ORGANIC LETTERS

2005
Vol. 7, No. 15
3351−3354

A Two-Stage Iterative Process for the Synthesis of Poly-oxazoles

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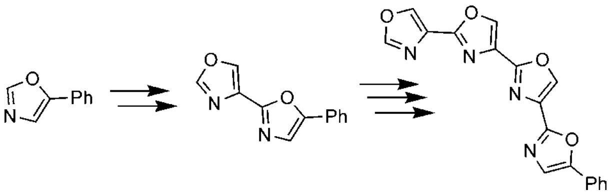
Received May 26, 2005

ABSTRACT



Methodology has been developed to prepare bis-oxazoles via a two-stage iterative process. The sequence begins with C_2-chlorination of a lithiated oxazole using hexachloroethane. Generation of the C_2–$C_{4'}$ bond by $\mathrm{S_NAr}$ substitution with TosMIC anion, followed by conversion to the heterocycle in a one-pot reaction with glyoxylic acid monohydrate, affords the desired bis-oxazole in good yield and purity. The two-stage process allows for efficient synthesis of a tris-oxazole and the first iterative preparation of a tetra-oxazole.

Potentially repeatable methods have been used to assemble the C_2−$C_{4'}$ linked bis-oxazole and tris-oxazole subunits of marine natural products and related structures.[1−13] With the recent discovery of the macrocyclic C_2-$C_{4'}$ linked hepta-oxazole telomestatin **1**,[14] these techniques may benefit from further refinement and comparison with new options for iterative oxazole assembly.

Among the prior methods that have been used to prepare tris-oxazoles, Panek's approach using an adaptation of the Hantzsch oxazole synthesis is probably the most efficient in terms of overall yield (ca. 80%) and number of steps (three) per iteration.[6] This procedure appends each new oxazole by elaborating a C_4−carboxamido group of an existing oxazole. The carboxamido carbon becomes $C_{2'}$ in the new oxazole ring, and the order of events corresponds to a "clockwise" strategy for assembly of an oligo-oxazole chain with respect to the telomestatin structure (Figure 1). Several other iterative approaches for a clockwise strategy are known (append to C_4−CO_2R or C_4−CN).[2,7,12] Convergent alternatives have also been reported involving oxazole synthesis by cyclization of

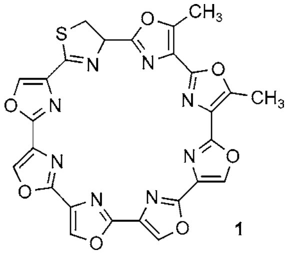


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Figure 1. Telomestatin.

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(1) Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 3604.
(2) Doyle, K. J.; Moody, C. J. *Tetrahedron* **1994**, *50*, 3761.
(3) Barrett, A. G. M.; Kohrt, J. T. *Synlett* **1995**, *5*, 415.
(4) Vedejs, E.; Luchetta, L. M. *J. Org. Chem.* **1999**, *64*, 1011.
(5) Chattopadhyay, S. K.; Pattenden, G. *Synlett* **1997**, *12*, 1342.
(6) Liu, P.; Celatka, C. A.; Panek, J. S. *Tetrahedron Lett.* **1997**, *38*, 5445.
(7) Magnus, P.; McIver, E. G. *Tetrahedron Lett.* **2000**, *41*, 831.
(8) Wipf, P.; Methot, J.-L. *Org. Lett.* **2001**, *3*, 1261.
(9) Celatka, C. A.; Panek, J. S. *Tetrahedron Lett.* **2002**, *43*, 7043.
(10) Yamada, S.; Shigeno, K.; Kitagawa, K.; Okajima, S.; Asao, T. PCT Int. Appl. WO 2002048153 A1 20020620, 2002; *Chem. Abstr.* **2002**, *137*, 47050.
(11) Endoh, N.; Tsuboi, K.; Kim, R.; Yonezawa, Y.; Shin, C. *Heterocycles* **2003**, *60*, 1567.
(12) Coqueron, P.-Y.; Didier, C.; Ciufolini, M. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1411.
(13) (a) Nicolaou, K. C.; Bella, M.; Chen, D. Y. K.; Huang, X. H.; Ling, T. T.; Snyder, S. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 3495. (b) Nicolaou, K. C.; Rao, P. B.; Hao, J. L.; Reddy, M. V.; Rassias, G.; Huang, X. H.; Chen, D. Y. K.; Snyder, S. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1753. (c) Burgett, A. W. G.; Li, Q.; Wei, Q.; Harran, P. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4961. (d) Magnus, P.; Mciver, E. G. *Tetrahedron Lett.* **2000**, *41*, 831. (e) Bagley, M. C.; Hind, S. L.; Moody, C. J. *Tetrahedron Lett.* **2000**, *41*, 6897.
(14) (a) Shin-ya, K.; Wierzba, K.; Matsuo, K.; Ohtani, T.; Yamada, Y.; Furihata, K.; Hayakawa, Y.; Seto, H. *J. Am. Chem. Soc.* **2001**, *123*, 1262. (b) Kim, M.-Y.; Vankayalapati, H.; Shin-ya, K.; Wierzba, K.; Hurley, L. H. *J. Am. Chem. Soc.* **2002**, *124*, 2098.

