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Synthesis of 2-substituted pyridines catalyzed by cobalt(I) complexes and promoted by light

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A series of pyridines substituted in the 2-position were synthesized by cobalt(I)-catalyzed co-trimerization of alkynes and nitriles. The reactions are usually enhanced by light. The reaction conditions are very mild. Activity and selectivity are satisfactory with respect to formation of pyridines, but depend on the type of nitrile.

Keywords: Acetylene, nitrile, pyridine, cobalt complexes, co-trimerization, photochemical activation

INTRODUCTION

The pyridine ring system represents an important building block in fine-chemical synthesis.[1] Besides a series of classical condensation reactions,[2,3] the cobalt(I)-catalyzed co-trimerization of alkynes and nitriles to functionalized pyridines has been developed to a convenient route (see Scheme 1).[4,5]

The thermally driven co-trimerization was investigated by Wakatsuki and co-workers[6,7] and Bönnemann *et al.*[8] Recently Bönnemann and Brijoux reviewed the synthesis of pyridine derivatives with respect to possible applications in heterocyclic chemistry.[9] The accessibility of optically active pyridine derivatives by this catalytic route may be of special interest.[10,11]

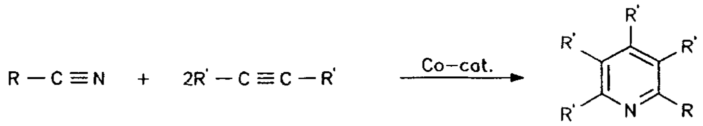
The thermal reactions generally seem to require relatively harsh conditions (i.e. high pressures and temperatures). (Using cobalt(I) carbonyl derivatives as catalysts, Vollhardt and co-workers[12,13] successfully activated catalytic co-cyclotrimerization reactions of higher substituted alkynes and nitriles by using light.

We recently found that the formation of 2-substituted pyridines by co-trimerization of acetylene and nitriles using cyclopentadienylcobalt(I)-bis-olefin complexes as catalysts is largely facilitated and proceeds under very mild conditions (i.e. ambient temperature and pressure) in the presence of light.[14] Good results have been achieved with alkyl, aryl, alkoxy- and amino-nitriles. Ethyl cyanoacetate also yielded 1-ethoxycarbonyl-2-amino-4-oxo-4*H*-quinolizine as a by-product (Cronin, K. G., Gesnig, E. F. R. and Vollhardt, K. P. C., unpublished work, cited in Ref. 5). With acrylonitrile, however, and in contrast to Bönnemann's findings,[7,15] 2-vinylpyridine formation under our conditions is sluggish. We presume that the cobalt(I) center is blocked by competing coordination of the vinyl instead of the cyano group of acrylonitrile. Likewise, 3-phenoxypropionitrile failed to co-trimerize, possibly due to decomposition of starting material. Generally, the purity and stability of starting materials appear to be decisive for the efficacy of the reaction. The purity of nitriles was checked by GLC, IR and NMR spectroscopy and by microanalysis.

Some catalytic systems with useful activity and excellent stability have been reported by several authors.[6–8] We have been using highly active catalysts of the type $CpCo(olefin)_2$, recommended by Bönnemann.[4] For many experiments, however, CpCoCOD (COD = cyclo-octadiene) was used.

EXPERIMENTAL

The experimental procedure for the co-cyclizations is relatively straightforward. In principle any thermostated reaction vessel is sufficient



Scheme 1

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Table 1 Selected data of 2-substituted pyridines (Scheme 1; R′ = H)

