Phenanthridine synthesis *via* [2+2+2] cyclotrimerization reactions†

Lakshminath Sripada, Jesse A. Teske and Alexander Deiters*

Received 26th October 2007, Accepted 23rd November 2007
First published as an Advance Article on the web 3rd December 2007
DOI: 10.1039/b716519f

A concise synthesis of phenanthridines *via* a microwave-assisted [2+2+2] cyclotrimerization reaction has been developed.

Phenanthridines are important core structures found in a variety of natural products and other biologically important molecules with a wide range of biological activities and applications, including antibacterial, antiprotozoal, and anticancer agents.[1–4] A well known member of this compound class is ethidium (**1**), a common DNA intercalator and stain. Many natural products containing a phenanthridine core structure are known and representative examples include trispheridine (**2**)[5] and bicolorine (**3**),[6] shown in Fig. 1.

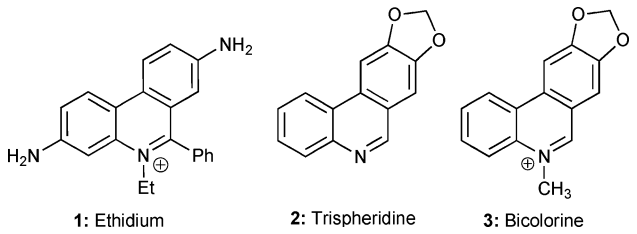
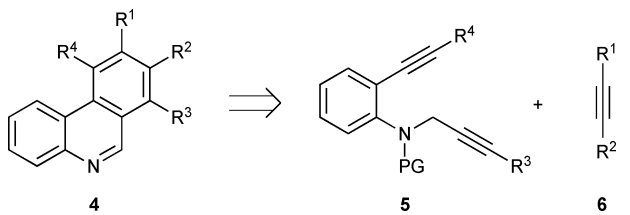


Fig. 1 Selected phenanthridines.

The [2+2+2] cyclotrimerization reaction represents a unique synthetic tool for the assembly of aromatic systems,[7–13] and we envisioned the synthesis of phenanthridines **4** through a microwave-assisted cyclotrimerization[14–17] of a diyne **5** with an alkyne **6** followed by protecting group removal and oxidation (Scheme 1). Several cyclotrimerization reaction conditions were investigated with different catalyst systems based on Co,[18,19] Ni,[20,21] Rh,[22–25] and Ru[24,26] and with and without microwave irradiation.

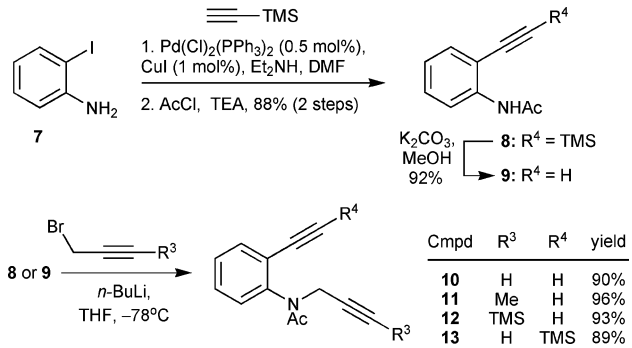


Scheme 1 Retrosynthetic analysis of the phenanthridine skeleton. PG = protecting group.

Department of Chemistry, North Carolina State University, Raleigh, NC 27695-8204, USA. E-mail: alex_deiters@ncsu.edu; Fax: +1-919-515-5079; Tel: +1-919-513-2958

† Electronic supplementary information (ESI) available: Experimental protocols for compounds **10–13**; general cyclotrimerization procedure; analytical data for compounds **14–30**, **33–40**; ^{1}H NMR spectra for compounds **10–30** and **33–40**. See DOI: 10.1039/b716519f