10.1021/ol051244x CCC: $30.25

a nitrogen-linked bis-oxazole intermediate (C_4−[$C_{2'}$−N−$C_{4'}$]−$C_{2''}$ connected in an amide group).[5,10,11] In principle, this method can be repeated, but the need for several protection-deprotection steps results in a lengthy sequence, as reported for the assembly of the telomestatin macrocycle (>40 steps overall).[10] We are aware of only one iterative approach to oligo-oxazoles that operates in the “counter-clockwise” mode and appends each new oxazole unit at preexisting oxazole C_2. This method relies on an LDA-induced Chan rearrangement, and has been used to prepare a tris-oxazole containing phenyl or *tert*-butyl groups at the C_5 position of each oxazole ring.[8] Alternatives that can be used to access C_5-unsubstituted oligo-oxazoles would be needed to prepare telomestatin analogues. As described below, this problem can be addressed using a route that involves activation and coupling of C_2-unsubstituted oxazoles.

Formation of a C−C bond at C_2 of oxazole poses a significant synthetic challenge. In principle, this can be done by reacting C_2-metalated oxazoles with carbon electrophiles,[15,16] or by displacing a C_2 leaving group using carbon nucleophiles. Oxazoles activated by the introduction of Cl at C_2 have been shown to undergo palladium-mediated Suzuki coupling[17] and to react with deprotonated alcohols and amines quite effectively.[18a,b] However, there are only limited examples of stabilized carbon nucleophiles reacting with activated oxazoles to form C−C bonds at C_2 via an S_NAr reaction.[18b,c] Displacement of the C_2 chloride with a carbon nucleophile that can be converted into a new oxazole unit was envisioned as a route for bis- and poly-oxazole synthesis.

Prior to this work, relatively few 2-chlorooxazoles were known in the literature. Construction of these compounds was typically achieved via the oxazolone or oxazole-2-thione using $POCl_3$/pyridine[19a,b] or PCl_5,[19c] or from the amino-oxazole under Sandmeyer conditions.[17] 2-Chlorooxazoles had also been generated by trapping a 2-lithiooxazole−BH_3 complex with hexachloroethane.[15] However, we have recently found that borane complexation prior to generating the lithiooxazole is not necessary for chlorination at C_2. Even though lithiation of oxazoles results in the ring-opened enolate isonitrile valence bond tautomer **3**,[20] reaction of the equilibrium mixture of **2** and **3** with hexachloroethane intercepts the cyclic tautomer (Table 1).[21] Despite the dominant presence of **3**,[20,22] good yields of 2-chlorooxazoles were obtained. Athough the formation of 4-chlorooxazole might have been expected,[4] this was not observed using the latent chlorine source. However, yields did increase by 5−15% using longer reaction times (42 h), suggesting that there may be more to the mechanism than simply trapping **2**.

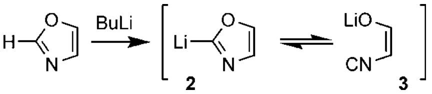
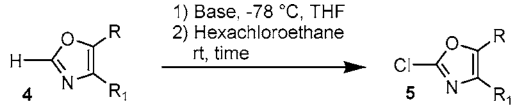
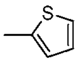


Table 1. Trapping of 2-Lithiooxazoles with Hexachloroethane To Form 2-Chlorooxazole



entry	R	R_1		equiv of Cl_3CCCl_3	time (h)	product	isolated yield (%)
1[a]	H	Ph	**4a**	2	18	**5a**	68
				1.5	42		73
2[a]	Ph	H	**4b**	2	18	**5b**	88
				1.5	42		98
3[a]	CH_2CH_2Ph	H	**4c**	2	3	**5c**	78
				1.5	42		93
4[a]		H	**4d**	2	18	**5d**	84
				1.5	42		80
5[b]	$CO_2C_2H_5$	H	**4e**	2	18	**5e**	61
				1.5	42		67

[a] Base = BuLi. [b] Base = LiHMDS.

