ORGANIC LETTERS

2001
Vol. 3, No. 5
751−754

Studies toward Gymnodimine: Development of a Single-Pot Hua Reaction for the Synthesis of Highly Hindered Cyclic Imines

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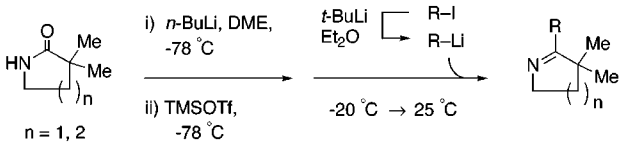
Received January 2, 2001

ABSTRACT



In studies directed toward gymnodimine and related marine toxins, a single-pot variation of the Hua cyclic imine synthesis has been developed. The reaction involves generation of *N*-trimethylsilyl lactams in situ followed by alkyllithium addition leading directly to cyclic imines. Importantly, this reaction proceeds efficiently with highly hindered α,α-dialkyl lactams, provided 1,2-dimethoxyethane (DME) is used as solvent, leading to stable cyclic imines. Overall, this transformation allows a one-pot coupling of an alkyliodide and a lactam to give a cyclic imine.

Gymnodimine is a potent marine toxin produced by the dinoflagellate *G.* cf. *mikimotoi* that is responsible for a neurotoxic shellfish poisoning incident that occurred on the North Island of New Zealand in 1993.[1] This toxin shares a common imine-containing spirocycle with the pinnatoxins[2] and the spirolides.[3] Interesingly, studies of the spirolides by Wright and co-workers have shown that these compounds do not inhibit *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), or kainic acid (KA) receptors nor do they inhibit PP1 or PP2a phosphatases, which are common targets of neurotoxins.[3a] Furthermore, the spirolides exhibited no effect on sodium channels but only showed weak activation of type L calcium channels at 1.7 mM. However, this latter activity does not appear to explain the highly potent effect of these toxins. Wright postulated that the imine was the pharmacophore of these toxins, as reduced (cyclic amine) or hydrolyzed (keto amine) derivatives were no longer toxic and modeling studies indicated that no significant conformational changes occurred upon reduction or hydrolysis.[3a]

The unusual architecture of gymnodimine along with its potential as a biochemical probe led us to pursue synthetic studies toward gymnodimine and derivatives.[4] Our previous studies toward the synthesis of (−)-gymnodimine (**1**) resulted in the synthesis of tetrahydrofuran **3a** and spirocyclic lactam **4a**.[5] Our strategy toward the macrocycle of gymnodimine (**1**) involves a diastereoselective ring closure[6] of **2** using an intramolecular Nozaki−Hiayama−Kishi[7] reaction and a convergent coupling of fragments **3a** and **4a** to afford cyclic

(1) (a) Seki, T.; Satake, M.; Mackenzie, L.; Kaspar, H. F.; Yasumoto, T. *Tetrahedron Lett.* **1995**, *36*, 7093−7096. (b) Stewart, M.; Blunt, J. W.; Munro, M. H. G.; Robinson, W. T.; Hannah, D. J. *Tetrahedron Lett.* **1997**, *38*, 4889−4890.

(2) (a) Pinnatoxin A: Chou, T.; Kamo, O.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 4023−4026. (b) Pinnatoxin D: Chou, T.; Haino, T.; Kuramoto, M.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 4027−4030.

(3) (a) Spirolides B and D: Hu, T.; Curtis, J. M.; Oshima, Y.; Quilliam, M. A.; Walter, J. A.; Watson-Wright, W.; Wright, J. L. C. *J. Chem. Soc., Chem. Commun.* **1995**, 2159−2161. (b) Spirolides E and F: Hu, T.; Curtis, J. M.; Walter, J. A.; Wright, J. L. C. *Tetrahedron Lett.* **1996**, *37*, 7671−7674.

(4) For other synthetic studies toward gynmnoodimine, see: (a) Ishihara, J.; Miyakawa, J.; Tsujimoto, T.; Murai, A. *Synlett* **1997**, 1417−1419. (b) Rainier, J. D.; Xu, Q. *Org. Lett.* **1999**, *1*, 27−29.

(5) Yang, J.; Cohn, S.; Romo, D. *Org. Lett.* **2000**, *2*, 763−767.

