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

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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.
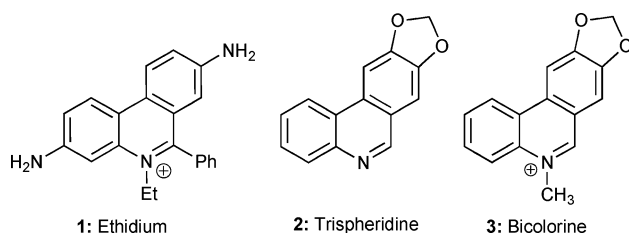

Fig. 1 Selected phenanthridines.

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.
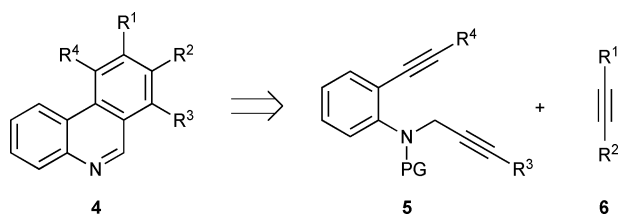

Scheme 1 Retrosynthetic analysis of the phenanthridine skeleton. PG = protecting group.

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† Electronic supplementary information (ESI) available: Experimental protocols for compounds **10–13**; general cyclotrimerization procedure; analytical data for compounds **14–30, 33–40**; ¹H NMR spectra for compounds **10–30** and **33–40**. See DOI: 10.1039/b716519f
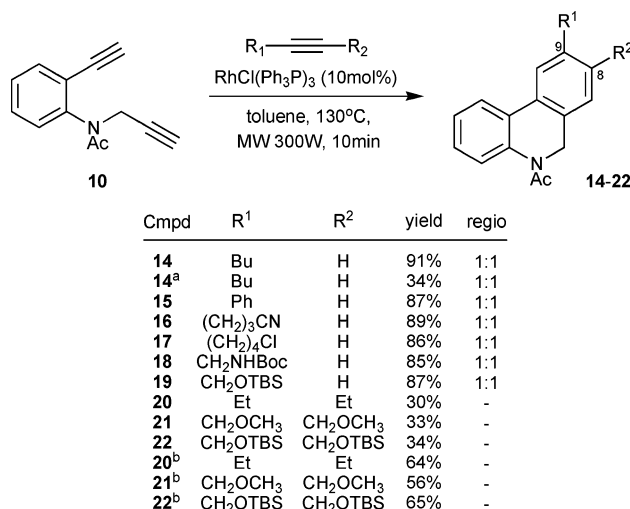
Four different diyne starting materials carrying various R³ and R⁴ groups were synthesized (Scheme 2) in order to probe the tolerance of sterically demanding alkyne substituents and to induce regioselectivity on the cyclotrimerization reaction. The synthesis of **10–13** commenced with the *ortho*-iodo 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 (R³ = H, CH₃, and TMS). All cyclotrimerization precursors **10–13** were obtained in excellent yields of 89–96%.‡
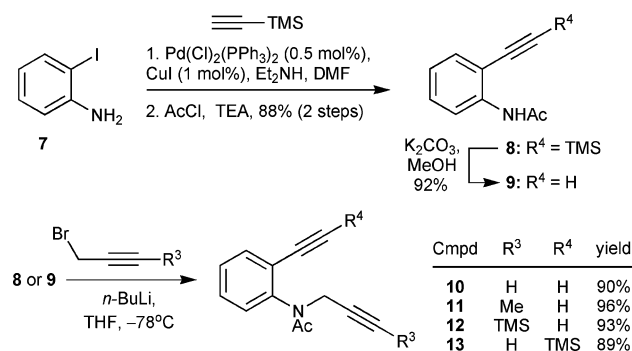
Scheme 2 Synthesis of diyne cyclotrimerization precursors.