Generation of the 2-lithiooxazole intermediate occurred readily upon the low-temperature addition of BuLi to the C_4 phenyl substituted oxazole **4a** in THF. The C_2 chlorinated oxazole **5a** was isolated in good yield and purity after addition of hexachloroethane and stirring for 18 h at room temperature. Similar successful results were seen with aryl, alkyl, and heteroaryl functionalities at oxazole C_5 (entries 2−4, Table 1). Sensitive functionality on the starting oxazole, such as the C_5 ethyl ester in **4e**, was tolerated if LiHMDS was used instead of BuLi. The products **5a-e** were readily purified by column chromatography on silica gel, provided that the excess hexachloroethane was removed by flushing the column with hexanes before eluting the product.

With a simple procedure in hand for chlorination at oxazole C_2, the next problem was to introduce functionality that can be used to assemble a new oxazole. The key finding

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(15) Vedejs, E.; Monahan, S. D. *J. Org. Chem.* **1996**, *61*, 5192.

(16) For coupling with oxazol-2-ylzinc chlorides, see: (a) Anderson, B. A.; Becke, L. M.; Booher, R. N.; Flaugh, M. E.; Harn, N. K.; Kress, T. J.; Varie, D. L.; Wepsiec, J. P. *J. Org. Chem.* **1997**, *62*, 8634. (b) Anderson, B. A.; Harn, N. K. *Synthesis* **1996**, *5*, 583. For coupling with 2-stanyloxazole, see: (c) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *Synthesis* **1987**, *8*, 693.

(17) Hodgetts, K. J.; Kershaw, M. T. *Org. Lett.* **2003**, *5*, 2911. (b) Hodgetts, K. J.; Kershaw, M. T. *Org. Lett.* **2002**, *4*, 2905. (c) Young, G. L.; Smith, S. A.; Taylor, R. J. K. *Tetrahedron Lett.* **2004**, *45*, 3797.

(18) (a) Padwa, A.; Cohen, L. A. *J. Org. Chem.* **1984**, *49*, 399. (b) Gompper, R.; Effenberger, F. *Chem. Ber.* **1959**, *92*, 1928. (c) Yamanaka, H.; Ohba, S.; Sakamoto, T. *Heterocycles* **1990**, *31*, 1115.

(19) (a) Gompper, R. *Chem. Ber.* **1956**, *89*, 1748. (b) Lee, L. F.; Schleppnik, F. M.; Howe, R. K. *J. Heterocycl. Chem.* **1985**, *22*, 1621. (c) Haviv, F.; Ratajczyk, J. D.; DeNet, R. W.; Kerdesky, F. A.; Walters, R. L.; Schmidt, S. P.; Holms, J. H.; Young, P. R.; Carter, G. W. *J. Med. Chem.* **1988**, *31*, 1719.

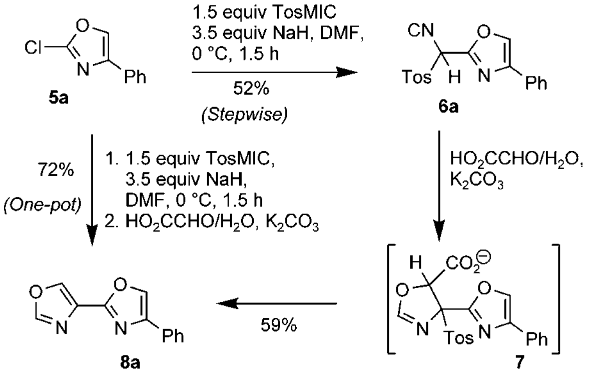
(20) Hilf, C.; Bosold, F.; Harms, K.; Marsch, M.; Boche, G. *Chem. Ber.* **1997**, *130*, 1213.

(21) It may be relevant that CCl_4 or trichloroacetyl chloride have been reported as electrophilic chlorine sources to generate 2-chlorothiazole via halogen−metal exchange. See: (a) Boga, C.; Del Vecchio, E.; Forlani, L.; Todesco, P. E. *J. Organomet. Chem.* **2000**, *601*, 233. (b) Boga, C.; Del Vecchio, E.; Forlani, L.; Milanesi, L.; Todesco, P. E. *J. Organomet. Chem.* **1999**, *588*, 155.