(6) (a) Pilli, R. A.; Victor, M. M. *Tetrahedron Lett.* **1998**, *39*, 4421−4424. (b) MacMillan, D. W. C.; Overman, L. E. *J. Am. Chem. Soc.* **1995**, *117*, 10391−10392.

10.1021/ol0155081 CCC: $20.00
Published on Web 02/06/2001

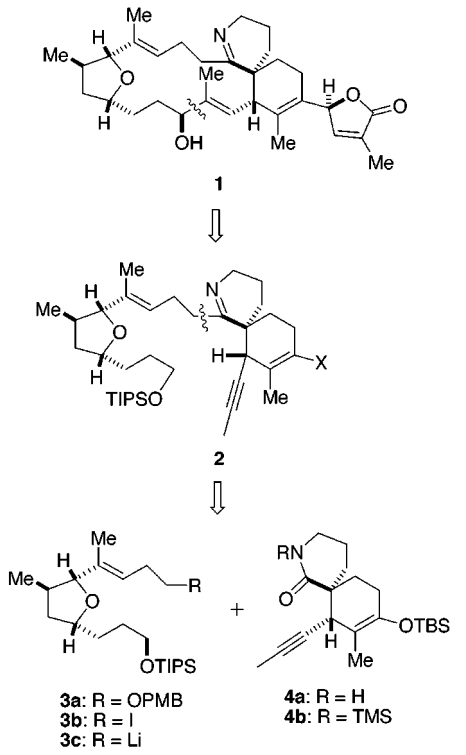
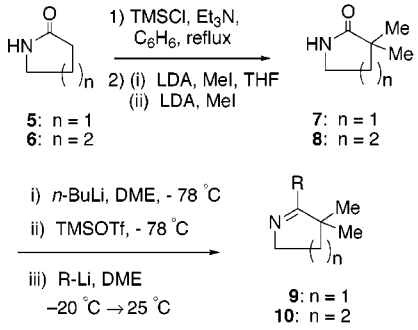


Figure 1. Fragment assembly strategy toward gymnodimine (**1**).

imine **2**. Herein, we report a single-pot method for the conversion of lactams to cyclic imines that is applicable to the synthesis of the proposed imine pharmacophore of gymnodimine and related toxins. The method builds on the work of Hua, who developed a method for the conversion of silyl lactams to cyclic imines.[8]

Scheme 1



Several procedures have been developed for the formation of cyclic imines.[9] Hua disclosed a concise, two-step procedure for the conversion of lactams to cyclic imines.[8] The procedure involves the preparation of *N*-silyl lactams followed by a Peterson-like reaction involving addition of organolithium reagents to the silylated lactams, directly generating imines by presumed elimination of silanoxides. We wished to apply Hua's reaction in the complex setting of a gymnodimine synthesis involving coupling of iodide **3b** and lactam **4a**. However, one of the key questions to be addressed was whether addition would occur to sterically hindered lactams (e.g., **4a**) possessing an adjacent quaternary center. Furthermore, we felt it would be convenient to develop a one-pot procedure that would avoid the need to isolate the labile silyl lactam **4b**.

α,α-Dimethylated lactams **7** and **8** with adjacent quaternary centers were chosen as model substrates. These substrates, which are effectively more hindered than the projected spirofused lactams (i.e., **4a**), should represent some of the most difficult cases for additions of nucleophiles to lactam carbonyls. Silylation of lactams **5** and **6** followed by a one-pot, double enolization/alkylation sequence gave dimethylated lactams **7** and **8**.[10] With these model substrates in hand, we then studied the single-pot Hua reaction. We determined that the lactams could be silylated in situ by treatment of a solution of the lactams **5** or **6** in ethereal solvents at −78 °C with *n*-BuLi followed by addition of trimethylsilyltriflate (TMSOTf). Concentration of the crude reaction mixture and ^{1}H NMR analysis indicated that silylation was ∼95% complete under these conditions. The product of silylation of the valerolactam **8** under these conditions was determined to be the *N*-silyllactam **11** and not the *O*-silyllactim ether **12** on the basis of GOESY experiments.[11] Enhancement of the C-6 proton signals was observed upon irradiation of the trimethylsilyl protons (Figure 2). This enhancement would not be expected for the

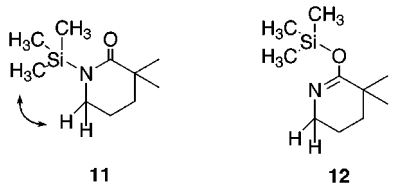


Figure 2. The two possible products from in situ silylation of lactams (observed NOE is indicated by the double-headed arrow).