	R	Method	Yield (%)	Bp (°C/mbar)	Molecular formula	Ref.[a] p	Ref.[a] n	MS (70 eV) *m/z* (%)	^{1}H and ^{13}C NMR
1	$—(CH_2)_2—O—(CH_2)_9—CH_3$	b	85	132/1	$C_{17}H_{29}NO$	21	20	263 (M^+, 3); 122 (100)	^{1}H: t: 0.84 (3H); m: 1.16–1.31 (14H); m: 1.43–1.57 (2H); t: 3.03 (2H); t: 3.39 (2H); t: 3.76 (2H); dd: 7.07 (1H); d: 7.18 (1H); ddd: 7.55 (1H); d: 8.59 (1H) ^{13}C: 14.1 (C-18); 22.7 (C-17); 26.1 (C-11); 29.3–29.6 (C-12–16); 31.9 (C-10); 38.7 (C-7); 70 (C-9); 71.1 (C-8); 121.3 (C-5); 123.6 (C-3); 136.2 (C-4); 149.2 (C-6); 159.3 (C-2)
2	$—(CH_2)_2—O—CH_2—CH(CH_3)_2$	a	80	57/1	$C_{11}H_{17}NO$	—	20	180 (M^+ + H, 2); 122 (100)	^{1}H: d: 0.81 (6H); m: 1.79 (1H); t: 3.03 (2H); d: 3.16 (2H); t: 3.75 (2H); m: 7.07 (1H); d: 7.19 (1H); ddd: 7.55 (1H); m: 8.49 (1H) ^{13}C: 19.3 (CH_3); 28.3 (C-10); 38.7 (C-7); 70.2 (C-8); 77.9 (C-9); 121.2 (C-5); 123.6 (C-3); 136.2 (C-4); 149.2 (C-6); 159.4 (C-2)
3	$—(CH_2)_2—O—CH_2—CH{=}CH_2$	a	83	72/1	$C_{10}H_{13}NO$	—	20	163 (M^+, 2); 122 (100)	^{1}H: t: 3.04 (2H); t: 3.78 (2H); m: 3.95 (2H); m: 5.08–5.24 (2H); m: 5.76–5.92 (1H); dd: 7.09 (1H); d: 7.19 (1H); ddd: 7.55 (1H); d: 8.49 (1H) ^{13}C: 38.7 (C-7); 69.5 (C-8); 71.9 (C-9); 116.8 (C-11); 121.3 (C-5); 123.6 (C-3); 134.8 (C-10); 136.3 (C-4); 149.3 (C-6); 159.2 (C-2)
4	$—(CH_2)_2—NH—(CH_2)_{11}—CH_3$	b	58	150/0.7	$C_{13}H_{19}NO$	—	20	290 (M^+, 37); 93 (100)	^{1}H: t: 0.91 (3H); m: 1.09 (16H); b: 1.16–1.28 (2H; NH); t: 2.59 (2H); b: 2.9–3.17 (2H); m: 7.01–7.18 (2H); ddd: 7.52 (1H); d: 8.49 (1H)
5	$—(CH_2)_2—N(C_2H_5)_2$	a	39	62/1	$C_{11}H_{18}N_2$	22	20	178 (M^+, 4); 86 (100)	^{1}H: t: 0.99 (3H); q: 2.55 (N—CH_2); m: 2.84 (4H); m: 7.00–7.06 (1H); d: 7.12 (1H); m: 7.52 (1H); m: 8.46 (1H) ^{13}C: 11.9 (CH_3); 35.7 (C-7); 46.9 (N—CH_2); 52.8 (C-8); 121.0 (C-5); 123.2 (C-3); 136.2 (C-4); 149.2 (C-6); 160.8 (C-2)
6	$—N(CH_3)_2$	a	46	80–82/20	$C_7H_{10}N_2$	23	—	122 (M^+, 57); 93 (100)	^{1}H: s: 3.04 (6H); m: 6.48 (2H); ddd: 7.40 (1H); ddd: 8.14 (1H) ^{13}C: 38.1 (CH_3); 105.8 (C-5); 111.4 (C-3); 137.1 (C-4); 147.8 (C-6); 159.3 (C-2)

Table 1 (*continued*)

