Synthesis and Reduction of 2,2-Diaryl-1-nitroethylenes by Using a Chiral and a non Chiral NADH Model in the Pyrrolopyridine Series

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Reduction of 2,2-diphenyl-1-nitroethylene (**1**) and 2-(2-pyridyl)-2-phenyl-1-nitroethylene (**5**) is achieved by using the NADH model in the pyrrolopyridine series **2a** to give 2,2-diphenyl-1-nitroethane (**3**) and 2-(2-pyridyl)-2-phenyl-1-nitroethane (**7**) respectively in 40% yield. The asymmetric reduction of 2-(2-pyridyl)-2-phenyl-1-nitroethylene by the chiral NADH model **2b** is studied. Thus, 2-(2-pyridyl)-2-phenyl-1-nitroethane (**7**) is obtained in 15 to 32% yield. The stereocontrol of the reduction proved to be dependent on the amount of magnesium ions.

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Introduction.

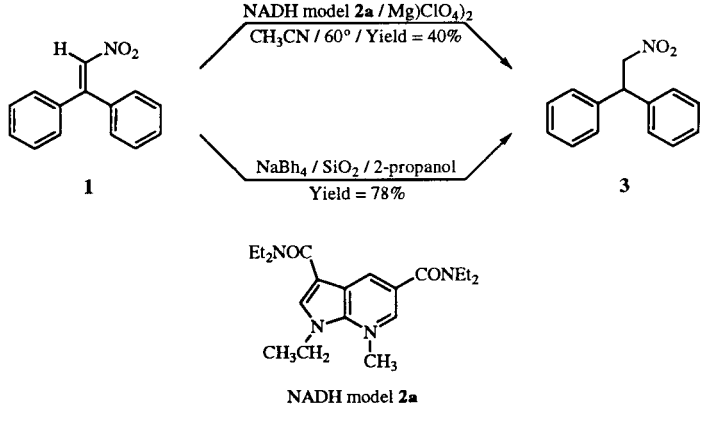
Organic nitro compounds which are easily transformed into amines, carbonyls or hydrocarbons have proven to be versatile synthetic intermediates in organic chemistry [1a-b]. Thus, optically pure nitro compounds should provide access to useful chiral building blocks for asymmetric synthesis. Methods are available for the preparation of optically pure 2-alkyl-2-arylnitroethanes which involved microbial reduction of nitroc efins [2a-c] or enantioselective Michael addition to nitroolefins [3a-c]. So far, asymmetric synthesis of 2,2-diaryl-1-nitroethanes has not been investigated. Nevertheless, these derivatives are of special interest since they provide access to a variety of diarylethylamines, precursors of optically active tetrahydroisoquinoline derivatives of great importance due to their pharmacological properties [4a-d]. In the light of these considerations, our previous interest in NADH models [5a-c] used as reducing agents prompted us to study the asymmetric reduction of prochiral 2,2-diaryl-1-nitroethylenes by chiral NADH models.

Results.

Firstly, we studied the reactivity of a non-chiral NADH model toward 2,2-diaryl-1-nitroethylenes. For this purpose, we made use of a NADH model in the pyrrolopyridine series (Scheme 1), which has previously proven to be stable and reactive toward a wide variety of substrates [5c]. Thus, 2,2-diphenyl-1-nitroethylene (**1**) [6] obtained by nitration of 1,1-diphenylethylene [7] in a 58% yield, was reacted with reagent **2a** under conditions usually described [5a-c] with NADH models (Mg^{2+} ions are involved in a ternary complex with the model and the substrate which facilates the hydrogen transfer).

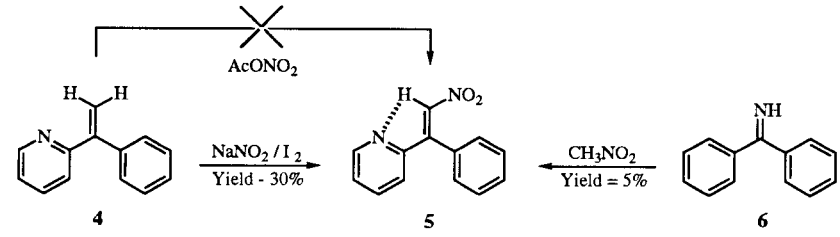
Although 2,2-diphenyl-1-nitroethane (**3**) was obtained in a moderate yield (40% after chromatography) (Scheme 1), it is the first report dealing with the reduction of a 2,2-diaryl-1-nitrostyrene by such a reagent [8a-c]. Alternatively, compound **3** was prepared in 78% yield according to a literature procedure [9] by reduction of compound **1** with sodium borohydride in the presence of silica gel (Scheme 1).

