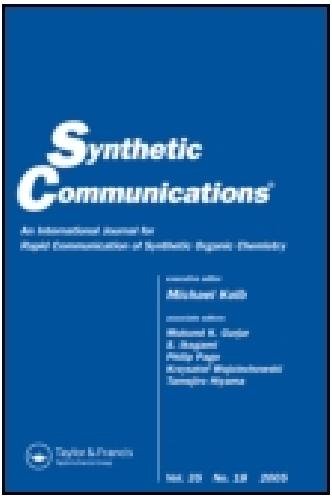

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Synthesis of Dicyanopyridines

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ABSTRACT

Synthesis of the title compounds in four steps using inexpensive collidine and lutidine as starting materials is described.

Key Words: Aldehyde; Hydrazone; Nitrile; Pyridine.

For many years, the synthesis of functionalized pyridines as versatile synthetic intermediates in the preparation of important chemicals has been

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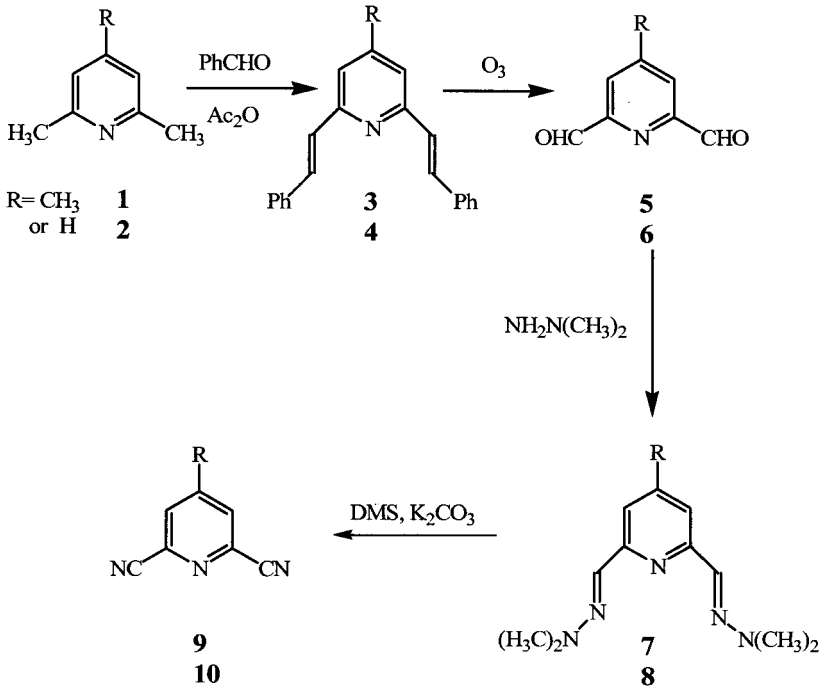
the subject of numerous studies. In particular, nitriles are of great interest due to their rich potential chemical transformations. During our ongoing studies on the synthesis of new polyaza heterocycles,[1] we have found a simple and efficient preparation of 2,6-dicyano-4-methylpyridine **9** and 2,6-dicyanopyridine **10** through the corresponding diformyl derivatives that are also exciting intermediates. The diformyl precursors **5** and **6** were prepared from the inexpensive 2,4,6-trimethylpyridine (collidine) **1** or 2,6-dimethylpyridine (lutidine) **2**, respectively, by initial conversion to the dibenzylidene derivatives **3** and **4**[2] followed by ozonolysis and reduction of the ozonides with trialkylphosphine as outlined in Sch. 1.

In the first step, the workup of compound **4** is easy, as this product precipitates in the reaction mixture after cooling and is simply isolated. On the contrary, the yield of compound **3** is much lower because of its higher solubility in the reaction mixture. In fact, in collidine **1**, the three methyl groups present equivalent reactivity to bases.[3] Preferential functionalization on the α positions can be achieved by introducing a benzylidene group. During the



Scheme 1.

course of the reaction, the nitrogen atom of the pyridine ring favors the reactivity on the α methyl groups leading to **3** as the major product in the presence of the tribenzylidene derivative (R = CH═CHPh in Sch. 1) which is difficult to separate from **3**. After two successive chromatographies on silica gel, compound **3** was finally obtained pure with no more traces of the tribenzylidene derivative as checked by mass spectrometry (see *Experimental* section).

