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Synthesis of Pyrrolo-isoquinolines Related to the Lamellarins Using Silver-Catalyzed Cycloisomerization/Dipolar Cycloaddition

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The lamellarin alkaloids are a family of novel marine natural products containing a highly substituted pyrrolo-isoquinoline core.[1] Lamellarin D **1** (Figure 1a) is a potent inhibitor of human topoisomerase I[2] and was recently shown to act on mitochondria to induce apoptosis.[3] Another member of the family, lamellarin α-20-sulfate **2**, displays selective inhibition against HIV-1 integrase in vitro.[4,5] We have considered development of methodology for rapid access to angular, pyrrolo-isoquinoline core structures[6] related to the lamellarins[7] using variants of the cycloisomerization of alkynyl imines[8] involving dipolar cycloaddition of derived azomethine ylides.[9] In this approach, treatment of alkynyl imines **3** with alkynophilic metal catalysts should afford azomethine ylides **4** which may undergo dipolar cycloaddition in the presence of dipolarophiles. Subsequent aromatization may lead to the formation of pyrrole frameworks **5** (Figure 1b).

To identify suitable conditions for the proposed metal-catalyzed domino cycloisomerization/dipolar-cycloaddition process, reaction screening[10] involving alkynyl *N*-benzylidene glycinate **6**, dimethyl acetylene dicarboxylate (DMAD) **7**, and a series of alkynophilic metals was carried out in DCE using DIEA as base (50 °C).[11] Fortunately, a number of catalysts including the Au, Ag, and Cu salts shown in Figure 2 and $Pd(OAc)_2$ were able to facilitate the transformation. AgOTf and $AgSbF_6$ provided the best results in comparison to other metals investigated and were effective in catalytic quantities (10 mol %). Control experiments in the absence of metal salts led to decomposition ruling out the possibility of spontaneous formation of **8** under thermal conditions.[12]

To improve the efficiency of the cycloisomerization/dipolar-cycloaddition process, further optimization was carried out using imine **6**, DMAD **7**, and AgOTf (10 mol %). Parameters including solvents, bases, reaction temperature, and inclusion of external oxidants (e.g., DDQ, MnO_2) were investigated. Reactions conducted at 60 °C under ambient conditions in toluene using 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) as base in the absence of oxidants afforded optimal results. Using this condition, select dipolarophiles were reacted with a number of alkynyl imines to generate diverse pyrrolo-isoquinolinone structures **8** and **24**−**37** (Table 1). Silver-mediated pyrrolo-isoquinoline formation was found to be workable with ortho alkynyl imines **9**−**17** bearing aryl, cyclopropane, propargyl ether, trimethylsilyl, terminal alkyne, and enyne functionality, as well as substrates with electron withdrawing and donating substituents on the aromatic backbone (entries **2**, **5**, and **7**−**9**). In addition to DMAD, alkynes **19**−**23** were also investigated to provide lamellarin-type structures with unsymmetrical substituents on the pyrrolo-isoquinoline core. Reactions involving alkynes **19**−**23** typically afforded the desired products with lower yield compared to those using DMAD owing to diminished reactivity. The addition of Lewis acids[13] to further activate the dipolarophiles led to only marginal improvement in reaction yields. Cycloisomerization/dipolar-cycloaddition was generally found to be highly

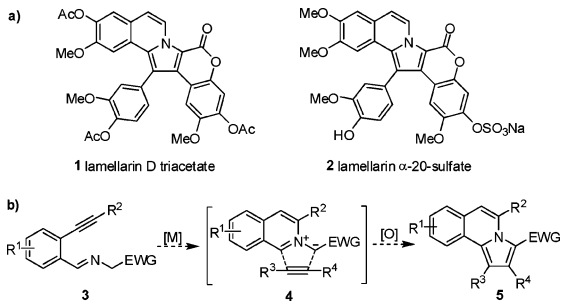

Figure 1.

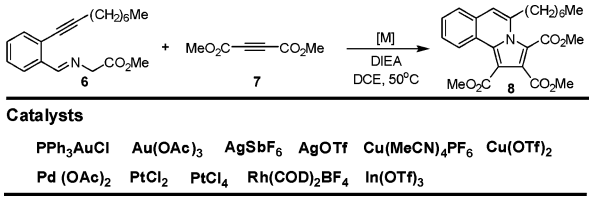

Figure 2. Reaction screening.