Scheme 1

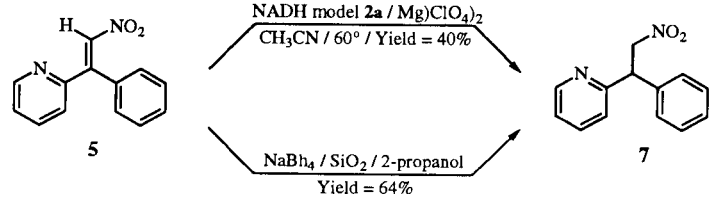


With this first promising result in hand, we set out to study the asymmetric reduction of a prochiral 2,2-diaryl-1-nitroethylene. For the present investigation, we turned our interest in the synthesis of 2-(2-pyridyl)-2-phenyl-1-nitroethylene (**5**). Whereas efficient methods leading to 2-alkyl-2aryl-1-nitroethylenes are available [10a-c], only few reports dealing with the preparation of 2,2-diaryl-1-nitroethylenes have been reported [11]. Our attempts to prepare the desired compound **5** by nitration of 1-(2-pyridyl)-1-phenylethylene (**4**) under the same conditions mentioned above were unsuccessful, leading to traces of byproducts resulting from the nitration at the benzene ring together with the starting material (Scheme 2) (under these conditions, the protonation of nitrogen at the pyridine ring is probably responsible of the deactivation of the double bond toward electrophilic attack). In a second approach, we explored a classical method involving the

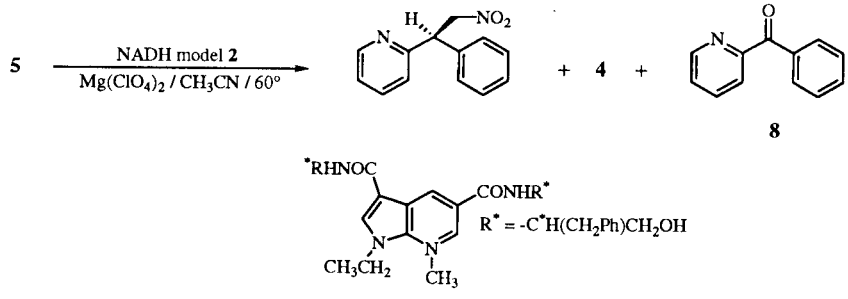
Scheme 2



Scheme 3



Scheme 4



NADH model **2a**

condensation of nitromethane with carbonyl derivatives. It is well known that Henry reaction undergoes an unfavourable equilibrium when ketones are employed as substrates with nitromethane. To circumvent this problem authors recommend the use of the corresponding ketimines [12]. Thus, the ketimine **6** obtained by reaction of 2-cyanopyridine with phenyl magnesium bromide was subsequently treated with nitromethane to give mainly unidentified products along with nitroolefine **5** in only 5% yield (Scheme 2). Finally, we succeeded in the preparation of the desired nitroolefin **5** in a moderate yield (30% after chromatography) by reaction of compound **4** with sodium nitrite, in the presence of iodine [13] (Scheme 2). According to ^{1}H nmr spectrum, compound **5** was obtained as a single isomer. The structure of the obtained (*E*)-2-(2-pyridyl)-2-phenyl-1-nitroethylene (**5**), was elucidated from noe experiments and molecular modelisation. In addition, the possible occurence of an hydrogen bond between the lone pair of pyridine nitrogen and the hydrogen of the ethylenic double bond, already mentioned for similar compounds in the literature [14] argue in favor of the (*E*) isomer.

The so-obtained compound **5** was first reduced by reagent **2a** and by sodium borohydride under the same conditions described above to afford compound **7** in 40% and 64% yield respectively (Scheme 3).

Asymmetric reduction of nitroalkene **5** was then studied with the chiral NADH model **2b** in acetonitrile with different amounts of magnesium perchlorate for 2 days at 60°. The desired 2-(2-pyridyl)-2-phenyl-1-nitroethane (**7**) was obtained in low yield (15-32%) along with compound **4** (12-22%) [15]. Use of a large excess of magnesium perchlorate (7 and 10 equivalents) led to the formation of 2-benzoylpyridine (**8**) (11-18%) [16] along with the desired compound **7** in a somewhat lower yield (15%) (Scheme 4, Table 1). In addition to the formation of the undesired compounds **4** and **8**, Michael-addition of the initial reduction intermediate to the parent nitroalkene **5** leading to a partial polymerization is also probably responsible of the low chemical yield of the reduction [17].