(22) (a) Chinchilla, R.; Najera, C.; Yus, M. *Chem. Rev.* **2004**, *104*, 2667. (b) Schroeder, R.; Schoellkopf, U.; Blume, E.; Hoppe, I. *Justus Liebigs Ann. Chem.* **1975**, *3*, 533. (c) Jacobi, P. A.; Ueng, S.; Carr, D. *J. Org. Chem.* **1979**, *44*, 2042. (d) Hodges, J. C.; Patt, W. C.; Connolly, C. J. *J. Org. Chem.* **1991**, *56*, 449. (e) Whitney, S. E.; Rickborn, B. *J. Org. Chem.* **1991**, *56*, 3058.

was the observation that deprotonated tosylmethyl isocyanide (TosMIC)[23] is capable of displacing the C_2 chloride via S_NAr substitution. Thus, conversion to the isonitrile **6a** occurred upon addition of **5a** to 1.5 equiv of TosMIC anion, generated by deprotonation with 3.5 equiv of NaH in DMF at 0 °C (Scheme 1). An excess of base was required for complete reaction because TosMIC anion deprotonates the intermediate **6a**. Consumption of **5a** and conversion to **6a** were confirmed by ESI-MS after 90 min. Subsequent addition of glyoxylic acid monohydrate and K_2CO_3 resulted in formation of the bis-oxazole **8a** (72% isolated after 12 h at rt) via fragmentation of an intermediate oxazoline **7**. One prior example of a similar sequence involving a substituted TosMIC anion addition to glyoxylic acid with fragmentation to an oxazole has been reported by Sisko et al., along with several examples of the analogous imidazole synthesis from glyoxylic acid imines.[24]

Scheme 1. Stepwise and One-Pot Routes to Bis-oxazole **8a**

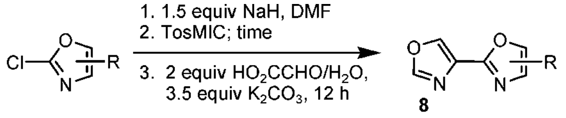


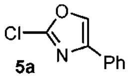
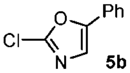
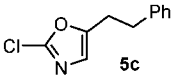
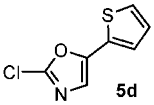
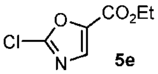
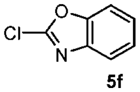
pTolSO$_2$CH$_2$NC = TosMIC

The best results for the one-pot conversion from **5a** to **8a** were obtained in DMF. Lower yields resulted in DMSO or THF, or with NaHMDS or LiH as the base, but attempted deprotonation of **6a** with BuLi/THF gave extensive decomposition.[25] Lower efficiency was also encountered in a stepwise sequence. If desired, **6a** could be isolated (52%) after the first stage, prior to addition of the glyoxylic acid, but **6a** could not be completely separated from unreacted TosMIC, and decomposed on standing. Although the partially purified **6a** could be converted to the bis-oxazole **8a** upon addition of glyoxylic acid/K_2CO_3 in DMF, the yield was only 59%.

Using the one-pot procedure, good yields of bis-oxazoles **8a−f** were obtained from 2-chlorooxazoles **5a−f** (Table 2).

Table 2. One-Pot Formation of [2,4′]-Bis-oxazoles



entry	2-chlorooxazole	temp (°C)	time (min)	product	isolated yield (%)
1	 5a	75 0	60 90	**8a**	68[a] 72[b]
2	 5b	75 0	45 90	**8b**	70[a] 81[b]
3	 5c	75 25	60 300	**8c**	67[a] 64[b]
4	 5d	65 0	30 60	**8d**	77[a] 74[b]
5	 5e	75 0	45 45	**8e**	17[a] 68[b]
6	 5f	80 0	60 60	**8f**	33[a] 73[b]

[a] 1.1 equiv of TosMIC. [b] 1.5 equiv of TosMIC.

For entry 2 and entries 4−6, conversion to the isonitrile was complete within 1.5 h at 0 °C after the addition of **5** to deprotonated TosMIC. Cyclization to the bis-oxazoles **8b** and **8d−f** occurred as before (12 h, rt, glyoxylic acid/K_2CO_3). The conversion of **5c** to **6c** was sluggish at 0 °C, but was complete after 5 h at rt. The reaction could also be perfomed at 75 °C for entries 1−4, but the lower temperature was necessary for entries 5 and 6 due to decomposition of the isonitrile intermediates **6e** and **6f**.

The bis-oxazole **8b** was chosen to prove the viability of poly-oxazole synthesis using an iterative version of this technique (Scheme 2). Generation of the lithiooxazole by low-temperature addition of BuLi to **8b** and trapping with hexachloroethane gave 2-chlorinated bis-oxazole **9** in 76% yield. The first attempt to convert **9** to the tris-oxazole **10** proceeded in only 52% yield, and decomposition of the isonitrile intermediate was evident from the dark color during TosMIC coupling. However, lowering the reaction temperature to −42 °C for the S_NAr step improved the isolated yield of **10** to 64%. As long as the temperature was kept below −10 °C, the solution mantained a light yellow color and decomposition of the bis-oxazole derived TosMIC intermediate was minimized.