	R	Method	Yield (%)	Bp (°C/mbar)	Molecular formula	Ref.[a]		MS (70 eV) *m/z* (%)	^{1}H and ^{13}C NMR
						p	n		
7	$-CH_2-C(O)OC_2H_5$	a	29	73/0.9	$C_9H_{11}NO_2$	24	—	165 (M^+, 22); 93 (100)	^{1}H: t: 1.2 (3H); s: 3.79 (2H); q: 4.13 (2H); ddd: 7.12 (1H); dd: 7.24 (1H); ddd: 7.59 (1H); m: 8.5 (1H) ^{13}C: 14.1 (CH_3); 43.9 (C-7); 60.9 (C-8); 122 (C-5); 123.8 (C-3); 136.5 (C-4); 149.4 (C-6); 154.5 (C-2); 170.6 (COO)
8	$-(CH_2)_2-$morpholine	a	41	105–6/1	$C_{11}H_{16}N_2O$	22	20	193 (M^+ + H, 2); 100 (100)	^{1}H: m: 2.48 (4H); m: 2.71 (2H); m: 2.94 (2H); t: 3.67 (4H); t: 7.07 (1H); d: 7.13 (1H); t: 7.54 (1H); d: 8.46 (1H) ^{13}C: 35.5 (C-7); 53.5 (C-9, 11); 58.6 (C-8); 66.9 (C-10, 11); 121.1 (C-5); 123.1 (C-3); 136.3 (C-4); 148.2 (C-6); 160.1 (C-2)
9	$-C_6H_5$	b	91	90/1	$C_{11}H_9N$	25	—	155 (M^+, 100)	^{1}H: m: 7.17–7.25 (1H); m: 7.37–7.51 (3H); m: 7.71 (2H); m: 8.0 (2H); ddd: 8.69 (1H) ^{13}C: 120.5 (C-5); 122.1 (C-3); 126.9, 128.7, 128.9 (5C—Ph); 136.7 (C-4); 139.4 (C-1/Ph); 149.7 (C-6); 157.5 (C-2)
10	$-(CH_2)_2-NH-CH(CH_3)C_6H_5$	b	49	160/1.3	$C_{15}H_{18}N_2$	—	20	226 (M^+, 2); 121 (100)	^{1}H: d: 1.32 (3H); b: 1.71 (NH); m: 2.92 (4H); dd: 3.78 (1H); m: 7.13–7.05 (2H); m: 7.3–7.16 (5H); ddd: 7.54 (1H); m: 8.49 (1H) ^{13}C: 24.5 (CH_3); 38.6 (C-7); 47.3 (CH); 58.2 (C-8); 121.2 (C-5); 123.2 (C-3); 126.6 (2C—Ph); 126.8 [C—H—(Ph)]; 128.4 (2C—Ph); 136.3 (C-4); 145.7 [C-1(Ph)]; 149.3 (C-6); 160.3 (C-2)
11	$-(CH_2)_8-CH_3$	b	74	120–21/0.7	$C_{14}H_{23}N$	26	—	205 (M^+, 4); 93 (100)	^{1}H: t: 0.84 (3H); m; 1.19–1.35 (12H); m: 1.69 (2H); t: 2.75 (2H); m: 7.02–7.13 (2H); ddd: 7.54 (1H); d: 8.49 (1H) ^{13}C: 14.1 (CH_3); 22.7 (C-14); 29.3–29.9 (C-9–13); 31.9 (C-8); 38.5 (C-7); 120.8 (C-5); 122.7 (C-3); 136.2 (C-4); 149.2 (C-6); 162.5 (C2)

Table 1 (*continued*)

	R	Method	Yield (%)	Bp (°C/mbar)	Molecular formula	Ref.[a]		MS (70 eV) *m/z* (%)	^{1}H and ^{13}C NMR
						p	n		
12	$—CH_2—O—(CH_2)_9—CH_3$	a	35	97/0.6	$C_{16}H_{27}NO$	—	27	249 (M^+; 34); 93 (100)	^{1}H: t: 0.95 (3H); m: 1.2 (14H); m: 1.6 (2H); t: 3.51 (2H); d: 4.58 (2H); m: 7.12 (1H); m: 7.65 (2H); d: 8.5 (1H) ^{13}C: 14.0 (CH_3); 22.6–31.8 (C-9–16); 71.2 (C-8); 73.7 (C-7); 121.2 (C-5); 122.1 (C-3); 136.5 (C-4); 148.9 (C-6); 159.0 (C-2)
13	$—CH_2—O—CH(CH_3)_2$	a	17	52–56/5	$C_9H_{13}NO$	29	27	152 (M^+ + H, 12); 93 (100)	^{1}H: m: 1.19 (6H); m: 3.78 (1H); m: 4.55 (2H); m: 7.09 (1H); d: 7.39 (1H); ddd: 7.58 (1H); d: 8.46 (1H) ^{13}C: 22.1 (CH_3); 71.1 (C-8); 71.8 (C-7); 121.2 (C-5); 122.1 (C-3); 136.5 (C-4); 148.9 (C-6); 159.3 (C-2)
14	$—CH_2—N(C_2H_5)_2$	a	88	71–72/3	$C_{10}H_{16}N_2$	30	28	164 (M^+, 6); 93 (100)	^{1}H: m: 0.98 (6H); m: 2.45–2.57 (4H); m: 3.65 (2H); m: 7.05 (1H); d: 7.22 (1H); m: 7.56 (1H); m: 8.46 (1H) ^{13}C: 11.8 (CH_3); 47.3 (C-8, 8′); 59.5 (C-7, 7′); 121.6 (C-5); 122.8 (C-3); 136.2 (C-4); 148.9 (C-6); 160.7 (C-2)
15	$—CH_2—NC_5H_{10}$	a	52	88–92/3	$C_{11}H_{16}N_2$	31	28	177 (M^+ + H, 92); 84 (100)	^{1}H: m: 1.27 (6H); m: 2.32 (4H); m: 3.5 (2H); m: 7.0 (1H); d: 7.32 (1H); m: 7.52 (1H); d: 8.41 (1H) ^{13}C: 24.2 (C-10); 25.9 (C-9–11); 54.7 (C-8, 12); 65.5 (C-7); 121.7 (C-5); 123.1 (C-3); 136.2 (C-4); 149.0 (C-6); 159.1 (C-2)