More interestingly, it should be noted that the magnesium ions concentration seems to affect the stereocontrol of the reduction (Table 1). Indeed, while the enantioselectivity is null in the presence of one or two equivalents of magne-

sium ions (entries 1, 2), the enantiomeric excess goes up to 40% by using seven or more equivalents (entries 5, 6). It should be specified that reagent **2b** behave in a similar manner during the asymmetric reduction of methyl benzoylformate [15].

Table 1

Entry	Equivalent Amount of Mg2+	Yields of **7** %	Enantiomeric excesses %	Yields of **4** %	**8** %
1	1	32	0	16	—
2	2	20	0	25	—
3	3.5	25	15	22	—
4	4	16	27	25	—
5	7	15	40	—	11
6	10	15	40	—	18

In spite of the fact that the enantioselectivity and the yield of the reduction are low, we report in here the first investigation dealing with asymmetric reduction of prochiral 2,2-diaryl-1-nitroethylenes. Studies are in progress to improve the stereocontrol of the reduction as well as the chemical yield and to obtain information about the structure of the ternary complex.

EXPERIMENTAL

The following compounds were prepared by literature methods: 1,1-diphenylethylene [16], 2,2-diphenyl-1-nitroethylene (**1**) [16], NADH model **2a** [15], NADH model **2b** [16]. Commercially available reagents were used unless otherwise stated. Tetrahydrofuran and diethyl ether were distilled from sodium/benzophenone ketyl prior to use. The ^{1}H nmr spectra were recorded in deuteriochloroform with tetramethylsilane (TMS) as an internal standard or in dimethylsulfoxide-d_6 with hexamethyldisilane as an internal standard at 200 MHz on a Bruker AC 200 spectrometer. The infrared spectra were recorded on a Beckman IR 4250 spectrometer. Elemental analyses were performed on a Carlo-Erba 1106 analyser. Enantiomeric excesses were measured by high pressure liquid chromatography (hplc) by using a Waters apparatus and a AGP chiral column (100 x 4 mm; 5 μm) purchased from Chrom Tech. Inc.

2,2-Diphenyl-1-nitroethane (**3**).

From reduction of 2,2-diphenyl-1-nitroethylene (**1**) with sodium borohydride: To a solution of 2,2-diphenyl-1-nitroethylene (**1**) (227 mg, 1 mmole) and 2 g of silica gel in 2-propanol (3 ml) and chloroform (16 ml) was added sodium borohydride (156 mg, 4.1 mmoles) in 40 mg portions over a period of fifteen minutes at 25°. The solution was treated with aqueous 0.5 *M* hydrochloric acid solution. The reaction mixture was filtered off and the precipitate washed with dichloromethane. The filtrate was washed with brine, dried (sodium sulfate) and evaporated to dryness. The residual yellow oil was purified by flash chromatography (silica gel-dichloromethane) to give **3** in 70% yield; ir: ν 1552, 1376, 1347 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 7.5-7.15 (m, 10H, phenyl), 5.38 (d, 2H, J = 8.0 Hz, CH_2NO_2), 4.63 (t, 1H, J = 8.0 Hz, CH).

Anal. Calcd. for $C_{14}H_{13}NO_2$: C, 73.98; H, 5.77; N, 6.17. Found: C, 74.19; H, 5.75; N, 6.25.

From reduction of 2,2-Diphenyl-1-nitroethylene (**1**) with Reagent **2a**.

To a solution of reagent **2a** (139 mg, 0.32 mmole) and magnesium perchlorate (79 mg, 0.35 mmole) in dry acetonitrile (2 ml) was added 2,2-diphenyl-1-nitroethylene (**1**) (70 mg, 0.31 mmole). The resulting solution was stirred at 60° for two days under nitrogen. The reaction mixture was hydrolyzed with water (1 ml). Acetonitrile was evaporated under vacuum and the aqueous layer was extracted with dichloromethane (2 x 10 ml). The combined organic phases were dried (magnesium sulfate). Evaporation of dichloromethane gave an oily residue which after flash chromatography (silica gel-dichloromethane) afforded **3** in 40% yield.

1-(2-Pyridyl)-1-phenylethylene (**4**).