To further extend the oxazole chain, the sequence was repeated from **10**, allowing isolation of 2-chloro tris-oxazole **11** (72%), and tetra-oxazole **12** (46%). Construction of the

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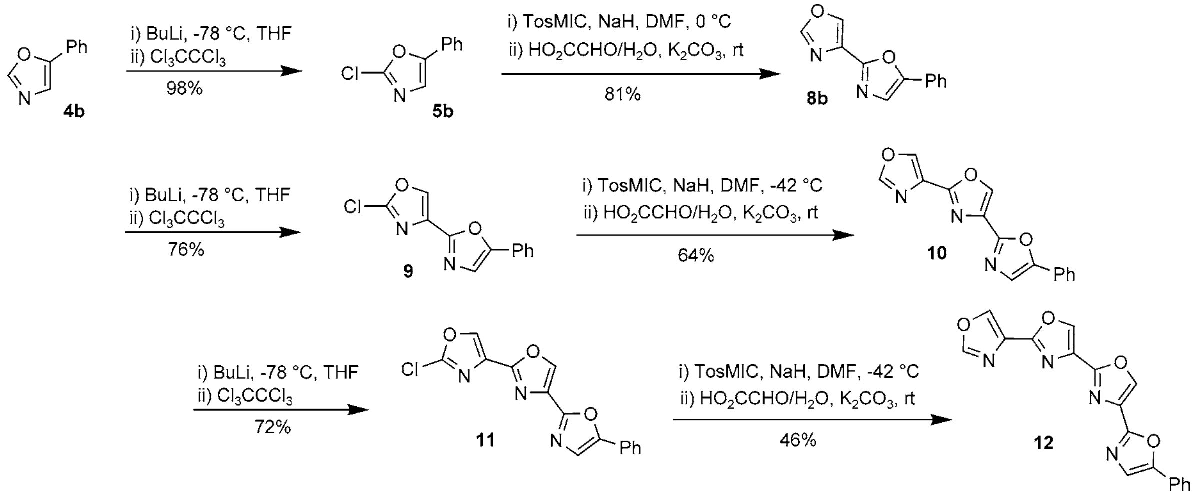
[23] (23) For reviews of TosMIC and α-metalated isocyanides, see: (a) van Leusen, A. M.; van Leusen, D. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, 1995; Vol. 7, p 4973. (b) Schöllkopf, U. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 339. (c) Tandon, V. K.; Rai, S. *Sulfur Rep.* **2003,** *24*, 307. (d) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3169. (e) Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 789. (f) Marcaccini, S.; Torroba, T. *Org. Prep. Proced. Int.* **1993**, *25*, 141.

[24] (24) Sisko, J.; Kassick, A. J.; Mellinger, M.; Filan, J. J.; Allen, A.; Olsen, M. A. *J. Org. Chem.* **2000**, *65*, 1516.

[25] (25) A half-life of ca. 15 min has been reported for TosMIC and NaH/DME. (van Leusen, A. M.; Wildeman, J.; Oldenziel, O. H. *J. Org. Chem.* **1977**, *42*, 1153.) We have found that TosMIC anion is substantially more stable in DMF as the solvent.

Scheme 2. Synthesis of Tetra-oxazole **12**



tris-oxazole **10** proceeds in 39% yield over four isolated intermediates from **4b**. Thus, the tetra-oxazole **12** was obtained in 13% overall yield via six isolated intermediates from **4b**.

In conclusion, methodology has been developed that assembles poly-oxazoles starting from a C_2-unsubstituted oxazole. Direct chlorination of 2-lithiooxazoles with hexachloroethane in THF provides a selective, general protocol for preparation of 2-chlorooxazoles. Subsequent S_NAr-type substitution with deprotonated TosMIC forms an isonitrile intermediate that affords the corresponding [2,4′]-bis-oxazole upon reaction with glyoxylic acid monohydrate in the one-pot mode. Repetition of the chlorination and coupling steps constitutes a two-stage iterative process for the incorporation of additional oxazole rings leading to bis-, tris-, and tetra-oxazoles.

Acknowledgment. This work was supported by the National Institutes of Health (CA17918).

Supporting Information Available: Experimental details and spectroscopic data for compounds **5c**−**e**, **8a**−**f**, and **9**−**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL051244X