COMMUNICATION

ChemComm
www.rsc.org/chemcomm

Cobalt-mediated cyclotrimerisation of bis-alkynes and cyanamides†

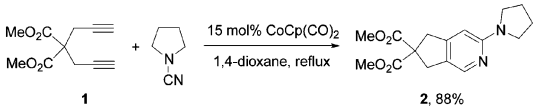
Llorente V. R. Boñaga, Han-Cheng Zhang and Bruce E. Maryanoff*
Drug Discovery, Johnson & Johnson Pharmaceutical Research & Development, Spring House, PA, 19477-0776, USA. E-mail: bmaryano@prdus.jnj.com; Fax: +1 215-628-4985

Received (in Corvallis, OR, USA) 2nd July 2004, Accepted 13th September 2004
First published as an Advance Article on the web 8th October 2004

$CpCo(CO)_2$-mediated cyclotrimerisation of bis-alkynes and cyanamides provides multisubstituted 2-aminopyridines, including macrocyclic products, such as 22 (50% yield).

Valuable synthetic methods have derived from cobalt-mediated reactions,[1] with [2 + 2 + 2] cycloadditions of alkynes receiving considerable attention.[2] Recent work has pursued issues of chemoselectivity, regioselectivity, macrocycle formation, and mild/"green" protocols.[2a,3,4] In our studies on the synthesis of pyridine and 2-oxopyridine macrocycles,[4] we became interested in the potential utility of cyanamide derivatives as reactants, and found that there has been just a limited amount of exploration on this aspect. Bönnemann and coworkers reported the reaction of acetylene with cyanamide in the presence of a η^6-borinato cobalt catalyst at high pressure (40 bar; 130 °C),[5] and Heller and coworkers reported a photo-induced cyclotrimerisation of acetylene with *N*-cyanopyrrolidine or *N*-cyanopiperidine by using $CpCo(cod)$ at 25 °C.[6] This type of reaction is also mentioned briefly in a patent.[7] We have now investigated the co-cyclotrimerisation of bis-alkynes with cyanamides catalysed by $CpCo(CO)_2$ under moderate thermal conditions. Annulated aminopyridines[8] or *meta*- and *para*-aminopyridinophanes can be obtained with good yields (50–90%) at *ca.* 100 °C without any photo-activation.

N-Cyanopyrrolidine and bis-alkyne **1** were used initially as a test case under the reaction conditions developed in our other studies.[4] Co-cyclotrimerisation of **1** with *N*-cyanopyrrolidine proceeded smoothly in refluxing dioxane with 15 mol% of $CpCo(CO)_2$ to furnish annulated aminopyridine **2** in 88% yield (eqn. (1)). We surveyed reactions of *N*-cyanopyrrolidine with several bis-alkynes, probing length and substitution of the tether, and substitution of the alkyne units (Table 1).



1 **2**, 88% (1)

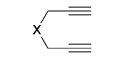
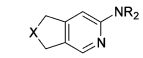
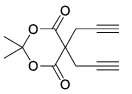
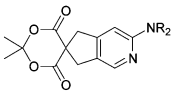
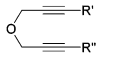
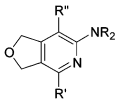
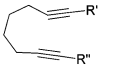
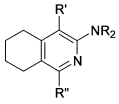
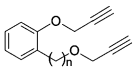
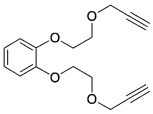
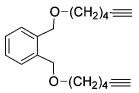
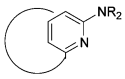
Various bis-alkynes underwent co-cyclotrimerisation with *N*-cyanopyrrolidine to give 2-pyrrolidinopyridines appended to a small or large ring in moderate to excellent yields (Table 1). 2-Aminopyridines annulated to five-membered (entries 1–7) or six-membered (entries 8 and 9) rings were obtained from 1,6- and 1,7-bis-alkynes, respectively. Substrates devoid of substitution in the tether, and thus lacking Thorpe–Ingold assistance in the cyclisation, cyclotrimerised with lower yields (entries 2 and 8). Attempted co-cyclotrimerisation of 1,9- and 1,10-diynes to form a pyridine attached to a medium-sized ring was unsuccessful (entries 10 and 11). Given our interest in cobalt-mediated macrocyclisation,[4] we also examined two representative α,ω-diynes. 1,15-Bis-alkyne gave exclusively the 16-membered *p*-pyridinophane **22** in 50% yield (entry 12).[9,10]

