Cobalt(I)-Catalyzed Cocyclotrimerization of Acetylene with 2,6-Dicyanopyridines

Giorgio Chelucci*, M. Antonietta Cabras and A. Saba

Dipartimento di Chimica, Universita' di Sassari,
via Vienna 2, I-07100 Sassari, Italy

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A procedure of general application to the synthesis of alkyl-substituted 2-cyano-6-(2-pyridyl)pyridines from alkylpyridines is outlined.

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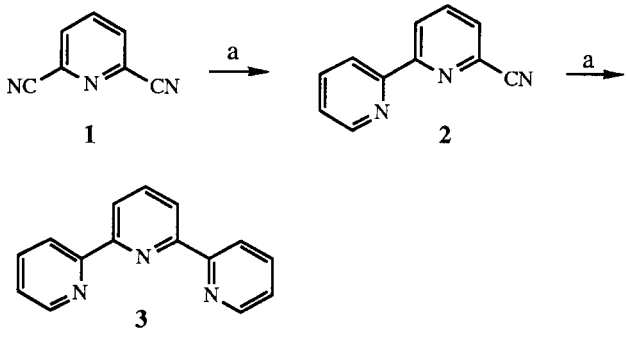
The cobalt(I)-catalyzed cocyclotrimerization reaction of alkynes with nitriles is one of the most useful methods for the preparation of pyridines and their derivatives [1]. In research aimed at the synthesis of heterocyclic compounds we used this reaction to obtained chiral alkylpyridines [2], 1-(2-pyridyl)alkylamines [3] and alkyl-2,2'-bipyridines [4]. More recently, pursuing our studies in this field, we focused our attention on chiral 2,2':6',2''-terpyridines [5], a new class of chiral ligands for asymmetric catalysis.

In this paper we report the results obtained in the synthesis of 2,2':6',2''-terpyridines [6] by the cobalt(I)-catalyzed cocyclotrimerization of acetylene with 2,6-dicyanopyridines.

As an initial goal, 2,6-dicyanopyridine (**1**) [7] was cyclotrimerized with acetylene in the presence of (π-cyclopentadienyl)cobalt-1,5-cyclooctadiene as the catalytic precursor and toluene as the solvent (Scheme 1). After 48 hours at 100° the 6-cyano-2,2'-bipyridine (**2**) was obtained in 70% yield (61% conversion). To gain the desired terpyridine **3** a variety of conditions (*e.g.* varying temperature, solvent and reaction time) were explored, but all the attempts were unsuccessful. For example, when the reaction was performed at 150° for 48 hours, compound **2** was recovered in 55% yield (60% conversion). The reaction carried out in *N,N*-dimethylformamide at 110° for 24 hours allowed complete reaction of the substrate but also in this case bipyridine **2** only in low yield (37%) was obtained.

Scheme 1

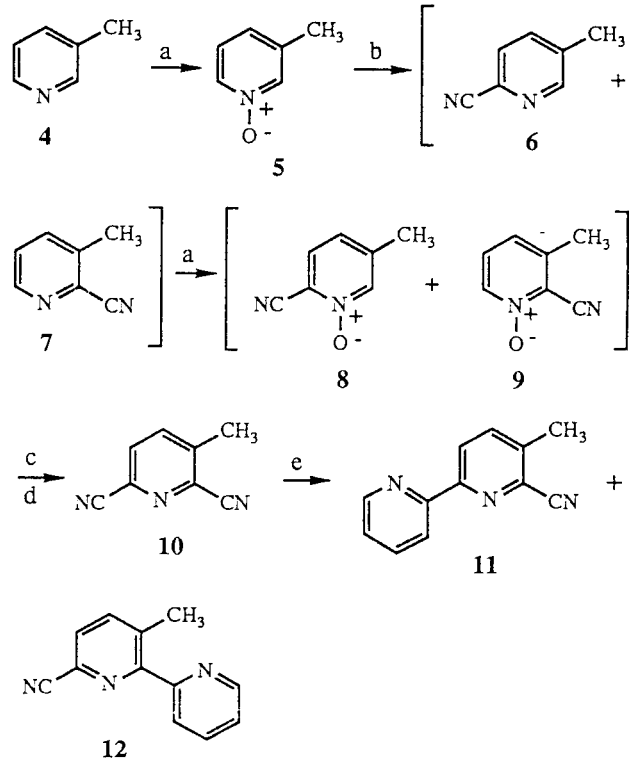


a: CpCo(COD), acetylene, toluene, 100 °C, 48 h.

The outcome of the reaction could be rationalized by considering the formation of the 2,2':6',2''-terpyridine (**3**) whose concentration increases as the concentration of 6-cyano-2,2'-bipyridine rises. Although low, the amount of formed 2,2':6',2''-terpyridine is enough to bind cobalt and give an inactive catalytic species. To confirm this hypothesis, we tried the cyclotrimerization of **1** in the presence of 2,2':6',2''-terpyridine. After 48 hours at 100° the starting material was recovered unchanged.