A solution of 2-bromopyridine (2.37 g, 15 mmoles) in dry tetrahydrofuran (70 ml) was cooled to -78°. A solution of *n*-butyllithium in hexane (9.38 ml, 1.6 *M*, 15 mmoles) was added under nitrogen. After stirring at -78° for thirty minutes, acetophenone (1.92 ml, 16.5 mmoles) was then added and the resulting solution was stirred at this temperature for five hours. The solution was then hydrolyzed with a 10% aqueous ammonium chloride solution (30 ml). Tetrahydrofuran was evaporated under vacuum and the resulting aqueous layer extracted twice with dichloromethane (50 ml). The dichloromethane phase was dried (magnesium sulfate) and evaporated. Sulfuric acid (96%, 0.6 ml) and glacial acetic acid (2.4 ml) were added to the residue. The resulting solution was stirred at 105° for twelve hours. After cooling, the solution was poured on water (100 ml) and the resulting aqueous phase was neutralized with 10% aqueous sodium carbonate solution. The aqueous phase was extracted with ether (2 x 100 ml). The combined ether layers were extracted with 1*M* aqueous hydrochloric acid (2 x 75 ml). The resulting acidic aqueous solution was then neutralized with 10% sodium hydrogen carbonate solution and extracted with ether (2 x 100 ml). The ethereal phase was dried (sodium sulfate) and ether was evaporated under vacuum to give an orange oil. The crude product was purified by column chromatography (silica gel-dichloromethane) to yield 2.17 g (80%) of **4**; ir: ν 3078, 3054, 3024, 1664, 1581, 1563, 1429, 913, 599 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 8.58 (dd, 1H, J = 5.0, 2.0 Hz, pyridyl H_6), 7.78 (td, 1H, J = 7.7, 2.0 Hz, pyridyl H_4), 7.4-7.25 (m, 7H, phenyl protons and pyridyl protons H_5 and H_3), 5.92 (d, 1H, J = 1.5 Hz, ethylenic proton), 5.58 (d, 1H, J = 1.5 Hz, ethylenic proton).

Anal. Calcd. for $C_{13}H_{11}N$: C, 86.15; H, 6.12; N, 7.73. Found: C, 86.34; H, 6.21; N, 7.63.

2-(2-Pyridyl)-2-phenyl-1-nitroethylene (**5**).

From Condensation of Ketimine **6** with Nitromethane.

To a solution of phenylmagnesium bromide in diethyl ether (4.1 ml, 3 *M*, 12.3 mmoles) cooled to 0° was dropwise added a solution of 2-cyanopyridine (1.28 g, 12.3 mmoles) in anhydrous diethyl ether (10 ml) with vigorous stirring after which the mixture was boiled for 2 hours. After cooling to room temperature, methanol (2.7 ml, 74 mmoles) was added dropwise to the reaction mixture and the solvents were evaporated under vacuum. To the crude ketimine **6**, nitromethane (5 ml) was added to the residue and the resulting solution was stirred at reflux for four hours. After adding methanol, nitromethane was eliminated by azeotrop-

ic distillation (nitromethane:methanol 92/8 v/v) to afford a brown oil which was subjected to column chromatography (silica gel) by eluting with dichloromethane to give compound **5** in a 5% yield.

mp 65° (cyclohexane); ir: ν 1518, 1340 cm^{-1}; ^1H nmr (DMSO-d_6): δ 8.69 (ddd, 1H, J = 5.0, 1.8, 1.0 Hz, pyridyl H_6), 8.23 (s, 1H, ethylenic proton), 7.84 (td, 1H, J = 7.5, 1.8 Hz, pyridyl H_4), 7.55-7.45 (m, 4H, phenyl protons), 7.32-7.25 (m, 2H, pyridyl H_5 and phenyl), 7.09 (dt, 1H, J = 7.5, 1.0 Hz, pyridyl H_3).

Anal. Calcd. for $C_{13}H_{10}N_2O_2$: C, 69.00; H, 4.46; N, 12.39. Found: C, 69.12; H, 4.43; N, 12.45.

From Reaction of 1-(2-Pyridyl)-1-phenylethylene (**4**) with Sodium Nitrite.

