Catalytic Co-cyclisation of α,ω-Cyanoalkynes with Alkynes: a Versatile Chemo- and Regio-selective Synthesis of 2,3-Substituted 5,6,7,8-Tetrahydroquinolines and Other Cycloalka[1,2-*b*]pyridines

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α,ω-Cyanoalkynes are catalytically cocylised with alkynes in the presence of dicarbonyl(cyclopentadienyl)-cobalt to furnish [*b*]annulated pyridines chemo- and regio-selectively.

Owing to the extensive and versatile medicinal properties of pyridine derivatives[1] novel approaches to the construction of this nucleus are the subject of intensive current research efforts. We have previously shown[2] that cycloalka[1,2-*c*]-pyridines can be synthesised from α,ω-diynes and nitriles using [$CpCo(CO)_2$] (Cp = cyclopentadienyl) as catalyst, and now report a complementary route from α,ω-cyanoalkynes to cycloalka[1,2-*b*]pyridines.

Typically the α,ω-cyanoalkyne (**1**) (1 equiv.), the alkyne (**2**) (1.1 equiv.) and $CpCo(CO)_2$ (0.2 equiv.) in *m*-xylene are added *via* a syringe pump (4—8 h) to refluxing and irradiated (visible light, GE-ENH, 250 W, slide projector lamp) *m*-xylene. The solvent is subsequently removed and the products (**3**) and/or (**4**) purified by chromatography on silica (see Table 1).

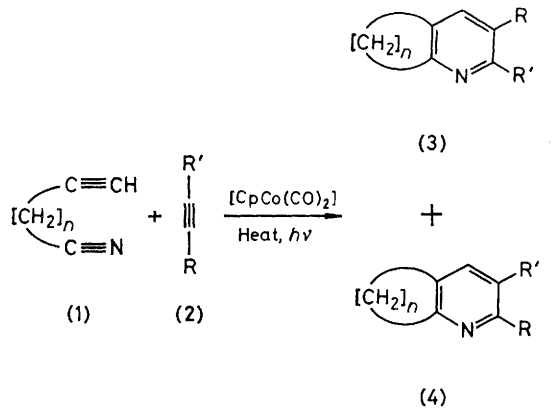


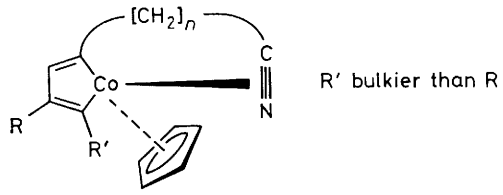
Table 1. Cyclization products from (**1**) and (**2**).

Entry	*n*	R	R′	% Yield[a] of (**3**)	% Yield of (**4**)
1	3	$SiMe_3$	$SiMe_3$	77[b]	—
2	3	CO_2Me	CO_2Me	68[b]	—
3	3	Me	$SiMe_3$	70[b]	0
4	4	$SiMe_3$	$SiMe_3$	77[c]	—
5	4	CO_2Me	CO_2Me	83[d]	—
6	4	CH_2OMe	CH_2OMe	33[b]	—
7	4	Ph	Ph	4[e]	—
8	4	Me	$SiMe_3$	70[b]	0
9	4	H	Bu^n	40[b,g]	1
10	4	Bu^n	$SiMe_3$	56[b]	0
11	4	Me	Bu^n	45[b]	35[b]
12	4	H	$SiMe_3$	29[b]	0
13	4	Me	CO_2Et	43[b]	11[b]
14	5	$SiMe_3$	$SiMe_3$	25[b]	—
15	5	CO_2Me	CO_2Me	95[f]	—
16	5	Me	$SiMe_3$	66[b]	0

[a] All new compounds gave satisfactory spectral and analytical data. [b] Colourless oil. [c] M.p. 35 °C. [d] M.p. 56–57 °C. [e] M.p. 123 °C. [f] M.p. 93–94 °C. [g] See reference 8b.

It is noteworthy that although cyclobutapyridines are not accessible *via* this route [through (**1**; $n = 2$)] five-, six-, and seven-membered fused ring system are obtained in moderate to excellent (unoptimized) yields. Lower yields pertain when terminal alkynes capable of competing self-trimerisation are employed (entries 9, 12), when the product is unstable under the reaction conditions (entry 6), or when the cobalt catalyst is rapidly depleted by cyclobutadiene complex formation (entry 7). The reasons for the low yield obtained (repeatedly) in entry 14 have not been elucidated.

We assume that the products are formed through the intermediacy of metallacycle (**5**) in which the bulkier of the two alkyne substituents emerges located α to cobalt.[3] This neatly accommodates the finding that the resulting annulated pyridines generally bear the larger group in the 2-position. This can be used to synthetic advantage since alk-1-ynes, depending on whether they bear a proton or a trimethylsilyl group at the 1-position, cyclise to give either the 2- or the 3-alkylpyridine derivatives. An exception to this steric rule is entry 13 (the methyl group is 'larger' than the ester function)[4] indicating the contribution of an electronic factor to the regiochemical outcome of the cyclisation. The relatively high yields obtained when acetylenedicarboxylic ester is the co-cyclisation partner (entries 2, 5, 15) suggest some sort of 'push–pull' effect in metallacycle (**5**) ensuring excellent chemoselectivity. When an equimolar mixture of a large excess of (**1**; $n = 3, 4, 5$) and the ester (**2**; $R = R' = CO_2Me$) is brought to competitive reaction the relative rates of formation of the respective products were 2 : 1.5 : 1. This implies that annulated ring formation is not rate determining, as observed earlier in cyclisations leading to benzocycloalkenes.[5]



(5)

The trimethylsilylated pyridine nucleus may be further transformed. Thus, (**3**; $n = 4$, $R' = SiMe_3$, R = Me, entry 8) is readily and quantitatively protodesilylated ($Me_4N^+F^-$, MeOH, 50 °C, 0.5 h).[6] Bromination (Br_2, CCl_4, room temp.) of (**3**; $n = 4$, $R = R' = SiMe_3$) occurs exclusively (71%, m.p. 241 °C) at the 3-position. Protodesilylation of this bromide gives 3-bromo-5,6,7,8-tetrahydroquinoline. The substitution pattern in this and other quinoline derivatives reported here is unambiguously assignable by spectral techniques.[7] The reaction reported in this communication should be readily applicable to the regiocontrolled synthesis of annulated pyridines of medicinal and commercial interest.[8]

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