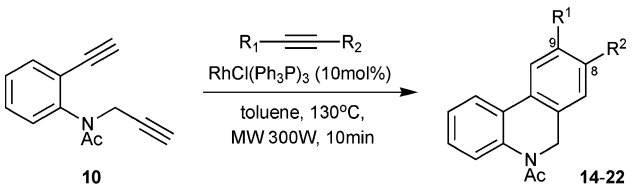
Four different diyne starting materials carrying various R^3 and R^4 groups were synthesized (Scheme 2) in order to probe the tolerance of sterically demanding alkyne substituents and to induce regioselectivity on the cyclotrimerization reaction. The synthesis of **10–13** commenced with the *ortho*-iodo aniline **7** which underwent a smooth Sonogashira coupling with TMS acetylene followed by *N*-acetylation delivering **8** in 88% over two steps.[27] In order to provide the terminal alkyne **9**, the TMS group was removed from **8** by treatment with K_2CO_3–MeOH in 92% yield.[28] Both **8** and **9** were then subjected to NH deprotonation with BuLi at low temperature, followed by alkylation with various propargyl bromides (R^3 = H, CH_3, and TMS). All cyclotrimerization precursors **10–13** were obtained in excellent yields of 89–96%.‡



Scheme 2 Synthesis of diyne cyclotrimerization precursors.

We initially screened four different catalyst systems ($RhCl(Ph_3P)_3$,[25] Cp*RuCl(COD),[24] $Ni(CO)_2(Ph_3P)_2$,[21] and $CpCo(CO)_2$[18]) for the microwave-mediated cyclotrimerization of the terminal diyne **10** and 1-hexyne (10 equiv.), revealing that 10 mol% Wilkinson's catalyst ($RhCl(Ph_3P)_3$) delivered the cyclotrimerization product **14** with the highest yield (86%). The other catalysts provided **14** in 60–80% yield. Reactions were conducted in microwave transparent toluene (0.1 mM) with a 300 W microwave irradiation for 10 min (CEM Discover), leading to a final reaction temperature of 130 °C (IR temperature sensor). Shorter reaction times or irradiations with less microwave power led to diminished yields. Importantly, when the cyclotrimerization **10** → **14** was conducted under purely thermal heating, while mimicking the temperature profile of the microwave reaction (10 min, 130 °C final temperature, 150 °C oil bath temperature), the product **14** was only obtained in 34% yield. The optimized microwave conditions were then used for the cyclotrimerization of **10** with a variety of alkynes, probing the functional group compatibility of the developed reaction conditions. A wide range of functional groups was tolerated, including a cyano group (in **16**), a chloro atom (in **17**), a carbamate (in **18**[29]), and a silyl ether

(in **19**[30]) (Scheme 3). The [2+2+2] cyclotrimerization reaction of terminal monoalkynes proceeded smoothly delivering **14–22** in 85–89% yield after silica gel chromatography.‡ As expected, no regioselectivity in the cyclotrimerization step was observed, leading to the formation of 1 : 1 mixtures of regioisomers at the 8- and 9-positions. Symmetrical internal alkynes alleviate the regioselectivity problem, but lead to diminished yields (30–34%) as seen in the synthesis of **20–22**. This low yield is due to the internal alkynes' lower reactivity in cyclotrimerization reactions, which induces the formation of diyne-dimerization and -trimerization side products typically observed in these cases.[15,24,25] We previously addressed this problem through the spatial seperation of substrates on a polymeric support.[15,26,31,32] Here, we are providing a solution through open-vessel microwave conditions,[33,34] which allowed the slow addition (over 60 min) of a solution of the diyne (0.01 mM) to the internal alkyne (0.1 mM) in refluxing toluene (110 °C) under microwave irradiation (300 W). By employing these conditions the yields of the cyclotrimerization products **20–22** were essentially doubled (56–65%).

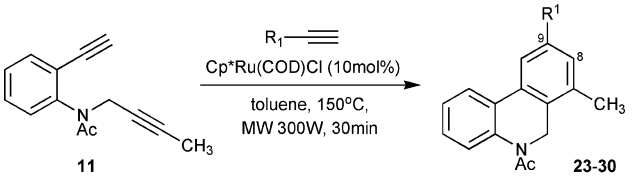


10 **14-22**

Cmpd	R^1	R^2	yield	regio
14	Bu	H	91%	1:1
14[a]	Bu	H	34%	1:1
15	Ph	H	87%	1:1
16	$(CH_2)_3CN$	H	89%	1:1
17	$(CH_2)_4Cl$	H	86%	1:1
18	CH_2NHBoc	H	85%	1:1
19	CH_2OTBS	H	87%	1:1
20	Et	Et	30%	-
21	CH_2OCH_3	CH_2OCH_3	33%	-
22	CH_2OTBS	CH_2OTBS	34%	-
20[b]	Et	Et	64%	-
21[b]	CH_2OCH_3	CH_2OCH_3	56%	-
22[b]	CH_2OTBS	CH_2OTBS	65%	-

Scheme 3 Cyclotrimerization reactions of the terminal diyne **10**. [a]Reaction under thermal conditions. [b]Reaction under open-vessel conditions.