These results while ruling out the possibility of obtaining 2,2':6',2''-terpyridines by this route, open a new entry to alkylsubstituted 2-cyano-6-(2-pyridyl)pyridines from al-

Scheme 2



a: CH_3COOH, H_2O_2, 80 °C, 72 h; b: $(CH_3)_3SiCN$, $(CH_3)_2NCOCl$, CH_2Cl_2,48 h; c: $(CH_3O)_2SO_2$, 80 °C, 24 h; then KCN/H_2O, O °C, 24 h; d: CpCo(COD), acetylene, toluene, 100 °C, 48 h.

kylpyridines. The strategy is based on the monoazaanellation of 2,6-dicyanopyridines obtained by regiospecific reiterative introduction of two cyano groups into the 2,6-positions of substituted pyridines [8]. We selected the 3-methylpyridine as the prototype from which to develop the basic methodology [9].

According to Fife [10], treatment of 3-methylpyridine 1-oxide (**5**) with trimethylsilylcarbonitrile and dimethylcarbamyl chloride gave a 9:1 mixture of 2-cyano-5-methylpyridine (**6**) and 2-cyano-3-methylpyridine (**7**) in 95% yield. The mixture of **6** and **7** was converted into the corresponding mixture of *N*-oxides by oxidation with 30% hydrogen peroxide in glacial acetic acid at 80° for 72 hours. By treatment with an equimolar amount of dimethyl sulphate at 80° for 24 hours, the crude mixture of *N*-oxides **8** and **9** gave the corresponding *N*-methoxymethylsulphate salts which were dissolved in water and added dropwise (0°) to an aqueous solution containing an excess of potassium cyanide [8]. The dinitrile **10** was obtained in 79% yield based on the mixture of **6** and **7**. Cocyclotrimerization of **10** with acetylene in the presence of (π-cyclopentadienyl)-cobalt-1,5-cyclooctadiene afforded at 48/52 mixture of the bipyridines **11** and **12** in 70% yield (65% conversion). Isomerically pure **11** and **12** were easily obtained by column chromatography on silica gel.

In summary, the regiospecific introduction of two cyano groups into the 2,6-positions of alkyl substituted pyridines, followed by monoazaanellation reaction of one of two cyano groups, affords a suitable procedure to obtain alkyl substituted 2-cyano-6-(2-pyridyl)pyridines [9].

EXPERIMENTAL

Melting points are uncorrected. The ^{1}H nmr Fourier trasform spectra were recorded on a Varian VXR-300 spectrometer with TMS as the internal standard.

3-Methylpyridine was purchased from Aldrich and 2,6-dicyanopyridine (**1**) was prepared according to a literature procedure [7]. A 9/1 mixture of 2-cyano-5-methylpyridine (**6**) and 2-cyano-3-methylpyridine (**7**) was obtained in 95% yield according to Fife [10].

2-Cyano-6-(2-pyridyl)pyridine (**2**).

A solution of 2,6-dicyanopyridine (**1**) (5.6 g, 0.04 mole) and (π-cyclopentadienyl)cobalt-1,5-cyclooctadiene (0.3 g) in degassed toluene (50 ml) was introduced by suction into a 0.2 autoclave, previously evacuated from air (0.1 mm, Hg). The reaction vessel was pressurized at 13 atmospheres with acetylene and then rocked at 100° for 48 hours. After cooling the reaction mixture and releasing the residual gas, the solvent was extracted with 10% aqueous hydrochloric acid. The aqueous phase was made alkaline with 10% sodium hydroxide and the organic products extracted with dichloromethane. Drying over sodium sulfate and evaporating the solvent left a solid which, after purification by column chromatography on silica gel using a benzene/acetone (95/5) mixture, gave pure **2**, 3.57 g (70% based on reacted **1**), mp 130° (lit [11] mp 130-131°); ^{1}H nmr (chloroform): δ (ppm) 8.64 (d, 1H), 8.61 (d, 1H), 8.40 (d, 1H), 7.91 (t, 1H), 7.81 (m, 1H), 7.65 (d, 1H); 7.32 (m, 1H). The toluene solution was dried (sodium sulfate), the solvent evaporated and the residue chromatographed on silica gel, using a benzene/acetone (95/5) mixture, to give pure **1**, 1.96 g.

2,6-Dicyano-3-methylpyridine (**10**).

A 9/1 mixture (5.9 g, 0.05 mole) of pyridines **6** and **7** was converted into the *N*-oxides by oxidation with 30% hydrogen peroxide in glacial acetic acid at 75-80° for 72 hours according to Ochiai [12]. The solvent was removed *in vacuo* and the formed *N*-oxides used as such in the following steps. Dimethyl sulfate (6.3 g, 0.05 mole) was slowly added to the mixture of the crude *N*-oxides (6.7 g, 0.05 mole) and then the reaction mixture was kept at 80° for 24 hours. The *N*-methoxymethylsulfate salts were dissolved in water (30 ml) and added dropwise, at 0° to a solution of potassium cyanide (6.6 g, 0.1 mole) in water (30 ml). After 24 hours at room temperature the reaction mixture was extracted with ether. The organic phase was dried (sodium sulfate), the solvent evaporated and the residue chromatographed on silica gel, using dichloromethane as the eluent to give pure **10**, 5.65 g (79% overall yield from **6** and **7**), mp 80-81° (lit [13], mp 78-80°); ^{1}H nmr (chloroform): δ (ppm) 7.94 (d, 1H), 7.85 (d, 1H), 2.68 (s, 3H).