In contrast, a 1,17-bis-alkyne provided a mixture (1:1) of the 17-membered *m*- and 18-membered *p*-pyridinophanes in 64% yield (entry 13).[9] This behaviour is consistent with our previous observations in the generation of pyridinophanes from nitriles.[4a]

We also explored the reactivity of substrates with different alkyne substituents, recognising the utility for generating highly substituted aminopyridines. Substrates with one internal alkyne, *e.g.*, substituted with an alkyl (entry 5) or aryl group (entry 6), resulted in good yields of annulated tetrasubstituted pyrrolidinopyridines. Bis-alkynes **13** and **17** with both internal alkynes co-cyclotrimerised to yield pentasubstituted pyridines appended to 5-membered or 6-membered rings, respectively (entries 7 and 9).

The observed regiochemical outcome can be explained by considering the cycloaddition mechanism in terms of cobaltacyclopentadiene intermediates (Scheme 1).[2a] For short-tethered bis-alkynes (Table 1, entries 1–9), the generation of annulated cycloadducts of type **IV** originates from the favoured formation of intermediate **I**. In the case of differentially substituted bis-alkynes, such as **9**, **11**, and **13**, product regiochemistry is further influenced by the nitrile-incorporation step, specifically by the developing steric interaction between the alkyne substituents,

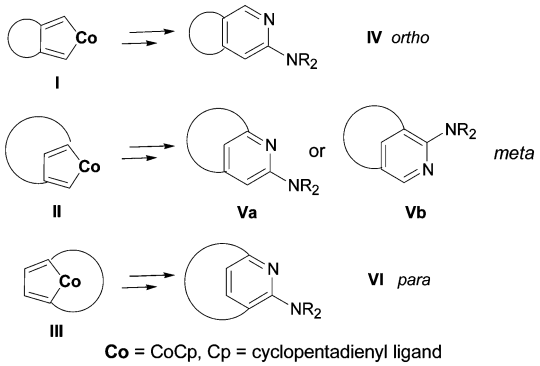
Table 1 Aminopyridines from bis-alkynes and *N*-cyanopyrrolidine[a]

Entry	1,n-Diyne		Aminopyridine		% Yield
1		**1** X = $C(CO_2Me)_2$	**2**		88
2		**3** X = CH_2	**4**		23
3		**5**	**6**		82
4		**7** R′ = R″ = H	**8**		76
5		**9** R′ = Bu, R″ = H	**10**		77
6		**11** R′ = Ph, R″ = H	**12**		80
7		**13** R′ = Bu, R″ = Me	**14**		16[b]
8		**15** R′ = R″ = H	**16**		34
9		**17** R′ = R″ = Et	**18**		66
10		**19** *n* = 0	—		0
11		**20** *n* = 1	—		0
12		**21**	**22**		50[c]
13		**23**	**24**		64[d]

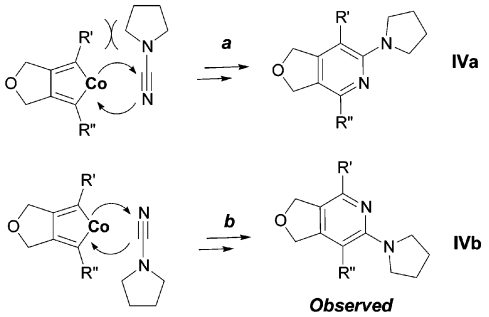
[a] 15 mol% $CpCo(CO)_2$, 1,4-dioxane (0.005 M), reflux, 18–24 h. NR_2 = $N(CH_2)_4$. [b] Isolated 8% of diyne **13**. [c] Isolated *para* cycloadduct. [d] Ratio of isolated isomeric *meta* and *para* products is 1:1.