We investigated a potential solution to the regiochemistry problem through the installation of a regio-directing group,[35] as previously demonstrated in the synthesis of indanones *via* a [2+2+2] cyclotrimerization reaction.[26] Hence, the precursor **11** carrying a methyl group was synthesized (Scheme 2). An initial catalyst screening with **11** and 1-hexyne revealed that $RhCl(Ph_3P)_3$, $Ni(CO)_2(Ph_3P)_2$ and $CpCo(CO)_2$ deliver the product **23** as a 1 : 1 mixture of regioisomers. Only Cp*RuCl(COD) displayed a preference for the formation of the 9- over the 8-isomer in a ratio of 4 : 1 by integration of the ^1H NMR signal of the CH_3 group. The 9-regioisomer could be easily assigned based on the two singlets for H-8 and H-10. Thus, 10 mol% of Cp*RuCl(COD) in toluene was used in the presence of 300 W microwave irradiation leading to a final reaction temperature of 150 °C after 30 min. Without microwave irradiation (30 min, 150 °C final temperature, 165 °C oil bath temperature), the yield dropped to 31% while maintaining the same ratio of regioisomers. Using the same mono-alkynes as before, the cyclotrimerization products **23–30** were obtained under mild conditions in 55–91% yield and with a regioselectivity of 4 : 1 (Scheme 4).‡ To our surprise, TBS protected propargyl alcohol led to the formation of **28** with no regioselectivity. By inserting additional methylene groups between the triple bond and the OTBS group (in **29**[36] and **30**[37]), the regioselectivity was increased to 4 : 1 as in case of the other alkynes.

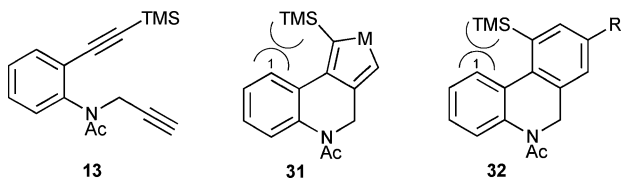


11 **23-30**

Cmpd	R^1	yield	regio
23	Bu	91%	4:1
23[a]	Bu	31%	4:1
24	Ph	66%	4:1
25	$(CH_2)_3CN$	89%	4:1
26	$(CH_2)_4Cl$	78%	4:1
27	CH_2NHBoc	55%	1:1
28	CH_2OTBS	78%	3:2
29	$(CH_2)_2OTBS$	82%	4:1
30	$(CH_2)_3OTBS$	78%	4:1

Scheme 4 Regiodirected [2+2+2] cyclotrimerization. [a]Reaction under thermal conditions.

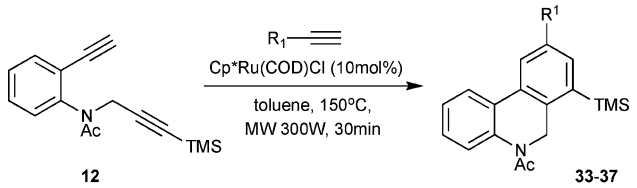
In order to increase the selectivity, we investigated the application of a sterically more demanding regio-directing group and selected a TMS group due to its potential conversion into a proton,[26] halide,[38] or hydroxy group[39] after cyclotrimerization. The precursors **12** and **13** were synthesized in high yields analogous to the other diynes. Surprisingly, all cyclotrimerization attempts with **13** using all four catalyst systems under various conditions failed (Fig. 2), presumably due to a pronounced strain between the TMS group and the CH group in position 1 of the metallacyclopentadiene intermediate **31** and the cyclotrimerization product **32**.[40] In all reaction attempts starting material and non-characterized byproducts were obtained; only $CpCo(CO)_2$ delivered trace amounts of **32** (with R = Bu).



13 **31** **32**

Fig. 2 Cyclotrimerization attempts with **13** did not lead to product formation. M = metal.

