Nickel-catalyzed cocyclotrimerization of oxa- and azabenzonorbornadienes with alkynes: reaction with multiple synthetic applications

Daw-Jen Huang, Thota Sambaiah and Chien-Hong Cheng*

Department of Chemistry, National Tsing Hua University, Hsinchu, Taiwan 300

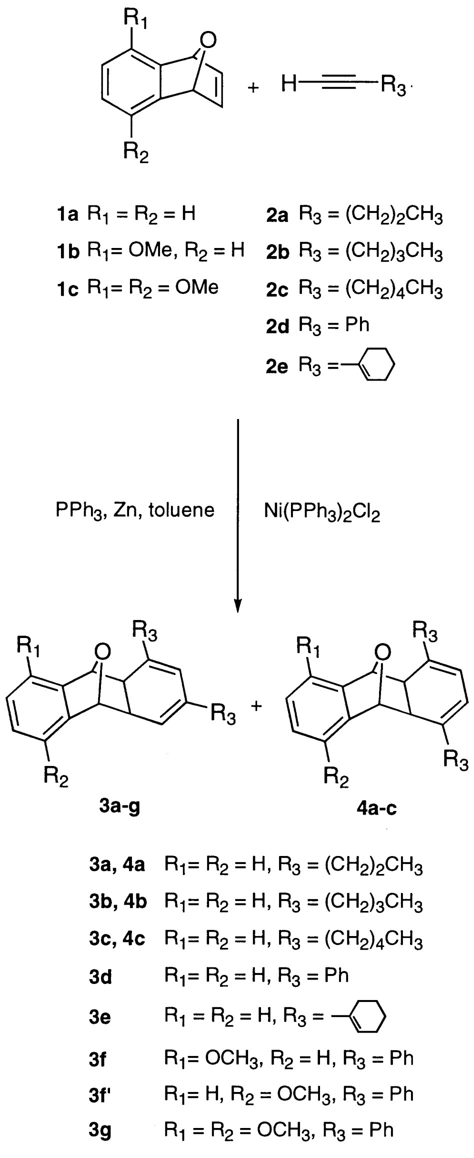
Oxa- and azabenzonorbornadienes react with alkynes in the presence of nickel complexes to give the corresponding [2 + 2 + 2] cycloadducts; these reactions can be applied to the construction of multiple fused rings, the preparation of precursors of isobenzofurans and isoindoles and aromatic compounds.

Metal-catalyzed [2 + 2 + 2] cycloaddition is a powerful method for the construction of cyclic compounds in a chemo- and regioselective manner.[1,2] Most examples of these cyclization reactions involve the use of three acetylenes.[3] Cocyclotrimerization of two acetylenes and an alkene using transition-metal complexes is much less studied.[4] Several reports on the latter cocyclotrimerization mediated by nickel complexes are known.[5,6] Here we report a nickel-catalyzed cocyclotrimerization of oxa- and aza-benzonorbornadienes with alkynes. This [2 + 2 + 2] cycloaddition not only provides an excellent method for constructing multiple fused rings, but also furnishes a convenient route for synthesizing new precursors of isobenzofurans and isoindoles and for preparing substituted aromatic compounds from alkynes and oxa- or aza-benzonorbornadienes.

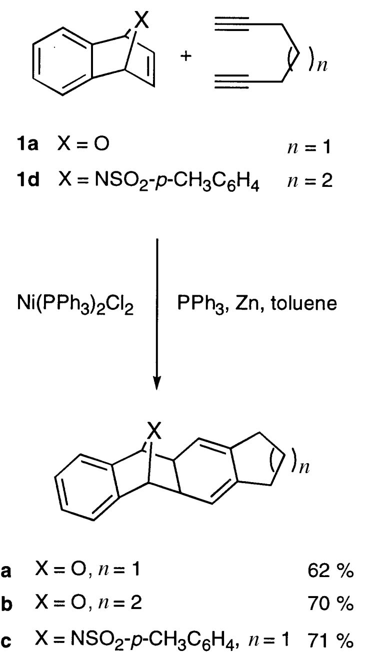
Treatment of oxabenzonorbornadiene (**1a**, 1.0 mmol) with pent-1-yne (**2a**, 2.0 mmol) in the presence of $Ni(PPh_3)_2Cl_2$ (0.050 mmol), PPh_3 (0.80 mmol) and zinc powder (2.75 mmol) in toluene at 18 °C for 24 h gave a pair of [2 + 2 + 2] cotrimerization isomers **3a** and **4a** (1 : 3.1) in 91% combined yield. Under similar catalytic conditions, hex-1-yne (**2b**) and hept-1-yne (**2c**) also reacted with **1a** to give **3b** and **4b** (1 : 2.1), and **3c** and **4c** (1 : 8.7) in 91 and 68% combined yields, respectively. On the other hand, terminal alkynes with bulkier substituents such as phenylacetylene (**2d**) and ethyn-1-ylcyclohex-1-ene (**2e**) afforded only the 1,3-isomers **3d** and **3e**, in high yields respectively (Scheme 1). Disubstituted alkynes and bisalkynes also undergo [2 + 2 + 2] cotrimerization. Thus, hepta-1,6-diyne and octa-1,7-diyne react with **1a** to give **5a** and **5b**, respectively (Scheme 2), while methylbut-2-ynoate affords presumably a tetrasubstituted [2 + 2 + 2] adduct **6**, which, however, undergoes further transformation due to thermal instability (*vide infra*).