† Electronic supplementary information (ESI) available: experimental details and characterisation data for the new compounds. See http://www.rsc.org/suppdata/cc/b4/b410012c/

DOI: 10.1039/b410012c

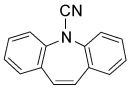
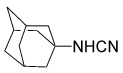


Scheme 1 Formation of 2-aminopyridines *via* a cyclopentadiene intermediate.



Scheme 2 Modes of nitrile incorporation (R′ > R″).

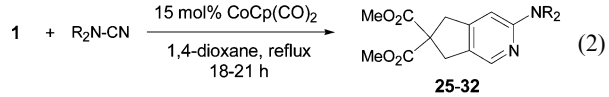
Table 2 Co-cyclotrimerisation of **1** with various cyanamides

Entry	Cyanamide	Product	% Yield
1		**25**	83
2	Me_2NCN	**26**	81
3	Et_2NCN	**27**	80
4	$(i\text{-}Pr)_2NCN$	**28**	29
5	Bn_2NCN	**29**	66
6	$(allyl)_2NCN$	**30**	30
7		**31**	19
8		**32**	32[a]

[a] 15% unreacted diyne **1**.

R′ and R″, and the in-bound cyanamide (Scheme 2). As a consequence, for **9** and **11** tetrasubstituted pyridine **IVb** formed in preference to regioisomeric **IVa** (R″ = H, pathway ***b*** *vs.* ***a***). This factor is evident in the cyclotrimerisation of 1-but-2-ynyloxy-hept-2-yne **13** (R′ = Bu, R″ = Me), wherein the isolated cycloadduct (form **IVb**)[9] derives from nitrile incorporation *via* pathway ***b***. Furthermore, in the case of α,ω-diynes, formation of the cobaltacycles **II** and **III** is preferred over formation of **I**.[4] DFT calculations[4b,10] indicated that formation of intermediate **III** is greatly favoured over formation of **I** and **II**; hence, the exclusive generation of pyridinophane **22** (form **VI**) in the macrocyclisation of diyne **21**.[11] On the contrary, this energy difference is not pronounced for intermediates **II** and **III** derived from diyne **23**;[12] hence, the formation of a 1:1 ratio of the *m*- and *p*-pyridinophanes. Likewise, isolation of a cycloadduct of the form **Va** was determined by the steric interactions described above.

The reactivity of representative cyanamides with bis-alkyne **1** was studied to gain a sense of the scope and limitations (eqn. (2); Table 2). *N*-Cyanomorpholine combined with **1** to give **25** in excellent yield (entry 1). Cyanamides disubstituted with alkyl (entries 2–5), allyl (entry 6), or aryl groups (entry 7) provided modest to excellent yields of annulated aminopyridines. Cyanamides with a remote alkene moiety also exhibited lower cycloaddition efficiencies under photoactivated Co(I) catalysis.[6] Heller also showed that primary and secondary amines are detrimental to Co(I)-catalyzed cyclotrimerisations.[6] Cyanamides that have the potential to interact and deactivate the catalyst, such as diphenyl cyanocarbonimidate, *N*-cyano-*N*′,*N*′-dimethylguanidine, and 2-cyaniminothiazolidine, were not tolerated; they failed to cyclotrimerise with **1**. Our method also accomplished cycloaddition with a cyanamide bearing a bulky adamantyl group (entry 8).



(2)

In summary, we have shown that cyanamides can undergo co-cyclotrimerisation with bis-alkynes in the presence of catalytic $CpCo(CO)_2$ under relatively mild and convenient conditions. This process offers an expeditious approach to highly elaborated 2-aminopyridines, including amino-substituted pyridinophanes.

We thank William Jones for HRMS determination, Jian Li for DFT studies, and Diane Gauthier for 2D-NMR experiments.