After a short ozonolysis[4] of **3** and **4**, the corresponding diformyl derivatives **5**[5] and **6**[6] were obtained in good yields (by using methyl sulfide in the reduction of the ozonide as described by Ref.[7], we obtained the formyl derivatives with a much lower yield). Compound **6** was also prepared from the commercially available and expensive 2,6-dihydroxymethylpyridine by MnO_2 oxidation with moderate yields. The last step deals with a recent method describing the conversion of aldehydes to nitriles via their *N*,*N*-dimethylhydrazones[8] and was performed on compounds **5** and **6** leading to **9** and **10**, respectively. Compound **9** was just cited in one article[9] without any experimental characterization, whereas **10** has been described[10] and already obtained by different methods in moderate yields. Cyano derivatives of pyridines were usually prepared by nucleophilic substitution with the cyanide anion on the bromo derivative or by using the Reissert–Henze reaction including the corresponding diformyl derivatives as intermediates. Recently, dehydration of the corresponding diamide was described by Drew[11] to obtain **10** as the starting material for the synthesis of triazines.[12]

In conclusion, we described a simple and efficient synthesis of cyano derivatives of pyridines from commercially available methyl pyridines.

EXPERIMENTAL

Preparation of 2,6-Dibenzylidene-4-methylpyridine: 3

A solution of 1.32 mL (10 mmol) of collidine, 5.1 mL (50 mmol) of freshly distilled benzaldehyde, and 9.4 mL (100 mmol) of acetic anhydride was heated to 170°C for 41 h. After cooling, most of the acetic anhydride was distilled off, and 10 mL of 5% aqueous sodium hydroxide were added, and the mixture was stirred at room temperature for 3 h. Organic material was extracted three times by dichloromethane, and the gathered organic phases were dried on magnesium sulfate, filtered, and evaporated to dryness under reduced pressure. The dark-brown oil was adsorbed on silica gel and purified through two successive flash column chromatographies (eluent: 90% pentane–10% ethylacetate) to afford 0.47 g of **3** (16%) as white needles. Mp = 130–131°C. **CAUTION**: we have observed *spontaneous ignition* of the pentane phase in the presence of the dibenzylidene derivative after moderate heating. ^{1}H-NMR (250 MHz,

$CDCl_3$): δ 7.70 (d, 2H, $J = 16.1$ Hz, HC═CH); 7.61 (dd, 4H, $J = 7.1$ and 1.4 Hz, *ortho* H*bz*); 7.42–7.30 (m, 6H, *meta* and *para* H*bz*); 7.19 (d, 2H, $J = 16.1$ Hz, HC═CH); 7.13 (s, 2H, Hpy); 2.37 (s, 3H, CH_3); ^{13}C-NMR (62.9 MHz, $CDCl_3$): δ 155.3; 147.8; 136.8; 132.6; 128.7; 128.3; 128.0; 127.1; 121.5; 21.0; MS (DCI/NH_3): m/z 298 $(M + H)^+$; elemental analysis: found (calculated) C: 88.66 (88.85); H: 6.15 (6.44); N: 4.59 (4.71). A second fraction of the chromatography afforded a mixture of the dibenzylidene and of the tribenzylidene derivatives which could not be separated and were evidenced by mass spectrometry.

2,6-Dibenzylidene-pyridine: 4

A solution of 2.3 mL (20 mmol) of lutidine in 10.2 mL (100 mmol) of benzaldehyde and 18.9 mL (200 mmol) of acetic anhydride were heated at 180°C for 41 h. After cooling, the precipitate was filtered off and rinsed with pentane to yield 2.8 g (49%) of a beige powder. Mp = 170°C; ^{1}H-NMR (250 MHz, $CDCl_3$): δ 7.71 (d, 2H, $J = 16.1$ Hz, HC═CH); 7.62 (dd, 4H, $J = 7.4$ and 1.8 Hz); 7.42–7.29 (m, 9H); 7.21 (d, 2H, $J = 16.1$ Hz, HC═CH); ^{13}C-NMR (62.9 MHz, $CDCl_3$): δ 155.4; 137.0; 136.7; 132.9; 128.7; 128.3; 127.2; 120.5; MS (DCI/NH_3): m/z 286 $(M + H)^+$; elemental analysis: found (calculated); C: 88.50 (89.01); H: 5.80 (6.05); N: 4.84 (4.94).