The regioselectivity problem was solved using the complementary silyl modified precursor **12**, which led to a smooth cyclotrimerization reaction with 1-hexyne, yielding **33** in 85% yield and as a single regiosiomer (Scheme 5). Thus, increasing the sterical demand from CH_3 to $Si(CH_3)_3$ led to a substantial increase in regioselectivity from 4 : 1 to 95 : 5 (as determined by GC). No cyclotrimerization product **33** was obtained under thermal reaction conditions resembling the temperature profile observed under microwave conditions (30 min, 150 °C final temperature, 165 °C oil bath temperature). Unfortunately, the microwave-mediated

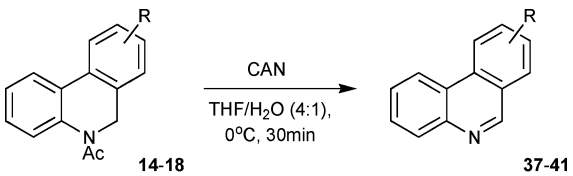


Cmpd	R^1	yield	regio
33	Bu	85%	95:5
33[a]	Bu	-	-
34	Ph	31%	95:5
35	$(CH_2)_4Cl$	46%	95:5
36	$(CH_2)_3OTBS$	49%	95:5

Scheme 5 Regioselective [2+2+2] cyclotrimerization.

cyclotrimerization reactions with the other monoalkynes were less successful and delivered the tricyclic products **33–36** in 31–49% yield, but with complete regioselectivity.

With a facile cyclotrimerization approach to protected dihydrophenanthridines in hand, the oxidation to the actual phenanthridine was subsequently investigated. We found that treatment of **14–18** with an excess of cerium ammonium nitrate (CAN) for 30 min at 0 °C delivered the phenanthridines **37–41** in good yields (71–78%)‡ through oxidation and simultaneous deacetylation (Scheme 6).[41,42]



Cmpd	R	yield
37	Bu	76%
38	Ph	71%
39	$(CH_2)_3CN$	78%
40	$(CH_2)_4Cl$	75%
41	CH_2NHBoc	77%

Scheme 6 Oxidation of **14–18** to phenanthridines **37–41**.

In summary, we developed a highly convergent and rapid assembly of the phenanthridine skeleton through a microwave-mediated [2+2+2] cyclotrimerization reaction towards dihydrophenanthridines followed by oxidation. Microwave irradiation led to substantially enhanced yields in the cyclotrimerization step. Regioselectivity issues have been solved through the choice of a sterically demanding regio-directing group, and chemoselectivity issues in the case of less reactive internal alkynes have been addressed through the application of open-vessel microwave conditions combined with syringe pump addition.

Acknowledgements

We gratefully acknowledge financial support by the Donors of the American Chemical Society Petroleum Research Fund and North Carolina State University. The NCSU Department of Chemistry MS Facility acknowledges financial support by the North Carolina Biotechnology Center.

Notes and references

‡ The identity of all compounds was confirmed by NMR and HRMS measurements. All yields were determined after flash-column chromatography on silica gel.