This [2 + 2 + 2] cotrimerization is successfully extended to substituted oxabenzonorbornadienes and azabenzonorbornadienes. In the presence of $Ni(PPh_3)_2Cl_2$, PPh_3 and zinc powder, treating **1b** and **1c** with phenylacetylene (**2d**) led to the formation of cotrimerization products **3f** and **3f′** and **3g**, respectively, in good yields. Similarly, the azabenzonorbornadiene **1d** reacts with bisalkynes affording **5c** and **5d** in 70 and 75% yields, respectively. It is noteworthy that in these reactions, the nickel system very selectively catalyzes the cotrimerization of an olefin and two alkyne moieties. Only a trace of the trimerization product of alkyne was observed in each reaction. However, in the absence of compound **1**, trimerization of alkynes became the sole pathway. The replacement of **1** by a less reactive olefin such as 2,3-dihydro-2*H*-pyran and cyclohexene did not give the expected [2 + 2 + 2] cotrimerization product.

An interesting property of the present [2 + 2 + 2] cotrimerization products **3**–**5** is that they are thermally unstable and undergo a retro Diels–Alder reaction to give isobenzofurans or isoindole (**7**) and aromatic compounds **8** (eqn 1). The stability of the products depend greatly on the substituent of the alkyne used in the cyclization. The products from



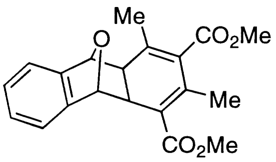
Scheme 1



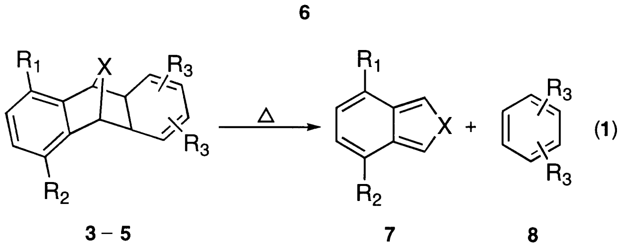
Scheme 2

alkylacetylenes and bisalkynes are most stable and can be kept at room temperature for a few days in solution and in the solid state for a long time. Compound **3e** from ethyn-1-ylcyclohex-1-ene is stable for only a few hours at room temperature in solution. The product from phenylacetylene (**3d**) can be observed only at temperatures below −5 °C. On the other hand, no [2 + 2 + 2] adduct was observed from methyl but-2-ynoate at −5 to 30 °C.

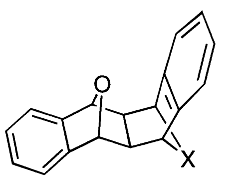
As indicated by the products **5** from **1a** and hepta-1,6-diyne and octa-1,7-diyne, the [2 + 2 + 2] cycloaddition is an efficient method for constructing multiple fused rings. In addition, the cycloaddition finds two other synthetic applications. First, these products are convenient precursors of isobenzofurans and isoindoles. For example, heating **5c** and **5d** with **1a** led to the isolation of the Diels–Alder cycloaddition product of isoindole **9** in 70% yield. Treatment of **5a** with cyclohex-2-en-1-one in toluene at 60 °C afforded *endo* and *exo* isomers of the Diels–Alder cycloadducts **10** and **11** (*ca.* 1 : 1) in 77% combined yield. Second, the present [2 + 2 + 2] cycloaddition can be employed to synthesize aromatic compounds (Scheme 3) in which compound **1a** serves as 'masked acetylene'. The cycloaddition of **1a** and methyl but-2-ynoate in the presence of the nickel catalyst demonstrates both applications. The reaction produced aromatic compound **12** regioselectively and the Diels–Alder cycloadducts **13** and **14** from isobenzofuran (**7**) generated *in situ* and **1a**.