[a] p, pyridine; n, nitrile.

as photoreactor. We tested two types of reactors. The first is illustrated in Ref. 16 and consists of a horizontal tube cooled by water and loaded with the nitrile. Acetylene was bubbled through the neat liquid nitrile. The formation of cyclic cotrimer proceeded with high turnover numbers and excellent selectivity. This type of reactor is, however, somewhat disadvantageous, in that the reactions proceed under diffusion control and reaction rate measurements have proved to be difficult. The second reactor consists of a water-jacketed reaction cell, connected with a gas burette for automatic acetylene delivery. Reaction mixtures were stirred magnetically and the irradiation lamps were fixed at specified distances. Acetylene consumption could be traced with high precision.

Co-trimerizations have been run successfully with and without additional solvent (i.e. toluene). Dichloromethane, methanol and chlorobenzene have likewise been used in the co-trimerization with hexyne by other authors.[17] Our results indicate that co-trimerization of alkyl-and alkoxy-nitriles (with acetylene), which proceeds in high yields, is largely independent of dilution by solvents, whereas in the case of aminoalkylnitriles dilution of the mixtures with toluene gives better yields.

The tested catalyst complexes appear to be prone to decomposition upon irradiation with light of wavelength below 360 nm. Good results were obtained at a wavelength around 400 nm. Some experiments were conducted successfully using sunlight. Studies of the photoreactions at different wavelengths, and kinetic and spectroscopic investigations, are in progress.

All operations were perfomed under an atmosphere of prepurified argon using standard Schlenck techniques. NMR spectra were recorded using Bruker AC 250 and 300 MHz spectrometers. Mass spectra were obtained with an AMD 402, operating at 70 eV and with an ion source temperature of 210 °C. GLC analyses were performed on an HP 5890 II chromatograph with OV 101 coated fused silica capillaries of length 12 m (temperature program: 10 min at 35 °C isothermally, then 10 °C min^{-1} up to 200 °C; argon as carrier gas, 1 $\mathrm{cm}^3\,\mathrm{min}^{-1}$). Acetylene of 99.5% purity (Linde) was generally used as received. For reasons of comparison, several co-trimerization runs were carried out with acetylene, purified as follows: it was consecutively passed through a −78 °C trap and drying columns containing blue gel, KOH pellets, $K_2Cr_2O_7/H_2SO_2$ on an SiO_2 support, and $Mn(NO_3)_2$ on Al_2O_3,[18] respectively. Solvents were purified by standard methods and distilled prior to use. Catalysts were prepared according to literature procedures.[19] Nitriles were purchased commercially from Fluka or prepared as described in Table 1, stored over activated molecular sieve 3A and distilled.

Examples of the experimental procedures

(a) 2-Nonylpyridines

Caprinitrile (octanenitrile) (10 g, 65.2 mmol) was loaded under an atmosphere of acetylene into a water-jacketed reaction vessel of 25 cm^3 volume, kept at 25 °C. After saturation with acetylene, a sample of CpCoCOD (23 mg, 0.1 mmol) was added. After connecting the vessel with a gas burette, delivering acetylene at constant normal pressure, the stirred mixture was irradiated for 2 h by a device comprising two Philips HPM 12 (460 W) lamps, placed at a short distance (1 cm). The reaction was quenched by opening the vessel to air. The product was isolated by vacuum distillation (b.p. 121 °C/0.7 mbar); yield 9.9 g (74%). The analytical purity of the product (99.6%) was checked by GLC.

(b) 2-(2-Dodecylaminoethyl)pyridine

A solution of 3-dodecylaminopropionitrile (4.46 g, 20 mmol) in 10 cm^3 toluene in the same reaction vessel was saturated with acetylene and a sample of CpCoCOD (13.9 mg, 0.06 mmol) was added. Acetylene was bubbled through (vented by a gas bubbler) and the stirred reaction mixture irradiated (see above) during this period. The reaction was quenched after 1 h and the product isolated by stripping the solvent off and vacuum-distilling the residue (b.p. 150 °C/0.7 mbar); yield 3.37 g (58%). The analytical purity of product (99.3%) was checked by GLC. If solvent is omitted, incomplete reaction conversions (<20%) result.

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