2-Cyano-3-methyl-6-(2-pyridyl)pyridine (**11**) and 2-Cyano-5-methyl-6-(2-pyridyl)pyridine (**12**).

Following the procedure reported for the preparation of bipyridine **2**, starting from **10** (4.29 g, 0.03 mole) a 48/52 mixture of **11** and **12** was obtained. Chromatography on silica gel using a benzene/acetone (95/5) mixture gave pure **11** and **12**.

Compound **11** (1.30 g, 34% yield based on reacted **10**) had mp 127°; ^{1}H nmr (chloroform): δ (ppm) 8.69 (m, 1H), 7.88 (m, 2H), 7.81 (d, 1H), 7.62 (d, 1H), 7.36 (m, 1H), 2.63 (s, 3H).

Anal. Calcd. for $C_{12}H_9N_3$: C, 73.82; H, 4.65; N, 21.53. Found: C, 73.72; H, 4.55; N, 21.73.

Compound **12** (1.41 g, 36% yield based on reacted **10**) had mp 113°; ^{1}H nmr (chloroform): δ (ppm) 8.66 (d, 1H), 8.54 (d, 1H), 8.43 (d, 1H), 7.85 (dt, 1H), 7.79 (d, 1H), 7.49 (m, 1H), 2.61 (s, 3H).

Anal. Calcd. for $C_{12}H_9N_3$: C, 73.82; H, 4.65; N, 21.53. Found: C, 73.65; H, 4.75; N, 21.63.

The toluene solution was dried (sodium sulfate), the solvent evaporated and the residue chromatographed on silica gel, using a benzene/acetone (95/5) mixture, to give pure **10**, 1.50 g.

Acknowledgement.

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REFERENCES AND NOTES

[1] For a review on the cobalt-catalyzed synthesis of pyridines see: H. Bönnemann, *Angew. Chem.*, **97**, 264 (1985); *Angew. Chem., Int. Ed. Engl.*, **24**, 248 (1985).

[2] U. Azzena, G. Chelucci, G. Delogu, S. Gladiali, M. Marchetti, F. Soccolini and C. Botteghi, *Gazz. Chim. Ital.*, **116**, 307 (1986).

[3] M. Falorni, G. Chelucci, S. Conti and G. Giacomelli, *Synthesis*, 872 (1992).

[4] G. Chelucci, *Gazz. Chim. Ital.*, **122**, 89 (1992).

[5] G. Chelucci, *Synth. Commun.*, **23**, 1897 (1993).

[6a] D. L. Jameson and L. E. Guise, *Tetrahedron Letters*, 1999 (1991); [b] K. T. Potts, D. A. Usifer, A. Guadalupe and H. D. Abruna, *J. Am. Chem. Soc.*, **109**, 3961 (1987).

[7] The dinitrile **1** is easily accessible from a variety of pyridine derivatives: [a] from 2,6-dibromopyridine by cyanation with cuprous cyanide (44%) [14]; [b] from the *N*-oxide of 2-pyridinecarbonitrile by cyanation with potassium cyanide (84%) [15]; [c] from 2,6-pyridinedicarboxamide by dehydration (52%) [16]; [d] from 2,6-dimethylpyridine by oxidative ammonolysis (75%) [17].

[8] For a review on the cyanation of pyridines, see: W. K. Fife, *Heterocycles*, **22**, 2375 (1984).

[9] Starting from symmetric substituted pyridines such as the 4-methyl- or 3,5-dimethylpyridine, only one isomer may be obtained as the final product.

[10] W. K. Fife, *J. Org. Chem.*, **48**, 1375 (1985).

[11] H. F. Case, *J. Org. Chem.*, **31**, 2398 (1966).

[12] E. Ochiai, *J. Org. Chem.*, **18**, 548 (1953).

[13] E. G. Warawa, , *J. Org. Chem.*, **40**, 2092 (1975).

[14] G. A. Pearse and J. Wisowaty, *J. Heterocyclic Chem.*, **10**, 647 (1973).

[15] H. Tani, *Chem. Pharm. Bull.*, **7**, 930 (1959).

[16] R. Bancks and R. Brookes, *Chem. Ind. (London)*, 617 (1974).

[17] L. K. Glubokovskikh, I. I. Kan, B. V. Suvorov and S. V. Berstenev, *Izv. Akad. Nauk. Kaz. SSR, Ser. Khim.*, **3**, 90 (1985); *Chem. Abstr.*, **104**, 88395g (1986).