2,6-Diformyl-4-methylpyridine: 5

A solution of 8.35 g (28 mmol) of 4 in 300 mL of a mixture 1/1 dichloromethane/methanol was ozonolysed at −70°C for 0.5 h. After bubbling oxygen then argon, the mixture was abandoned at room temperature. Tricyanoethylphosphine (500 mg per mmol) was added, and the solution was left overnight. After filtration, the solvents are evaporated off and the crude product was chromatographied on silica gel and eluted with 90% pentane-10% ethylacetate. 3.93 g (94%) of a white solid was obtained. Mp = 162°C; ^{1}H-NMR (250 MHz, $CDCl_3$): δ 10.13 (s, 2 H); 7.97 (s, 2 H); 2.53 (s, 3 H). ^{13}C-NMR (62.9 MHz, $CDCl_3$): δ 192.6; 152.9; 150.3; 126.1; 21.1; MS (DCI,NH_3): 150 $(M + H)^+$; 167 $(M + NH_4)^+$; elemental analysis: found (calculated), C: 64.53 (64.42); H: 4.33 (4.73); N: 9.18 (9.39).

2,6-Diformylpyridine: 6

Compound **6** was synthesized according to the procedure used for **5**. Yield 98%; Mp = 124°C.

2,6-*bis*(*N*,*N*-Dimethyl)hydrazono-4-methylpyridine: 7

To a solution of 1.78 g of **6** (12 mmol) in 84 mL methanol were added 5.1 mL (67 mmol) of *N*,*N*-dimethylhydrazine. After stirring at room temperature for 12 h, the mixture was evaporated to dryness. An addition of ethyl acetate gave the product as 2.5 g (89%) of a yellow precipitate. Mp = 73°C; ^{1}H-NMR (250 MHz, $CDCl_3$): δ 7.45 (s, 2H); 7.28 (s, 2H); 3.02 (s, 12H); 2.31 (s, 3H). ^{13}C-NMR (62.9 MHz, $CDCl_3$): δ 150.8; 147.2; 132.2; 117.4; 42.6; 21.1; MS (DCI, NH_3): 234 $(M + H)^+$; elemental analysis: found (calculated), C: 61.77 (61.83); H: 8.21 (8.12); N: 30.02 (28.75).

2,6-*bis*(N,N-Dimethyl)hydrazonopyridine: 8

To a solution of 2.31 g (17 mmol) of 2,6-diformylpyridine in 50 mL methanol were added 5.2 mL (68 mmol) of *N*,*N*-dimethylhydrazine, and the reaction was stirred at room temperature for 12 h. After evaporation, 3.67 g (98%) of pale yellow product were obtained. Mp = 125°C. ^{1}H-NMR (250 MHz, $CDCl_3$): δ 7.55 (m, 3 H); 2.99 (s, 12 H, CH_3); ^{13}C-NMR (62.9 MHz, $CDCl_3$); δ 135.5; 130.7; 115.7; 41.9; 40.3; MS (DCI,NH_3): 220 $(M + H)^+$; elemental analysis: found (calculated), C: 60.10 (60.25); H: 7.22 (7.81); N: 32.00 (31.94).

Preparation of the Dicyanopyridines: 9 and 10

2,6-Dicyano-4-methylpyridine: **9**

To a solution of **7** (2.5 g, 11 mmol) in 70 mL of acetonitrile, were added dimethylsulfate (5.25 mL, 56 mmol) and potassium carbonate (3.82 g, 28 mmol). The reaction mixture was heated to reflux for 16 h. After cooling, potassium carbonate was filtered off, and the filtrate was evaporated to dryness. The solid was adsorbed on silica gel and eluted with a mixture of pentane/ethylacetate (50/50). An amount of 1.46 g (95%) was obtained after evaporation of the solvent. mp: 138–140°C. ^{1}H-NMR (250 MHz, $CDCl_3$): δ 7.73 (s, 2H); 2.53 (s, 3H). ^{13}C-NMR (62.9 MHz, $CDCl_3$): δ 151.3; 135.0; 131.9; 115.6; 20.9; MS (DCI,NH_3): m/z 178 ($MN_2H_7^+$); elemental analysis: found (calculated), C: 66.77 (67.13); H: 3.25 (3.52); N: 28.98 (29.35).

2,6-Dicyanopyridine: **10**

Compound **10** was prepared from **8** as described for **9** (Yield: 90%. Mp = 114°C).

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