To a solution of sodium nitrite (662 mg, 9.6 mmoles) and ethylene glycol (477 mg, 7.2 mmoles) in water (1 ml) precooled to 0°, was added a solution of 1-(2-pyridyl)-1-phenylethylene (**4**) (434 mg, 2.4 mmoles) in ethyl acetate (15 ml) and iodine (913 mg, 3.16 mmoles). The resulting solution was stirred at 20° for three days. After adding 10% sodium hydrogen carbonate solution (10 ml) and ethyl acetate (20 ml), the organic layer was washed in succession with water (20 ml) and with a 10% aqueous sodium thiosulfate solution (20 ml). Drying (sodium sulfate) and evaporation of ethyl acetate afforded an oil which after chromatography (silica gel-dichloromethane/cyclohexane: 7/3) gave compound **5** in 30% yield.

2-(2-Pyridyl)-2-phenyl-1-nitroethane (7).

From reduction of 2-(2-pyridyl)-2-phenyl-1-nitroethane (**2**) with sodium borohydride: This compound was prepared using the same method as for 3 from 2-(2-pyridyl)-2-phenyl-1-nitroethylene (**5**) (226 mg, 1 mmole) and silica gel (2 g) in 2-propanol (3 ml) and chloroform (16 ml). Sodium borohydride (156 mg, 4.1 mmoles) was added in 40 mg portions over a period of fifteen minutes at 25°. After adding an aqueous 0.5 *M* hydrochloric acid solution (5 ml), the solution was then neutralized with 10% aqueous sodium hydrogen carbonate solution. The reaction mixture was filtered off and the precipitate washed with dichloromethane. The filtrate was washed with brine, dried (sodium sulfate) and evaporated to dryness. The residual yellow oil was purified by flash chromatography on a silica column, eluting with cyclohexane/ethyl acetate (8/2) to give **7** in 64% yield; ir: ν 1550, 1376 cm^{-1}; ^1H nmr (DMSO-d_6): δ 8.51 (dd, 1H, J = 5.0, 1.5 Hz, pyridyl H_6), 7.72 (td, 1H, J = 7.5, 1.5 Hz, pyridyl H_4), 7.40-7.20 (m, 7H, phenyl and pyridyl protons), 5.49 (dd, 1H, J = 13.5, 9.0 Hz, CH_2NO_2), 5.17 (dd, 2H, J = 13.5, 6.5 Hz, CH_2NO_2), 5.01 (dd, 1H, J = 9.0, 6.5 Hz, CH).

From Reduction of 2-(2-Pyridyl)-2-phenyl-1-nitroethylene (**5**) with Reagent **2a**.

To a solution of reagent **2a** (139 mg, 0.32 mmole) and magnesium perchlorate (79 mg, 0.35 mmole) in dry acetonitrile (2 ml) was added 2-(2-pyridyl)-2-phenyl-1-nitroethylene (**5**) (80 mg, 0.29 mmole). The resulting solution was stirred at 60° for two days under nitrogen. The reaction mixture was hydrolyzed with water (1 ml). Acetonitrile was evaporated under vacuum and the aqueous layer was extracted with dichloromethane (2 x 10 ml). The combined organic phases were dried (magnesium sulfate). Evaporation of dichloromethane gave an oily residue which after flash chromatography (silica gel-dichloromethane) afforded **3** in 40% yield.

Typical Procedure for the Reduction of 2-(2-Pyridyl)-2-phenyl-1-nitroethylene (**5**) with Reagent **2b**.

This compound was prepared using the same method as described above, from reagent **2b** (374 mg, 1 mmole), magnesium perchlorate (223 mg, 1 mmole) and 2-(2-pyridyl)-2-phenyl-1-nitroethylene (**5**) (204 mg, 0.9 mmole) in dry acetonitrile (2 ml). Chromatography of the crude product (silica gel-dichloromethane) gave **7** in 32% yield along with 1-(2-pyridyl)-1-phenylethylene (**4**) in 16% yield. Enantiomeric excesses were measured by high pressure liquid chromatography; chromatographic conditions, uv detection (λ = 210 nm); mobile phase, phosphonate buffer/2-propanol (95/5); flow rate, 0.9 ml/minute; temperature: 23°; injection, 20 μl (1 mg of sample in 20 ml of water).

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[15] It should be noted that compound **4** could not be detected when reagent **2a** or sodium borohydride were used. Compound **4** does not result from elimination of nitrous acid of compound **7** as proved by a blank experiment performed with compound **7** in the presence of reagent **2b** (1eq) and magnesium perchlorate (2 equivalents) (acetonitrile/60°/two days). It can thus be assumed that compound **4** is obtained either by reduction of 2-(2-pyridyl)-2-phenyl-1-nitroethylene **5**

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