1 S. D. Phillips and R. N. Castle, *J. Heterocycl. Chem.*, 1981, **18**, 223–232.
2 T. Ishikawa, *Med. Res. Rev.*, 2001, **21**, 61–72.
3 P. Borst, *IUBMB Life*, 2005, **57**, 745–747.
4 W. A. Denny, *Curr. Med. Chem.*, 2002, **9**, 1655–1665.
5 O. B. Abdel-Halim, T. Morikawa, S. Ando, H. Matsuda and M. Yoshikawa, *J. Nat. Prod.*, 2004, **67**, 1119–1124.
6 F. Viladomat, J. Bastida, G. Tribo, C. Codina and M. Rubiralta, *Phytochemistry*, 1990, **29**, 1307–1310.
7 P. R. Chopade and J. Louie, *Adv. Syn. Catal.*, 2006, **348**, 2307–2327.
8 Y. Yamamoto, *Curr. Org. Chem.*, 2005, **9**, 503–519.
9 S. Kotha, E. Brahmachary and K. Lahiri, *Eur. J. Org. Chem.*, 2005, 4741–4767.
10 J. A. Varela and C. Saa, *Chem. Rev.*, 2003, **103**, 3787–3801.
11 N. E. Schore, in *Comprehensive Organic Synthesis*, ed. B. M. Trost, I. Fleming and L. A. Paquette, Pergamon Press, Oxford, 1991, vol. 5, pp. 1129–1162.
12 K. P. C. Vollhardt, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 539–556.
13 K. P. C. Vollhardt, *Acc. Chem. Res.*, 1977, **10**, 1–8.
14 D. D. Young, L. Sripada and A. Deiters, *J. Comb. Chem.*, 2007, **9**, 735–738.
15 D. D. Young and A. Deiters, *Angew. Chem., Int. Ed.*, 2007, **46**, 5187–5190.
16 Y. Zhou, J. A. Porco and J. K. Snyder, *Org. Lett.*, 2007, **9**, 393–396.
17 S. Saaby, I. R. Baxendale and S. V. Ley, *Org. Biomol. Chem.*, 2005, **3**, 3365–3368.
18 N. Agenet, V. Gandon, K. P. Vollhardt, M. Malacria and C. Aubert, *J. Am. Chem. Soc.*, 2007, **129**, 8860–8871.
19 E. D. Sternberg and K. P. C. Vollhardt, *J. Org. Chem.*, 1982, **47**, 3447–3450.
20 M. M. McCormick, H. A. Duong, G. Zuo and J. Louie, *J. Am. Chem. Soc.*, 2005, **127**, 5030–5031.
21 L. Meriwether, G. W. Kennerly, R. N. Reusch and E. C. Colthup, *J. Org. Chem.*, 1961, **26**, 5155.
22 J. Clayden and W. J. Moran, *Org. Biomol. Chem.*, 2007, **5**, 1028–1030.
23 R. T. Yu and T. Rovis, *J. Am. Chem. Soc.*, 2006, **128**, 2782–2783.
24 Y. Yamamoto, T. Arakawa, R. Ogawa and K. Itoh, *J. Am. Chem. Soc.*, 2003, **125**, 12143–12160.
25 R. Grigg, R. Scott and P. Stevenson, *J. Chem. Soc., Perkin Trans. 1*, 1988, 1357–1364.
26 R. S. Senaiar, J. A. Teske, D. D. Young and A. Deiters, *J. Org. Chem.*, 2007, **72**, 7801–7804.
27 G. Dominguez, L. Casarrubios, J. Rodriguez-Noriega and J. Perez-Castells, *Helv. Chim. Acta*, 2002, **85**, 2856–2861.
28 D. E. Rudisill and J. K. Stille, *J. Org. Chem.*, 1989, **54**, 5856–5866.
29 S. Cheng, C. M. Tarby, D. D. Comer, J. P. Williams, L. H. Caporale, P. L. Myers and D. L. Boger, *Bioorg. Med. Chem.*, 1996, **4**, 727–737.
30 J. A. John and J. M. Tour, *Tetrahedron*, 1997, **53**, 15515–15534.
31 R. S. Senaiar, D. D. Young and A. Deiters, *Chem. Commun.*, 2006, 1313–1315.
32 D. D. Young, R. S. Senaiar and A. Deiters, *Chem.–Eur. J.*, 2006, **12**, 5563–5568.
33 N. E. Leadbeater, V. A. Williams, T. M. Barnard and M. J. Collins, *Org. Proc. Res. Dev.*, 2006, **10**, 833–837.
34 N. E. Leadbeater, V. A. Williams, T. M. Barnard and M. J. Collins, *Synlett*, 2006, 2953–2958.
35 R. L. Hillard, C. A. Parnell and K. P. C. Vollhardt, *Tetrahedron*, 1983, **39**, 905–911.
36 R. S. Narayan and B. Borhan, *J. Org. Chem.*, 2006, **71**, 1416–1429.
37 A. R. Pereira and J. A. Cabezas, *J. Org. Chem.*, 2005, **70**, 2594–2597.
38 L. A. Jacob, B. L. Chen and D. Stec, *Synthesis*, 1993, 611–614.
39 J. R. Kalman, S. Sternhel and J. T. Pinhey, *Tetrahedron Lett.*, 1972, 5369.
40 To the best of our knowledge, no 9,10-dihydrophenanthrenes (or heterocyclic derivatives thereof) with a 4-silyl substituent are known.
41 W. R. Li, Y. S. Lin and N. M. Hsu, *J. Comb. Chem.*, 2001, **3**, 634–643.
42 W. R. Li, N. M. Hsu, H. H. Chou, S. T. Lin and Y. S. Lin, *Chem. Commun.*, 2000, 401–402.