We initially screened four different catalyst systems (RhCl(Ph₃P)₃,[25] Cp*RuCl(COD),[24] Ni(CO)₂(Ph₃P)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(Ph₃P)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
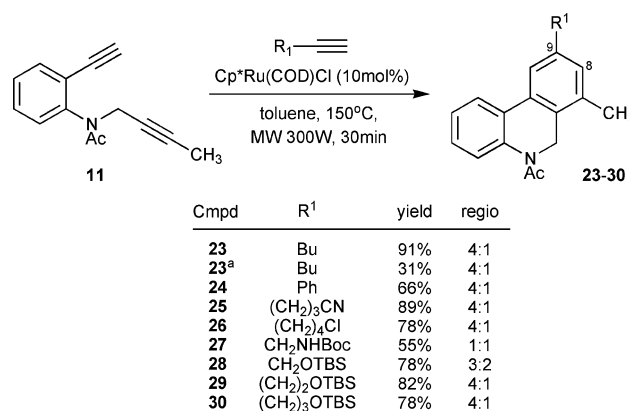
(in **19**[30]) (Scheme 3). The [2+2+2] cyclotrimerization reaction of terminal monoalkynes proceeded smoothly delivering **14–22** in 85–89% yield after silica gel chromatography.‡ As expected, no regioselectivity in the cyclotrimerization step was observed, leading to the formation of 1 : 1 mixtures 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%).

Cmpd	R¹	R²	yield	regio
14	Bu	H	91%	1:1
14[a]	Bu	H	34%	1:1
15	Ph	H	87%	1:1
16	(CH₂)₃CN	H	89%	1:1
17	(CH₂)₄Cl	H	86%	1:1
18	CH₂NHBoc	H	85%	1:1
19	CH₂OTBS	H	87%	1:1
20	Et	Et	30%	-
21	CH₂OCH₃	CH₂OCH₃	33%	-
22	CH₂OTBS	CH₂OTBS	34%	-
20[b]	Et	Et	64%	-
21[b]	CH₂OCH₃	CH₂OCH₃	56%	-
22[b]	CH₂OTBS	CH₂OTBS	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(Ph₃P)₃, Ni(CO)₂(Ph₃P)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 CH₃ 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.

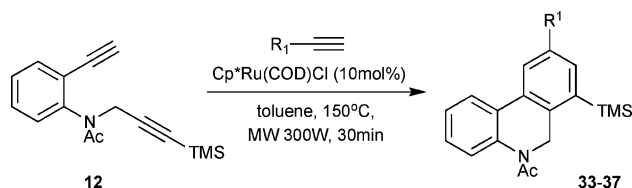| Cmpd	R¹	yield	regio
23	Bu	91%	4:1
23[a]	Bu	31%	4:1
24	Ph	66%	4:1
25	(CH₂)₃CN	89%	4:1
26	(CH₂)₄Cl	78%	4:1
27	CH₂NHBoc	55%	1:1
28	CH₂OTBS	78%	3:2
29	(CH₂)₂OTBS	82%	4:1
30	(CH₂)₃OTBS	78%	4:1

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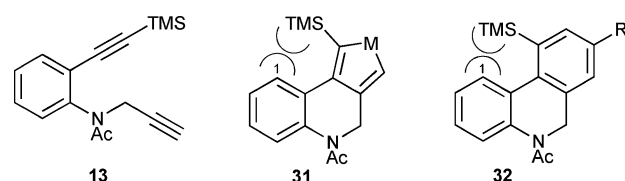
Fig. 2 Cyclotrimerization attempts with **13** did not lead to product formation. M = metal.

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 CH₃ to Si(CH₃)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	R¹	yield	regio
33	Bu	85%	95:5
33ᵃ	Bu	-	-
34	Ph	31%	95:5
35	(CH₂)₄Cl	46%	95:5
36	(CH₂)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]
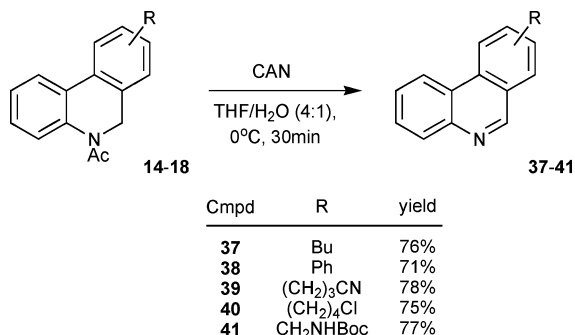
Cmpd	R	yield
37	Bu	76%
38	Ph	71%
39	(CH₂)₃CN	78%
40	(CH₂)₄Cl	75%
41	CH₂NHBoc	77%

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

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.