound **3f** was obtained in 80% yield, mp 127-129°C; ^{1}H- and ^{13}C-NMR see Table 1 and 2.

Anal. Calcd. for $C_{20}H_{22}N_2O_2$: C, 74.53; H, 6.83. Found: C, 74.50; H, 6.84.

Compound **3g** was obtained in 85% yield, mp 138-140°C; ^{1}H- and ^{13}C-NMR see Table 1 and 2.

Anal. Calcd. for $C_{20}H_{22}N_2O$: C, 78.43; H, 7.18. Found: C, 78.43; H, 7.19.

Compound **3h** was obtained in 86% yield, mp 135-137°C; ^{1}H- and ^{13}C-NMR see Table 1 and 2.

Anal. Calcd. for C21H24N2O2: C 75.00; H, 7.14. Found: C, 75.10; H,7.11.

Compound **3i** was obtained in 79% yiled, mp 176-178°C; ^{1}H- and ^{13}C-NMR see Table 1 and 2.

Anal. Calcd. for $C_{23}H_{20}N_2O$: C, 81.17; H, 5.88. Found: C, 81.20; H, 5.85.

Compound **3j** was obtained in 79% yield, mp 188-190°C; ^{1}H- and ^{13}C-NMR see Table 1 and 2.

Anal. Calcd. for $C_{24}H_{22}N_2O_2$: C, 77.83; H, 5.94. Found: C, 77.79; H, 5.92.

Compound **3k** was obtained in 80% yield, mp 196-198°C; ^{1}H- and ^{13}C-NMR see Table 1 and 2.

Anal. Calcd. for $C_{23}H_{19}ClN_2O$: C, 73.69; H, 5.07. Found: C, 73.71; H, 5.10.

Compound **3l** was obtained in 83% yield, mp 158-160°C; ^{1}H- and ^{13}C-NMR see Table 1 and 2.

Anal. Calcd. for $C_{24}H_{22}N_2O$: C, 81.35; H, 6.21. Found: C, 81.31; H, 6.25.

Compound **3m** was obtained in 77% yield, mp 180-182°C; ^{1}H- and ^{13}C-NMR see Table 1 and 2.

Anal. Calcd. for $C_{25}H_{24}N_2O_2$: C, 78.12; H, 6.25. Found: C, 78.00; H, 6.02

Compound **3n** was obtained in 82% yield, mp 180-182°C; ^{1}H- and ^{13}C-NMR, see Table 1 and 2.

Anal. Calcd. for $C_{24}H_{21}ClN_2O$: C, 74.13; H, 5.40. Found: C, 74.13; H, 5.39.

Hydrolysis of Adducts **3**.

A solution of of the adduct (4.0 mmol) in ethanol (20 mL) and 12 *N* hydrochloric acid (1 mL) was refluxed for 90 minutes. The mixture was allowed to cool and quenched with chilled

water (80 mL). The organic phase was separated and the aqueous phase extracted with diethyl ether (3 (50 mL). The organic phases were combined, dried over sodium sulfate, and concentrated *in vacuo* to yield the corresponding oxime as an oil.

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