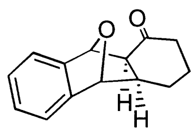
6



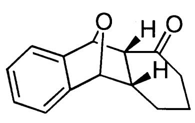
3 – 5 **7** **8**



9 X= NSO$_2$-p-CH$_3$C$_6$H$_4$



10



11

Isobenzofuran and its derivatives are versatile synthons in organic synthesis, particularly in the Diels–Alder reactions[7] to provide substituted 7-oxabicyclo[2.2.1]heptanes, key intermediates in natural product synthesis.[8,9] However, both isobenzofurans and isoindoles are highly reactive and readily undergo polymerization at low temperature and the preparation of the corresponding precursors is required.[10]

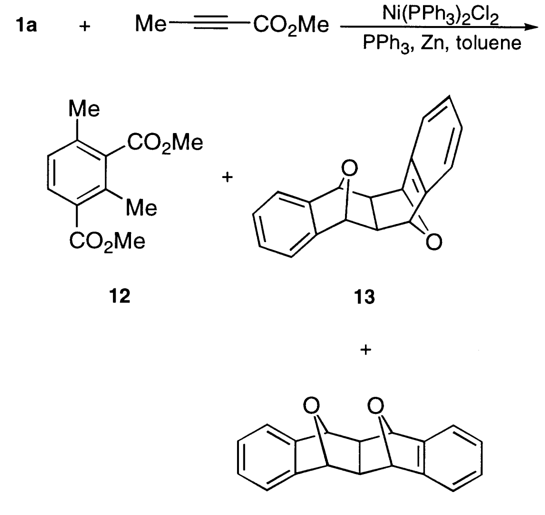
In most regioselective cotrimerizations of alkynes to arenes catalyzed by cobalt complexes, a diyne was used as one component and bis(trimethylsilyl)acetylene as the other. It generally led to the formation of a mixture of isomers when a sterically less hindered monoalkyne is used.[11] The present [2 + 2 + 2] cycloaddition reactions provide a new alternative for the construction of arenes by employing masked acetylenes.

We have demonstrated that the present nickel-catalyzed [2 + 2 + 2] cycloaddition shows various utilities in organic synthesis including construction of multiple rings, synthesis of precursors of isobenzofurans and isoindoles and regioselective synthesis of substituted aromatic compounds. Application of these methodologies to the synthesis of useful organic compounds is in progress.

Experimental

General procedure for the cocyclotrimerization of oxa- and azabenzonorbornadienes with alkynes

A 50 ml round-bottom side-arm, flask was charged with an oxa- or azabenzonorbornadiene (1.0 mmol), NiCl$_2$(PPh$_3$)$_2$ (0.0325 g, 0.0500 mmol), PPh$_3$ (0.210 g, 0.801 mmol) and zinc powder (0.180 g, 2.75 mmol). The system was evacuated and purged with nitrogen gas three times. Freshly distilled toluene



Scheme 3

Table 1 Cocyclotrimerization of oxabenzonorbornadienes with terminal alkynes

Entry	Substrate	Temp/°C	Alkyne	Product (yield %)[a]
1	**1a**	18	**2a**	**3a** (22) + **4a** (69)
2	**1a**	18	**2b**	**3b** (29) + **4b** (62)
3	**1a**	18	**2c**	**3c** (7) + **4c** (61)
4	**1a**	−5	**2d**	**3d** (95)
5	**1a**	18	**2e**	**3e** (95)
6	**1b**	0	**2d**	**3f** + **3f′** (72)
7	**1c**	0	**2d**	**3g** (74)

[a] Yields were measured by ^{1}H NMR integration method using norbornene as internal standard.

(2.0 ml) and an appropriate alkyne (alkyne, 2.0 mmol or a bisalkyne, 1.0 mmol) were added. The reaction mixture was stirred for 24 h at a specified temperature as shown in Table 1. The solution was filtered through Celite and silica gel, and the filtrate was concentrated. The residue was separated on a silica gel column using hexane–dichloromethane as eluent to afford the [2 + 2 + 2] products. Compounds **3a**–**3c** and **4a**–**4c** were thus prepared following the above procedure. For compounds **5a**–**5d**, the reaction temperature was 18 °C and the reaction time was 48 h and for **3d**, **3f**–**3g**, no purification on silica gel column was carried out due to thermal instability. The residues were used directly for spectral analysis.

A similar procedure was also employed for the reaction of **1a** with methyl but-2-ynoate. Compounds **12**, **13** and **14** in 92, 58 and 40% yields, respectively, were obtained from this reaction.