Notes and references

1 M. Malacria, C. Aubert and J. L. Renaud, in *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*, ed. M. Lautens and B. M. Trost, Georg Thieme Verlag: Stuttgart, 2001, vol 1, pp. 439–530; M. E. Welker, *Curr. Org. Chem.*, 2001, **5**, 785–807.

2 (*a*) J. A. Varela and C. Saa, *Chem. Rev.*, 2003, **103**, 3787–3801; (*b*) D. B. Grotjahn, in *Comprehensive Organometallic Chemistry II*, ed. L. S. Hegedus, E. W. Abel, F. G. A. Stone, and G. Wilkinson, Pergamon, Oxford, 1995, vol. 12, pp. 741–770; (*c*) N. E. Schore, in *Comprehensive Organometallic Chemistry II*, ed. L. S. Hegedus, E. W. Abel, F. G. A. Stone and G. Wilkinson, Pergamon, Oxford, 1995, vol. 12, pp. 703. See also: (*d*) S. E. Gibson and A. Stevenazzi, *Angew. Chem. Int. Ed.*, 2003, **42**, 1800–1810.

3 For recent examples, see: (*a*) Y. Yamamoto, J. Ishii, H. Nishiyama and K. Itoh, *J. Am. Chem. Soc.*, 2004, **126**, 3712–3713; (*b*) G. Chouraqui, M. Petit, C. Aubert and M. Malacria, *Org. Lett.*, 2004, **6**, 1519–1521; (*c*) L. Hong and H. Butenschön, *Chem. Commun.*, 2002, **23**, 2852–2853; (*d*) S. Saito and Y. Yamamoto, *Chem. Rev.*, 2000, **100**, 2901–2915.

4 (*a*) A. F. Moretto, H.-C. Zhang and B. E. Maryanoff, *J. Am. Chem. Soc.*, 2001, **123**, 3157–3158 [correction: *J. Am. Chem. Soc.*, 2001, **124**, 6792]; (*b*) L. V. R. Boñaga, H.-C. Zhang, D. A. Gauthier, I. Reddy and B. E. Maryanoff, *Org. Lett.*, 2003, **5**, 4537–4540.

5 H. Bönnemann and W. Brijoux, *Adv. Heterocycl. Chem.*, 1990, **48**, 177–222; H. Bönnemann and W. Brijoux, *Aspects Homogen. Catal.*, 1984, **5**, 75–196; H. Bönnemann, W. Brijoux, R. Brinkmann and W. Meurers, *Helv. Chim. Acta*, 1984, **67**, 1616–1624.

6 B. Heller, B. Sundermann, H. Buschmann, H.-J. Drexler, J. You, U. Holzgrabe, E. Heller and G. Oehme, *J. Org. Chem.*, 2002, **67**, 4414–4422; B. Heller, J. Reihsig, W. Schulz and G. Oehme, *Appl. Organometal. Chem.*, 1993, **7**, 641–646 (Cp = cyclopentadienide; cod = 1,5-cyclooctadiene).

7 K. P. C. Vollhardt and A. Naiman, U.S. Patent 4,328,343 (1982) [*Chem. Abstr.* **90**:186806 (1978)].

8 Aminopyridines, which are important as pharmaceutical agents, ligands in inorganic/organometallic chemistry, and fluorescent dyes, are typically prepared by substituting halogenated pyridines. For a leading reference, see: S. Thomas, S. Roberts, L. Pasumansky, S. Gamsey and B. Singaram, *Org. Lett.*, 2003, **5**, 3867–3870.

9 Structures were confirmed by 2D-NMR experiments (COSY, NOESY, HMQC, HMBC). See Electronic Supporting Information.

10 R. G. Parr and W. Yang, *Density-Functional Theory of Atoms and Molecules*, Oxford University Press, Oxford, 1989.

11 In the case of **21**, intermediate **III** is favoured over **II** by 4.5 kcal mol^{-1}, and over **I** by 14.5 kcal mol^{-1}.

12 In the case of **23**, **III** is favoured over **II** by 0.5 kcal mol^{-1}, and over **I** by 7.5 kcal mol^{-1}.