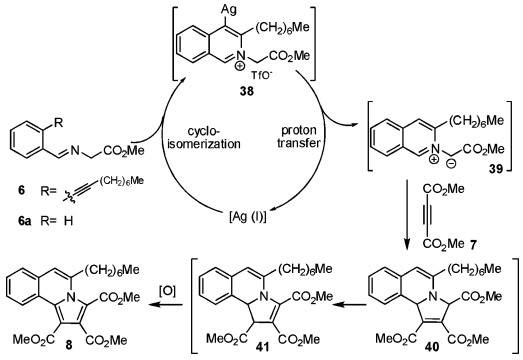

Figure 3. Proposed reaction pathway.

regioselective, providing **33**−**34** and **36**−**37** as single regioisomers.[11] However, reaction involving alkynoate **21** produced **35** as a 1.3:1 mixture of regioisomers[14] and a desilylation product derived from **37** was observed when using alkyne **23** as dipolarophile. Thus far, alkynes lacking electron withdrawing groups have not been workable as dipolarophiles.

To probe possible reaction pathways for the cycloisomerization/dipolar-cycloaddition, we conducted a series of NMR experiments. Treatment of substrate **6** with AgOTf, DMAD, and DTBMP (toluene-d_8, room temperature, 6 min) afforded dihydropyrrole **41**, presumably via dihydropyrrole **40** (Figure 3). The structure of intermediate **41** was determined by extensive 2-D NMR experiments.[11,15] Subsequent thermolysis of a solution of **41** at 60 °C under aerobic conditions led to the formation of **8**. Additional experiments were conducted to rule out a dipolar-cycloaddition/

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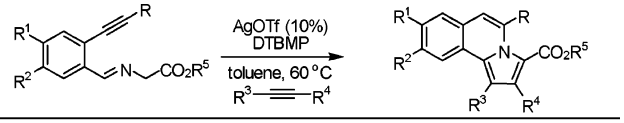
Table 1. Reaction Scope[a]



entry	R	R^1, R^2	R^3, R^4	product	yield(%)[a,b]
1	$(CH_2)_6Me$ **6**	H, H	MeO_2C, CO_2Me	**7**	**8** 72
2	$(CH_2)_6Me$ **9**	H, F	MeO_2C, CO_2Me	**7**	**24** 59
3	Me **10**	H, H	EtO_2C, CO_2Et	**18**	**25** 83
4	Ph **11**	H, H	MeO_2C, CO_2Me	**7**	**26** 78
5	$(CH_2)_5Me$ **12**	OMe, OMe	MeO_2C, CO_2Me	**7**	**27** 78
6	**13**	H, H	MeO_2C, CO_2Me	**7**	**28** 63
7	OMe **14**	OCH_2O	MeO_2C, CO_2Me	**7**	**29** 68
8	$SiMe_3$ **15**	OMe, OMe	MeO_2C, CO_2Me	**7**	**30** 70
9	H **16**	OMe, OMe	MeO_2C, CO_2Me	**7**	**31** 42
10	Me **17**	H, H	MeO_2C, CO_2Me	**7**	**32** 29
11	$(CH_2)_6Me$ **6**	H, H	OHC, C_6H_9	**19**	**33** 46
12	$(CH_2)_6Me$ **6**	H, H	MeOC, Ph	**20**	**34** 56
13	$(CH_2)_6Me$ **6**	H, H	MeO_2C, Ph	**21**	**35** regioselectivity 1.3:1 57[c]
14	Me **10**	H, H	MeO_2C, H	**22**	**36** 52
15	$(CH_2)_6Me$ **6**	H, H	EtO_2C, $SiMe_3$	**23**	**37** 28[c,d]

[a] Yields based on the corresponding alkynyl benzylaldehydes.[11] [b] R^5 = Me, for entries **7** and **10**, R^5 = ^{t}Bu. [c] Yb(OTf)$_3$ (5 mol %) was added. [d] 16% of a desilylation product was also isolated.

cycloisomerization pathway. Reaction of *des*-alkyne substrate **6a** under conditions employed for formation of **8** led to recovered starting material. In the absence of DMAD, treatment of **6** with AgOTf and DTBMP (toluene-d_8, room temperature) led to the formation of a complex mixture by ^{1}H NMR analysis. Mass spectrograph analysis[11] of the mixture indicated the presence of **39** and the corresponding dimer.[11,16] Subsequent addition of DMAD also led to the formation of **41**. The available mechanistic data supports initial cycloisomerization of **6** to isoquinolinium species **38**.[8e] Subsequent proton transfer and regeneration of Ag (I) affords azomethine ylide **39**, which may be followed by dipolar cycloaddition to dihydropyrrole **40**. Isomerization and final oxidation affords pyrrolo-isoquinoline **8**.

In summary, we have developed an efficient synthesis of pyrrolo-isoquinolines related to the lamellarin natural products involving domino cycloisomerization/dipolar-cycloaddition of readily available alkynyl *N*-benzylidene glycinates. Mechanistic studies revealed Ag(I)-catalyzed cycloisomerization to an azomethine ylide as a key step for formation of pyrrolo-isoquinoline structures. Further studies, including applications toward the syntheses of the lamellarin alkaloids, are currently in progress and will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. X-ray crystal structure coordinates and files in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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