Diels–Alder cycloaddition of *in situ* generated isobenzofuran or isoindole with 1a

To a 50 ml round-bottom side-arm flask consisting of **5c** (or **5d**) (0.0720 mmol) and **1a** (0.0104 g, 0.0720 mmol) was added freshly distilled xylene (5.0 ml). The system was evacuated and purged with nitrogen gas three times. The reaction mixture was then heated at 90 °C for 7.5 h. The solvent was removed under vacuum and the resultant solid was purified by silica gel column using hexane–ethyl acetate (v/v, 7 : 3) as eluent to give **9** in 70%.

Similarly, **10** and **11** were prepared by reacting **5a** with cyclohex-2-en-1-one at 60 °C in toluene for 3 h. The combined yield of these products is 77%.

Acknowledgements

We are grateful to the National Science Council of the Republic of China for financial support of this research (NSC87-2811-M-007-0042).

References

1 K. P. C. Vollhardt, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 539; M. Lautens, W. Klute and W. Tam, *Chem. Rev.*, 1996, **96**, 49; I. Ojima, M. Tzamarioudaki, Z. Li and R. J. Donovan, *Chem. Rev.*, 1996, **96**, 635.

2 S. H. Lecker, N. H. Nguen and K. P. C. Vollhardt, *J. Am. Chem. Soc.*, 1986, **108**, 856; E. Negishi, L. S. Harring, Z. Owczarczyk, M. M. Mohamud and M. Ay, *Tetrahedron. Lett.*, 1992, **33**, 3253; H. E. Helson, K. P. C. Vollhardt and Z.-Y. Yang, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 114; R. Grigg, R. Scott and P. Stevenson, *Tetrahedron Lett.*, 1982, **23**, 2691.

3 V. O. Reikhstel'd and K. L. Makovetskii, *Russ. Chem. Rev.*, 1966, **35**, 510; N. E. Schore, *Chem. Rev.*, 1988, **88**, 1081; B. M. Trost, *Science*, 1996, **96**, 49.

4 A. J. Chalk, *J. Am. Chem. Soc.*, 1972, **94**, 5928; H. Suzuki, K. Itoh, Y. Ishii, K. Simon and J. A. Ibers, *J. Am. Chem. Soc.*, 1976, **98**, 8494.

5 T. Tsuda, S. Morikawa, R. Sumiya and T. Saegusa, *J. Org. Chem.*, 1988, **53**, 3140; T. Tsuda, R. Sumiya and T. Saegusa, *Synth. Commun.*, 1987, **17**, 147.

6 R. A. Earl and K. P. C. Vollhardt, *J. Org. Chem.*, 1984, **49**, 4786.

7 W. Friedrichsen, *Adv. Heterocycl. Chem.*, 1980, **26**, 135; B. Rickborn, in *Advances in Theoretically Interesting Molecules*, ed. R. P. Thummel, JAI Press, Greenwich, CT, 1989, Vol. 1, Ch. 1; W. Friedrichsen, in *Houben-Weyl, Methoden der Organischen Chemie*, ed. R. Kreher, Thieme Verlag, Stuttgart, 1994, Vol. E6b, pp. 163–216.

8 P. Vogel, D. Fattori. F. Gasparini and C. Le Drian, *Synlett*, 1990, **56**, 2128; P. Renaud and J.-P. Vionnet, *J. Org. Chem.*, 1993, **58**, 5895; T. A. Eggette, H. de Koning and H. O. Huisman, *J. Chem. Soc., Perkin Trans. 1*, 1978, 980; G. Just and S. Kim, *Tetrahedron Lett.*, 1976, 1063.

9 A. Padwa, C. O. Kappe and T. S. Reger, *J. Org. Chem.*, 1996, **61**, 4888; A. Padwa, C. O. Kappe, J. E. Cochran and J. P. Snyder, *J. Org. Chem.*, 1997, **62**, 2786.

10 L. F. Fieser and M. J. Haddadin, *Can. J. Chem.*, 1965, **43**, 1599; R. N. Warrener, *J. Am. Chem. Soc.*, 1971, **93**, 2346; J. Luo and H. Hart, *J. Org. Chem.*, 1989, **54**, 1762; S. E. Whitney, M. Winters and B. Rickborn, *J. Org. Chem.*, 1990, **55**, 929; G. M. Priestley and R. N. Warrener, *Tetrahedron Lett.*, 1972, 4295.

11 L. S. Hegedus, in *Transition Metals in the Synthesis of Complex Organic Molecules*, University Science Books, Mill Valley, CA, 1994, Ch. 8, pp. 248–255.

Received 25th *June* 1998;
revised M/S received 10th *August* 1998; *Letter* 8/06340K