O-silyllactim ether **12**. Furthermore, irradiation of the *gem*-dimethyl did not show enhancement of the trimethylsilyl protons. The generation of an *N*-silyllactam supports a

(7) (a) Jin, H.; Uenishi, J.-I.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644−5646. (b) Takai, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1983**, *24*, 5281−5284

(8) Hua, D. H.; Miao, S. W.; Bharathi, S. N.; Katsuhira, T.; Bravo, A. A. *J. Org. Chem.* **1990**, *55*, 3682−3684.

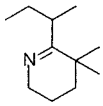
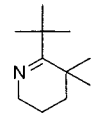
(9) (a) Zezza, C. A.; Smith, M. B.; Ross, B. A.; Arhin, A.; Cronin P. L. E. *J. Org. Chem.* **1984**, *49*, 4397−4399. (b) Larcheveque, M.; Debal, A.; Cuvigny, T. *Bull. Soc. Chim. Fr.* **1974**, 1710−1714. (c) Pearson, W. H.; Stevens, E. P. *J. Org. Chem.* **1998**, *63*, 9812−9827. (d) Tsuge, O.; Kanemasa, S.; Yamada, T.; Matsuda, K. *J. Org. Chem.* **1987**, *52*, 2523−2530. (e) Padwa, A.; Gasdaska, J. R.; Haffmanns, G.; Rebello, H. *J. Org. Chem.* **1987**, *52*, 1027−1035. (f) Hoffman, R. V.; Buntain, G. A. *J. Org. Chem.* **1988**, *53*, 3316−3321.

(10) (a) Fisher, M. J.; Overman, L. E. *J. Org. Chem.* **1990**, *55*, 1447−1459. (b) Grieco, P. A.; Kaufman, M. D. *J. Org. Chem.* **1999**, *64*, 6041−6048. (c) Padwa, A.; Coats, S. J.; Semones, M. A. *Tetrahedron* **1995**, *51*, 6651−6668.

mechanism involving Peterson-like reaction rather than an addition−elimination sequence to the *O*-silyllactim ether **12**. The identical *N*-silyllactam **11** is also prepared when using Hua's method (TMSCl, Et_3N, reflux).

Having established that the silylation proceeds efficiently, addition of alkyllithiums to the in situ generated *N*-silyllactams was investigated. Generation of the *N*-silyllactam **11** in Et_2O, as described above, followed by addition of *n*-BuLi at −20 °C gave only recovered starting material even after warming to 25 °C. Presumably the reactivity of the alkyllithium is not sufficient to overcome the energy barrier for addition to a highly hindered lactam carbonyl. It is well documented that addition of certain additives to organolithium solutions can result in more reactive nucleophiles by deaggregation of the reagent.[12] After some experimentation, we found that use of DME as solvent promoted nucleophilic addition of alkyllithium reagents to the silylated lactams. Thus, in situ silylation of lactam **8** followed by addition of MeLi or *n*-BuLi gave imines **10a** and **10b**, respectively, in good crude yields (entries 1 and 2, Table 1). However, purification by chromatography or distillation led to loss of material apparently as a result of the polar nature of these products and also their volatility. Alkylamines, derived from double addition and previously obtained in related reactions,[9a] were not observed.

Table 1. Cyclic Imines Synthesized Using the Single-Pot Variant of the Hua Synthesis (Scheme 1)

entry	RLi	cyclic imines	cmpd.	time (h)	% yield[a]
1	MeLi		**10a**	6	58(93)
2	*n*-BuLi		**10b**	6	49(80)
3	*s*-BuLi		**10c**	24	~10[b]
4	*t*-BuLi		**10d**	24	0

[a] Isolated yield obtained after Kugelrohr distillation or flash column chromatography. Crude yields, which were >90% pure (^{1}H NMR), are given in parantheses. [b] This imine was not isolated. Yield is based on crude ^{1}H NMR (300 MHz).

Although use of DME as solvent led to addition of primary alkyllithiums, not surprisingly, as the steric bulk of the nucleophile increased (i.e., addition of *s*-BuLi), a significant decrease in conversion of lactam to imine was observed (Table 1, entry 3). Attempted addition of *t*-BuLi gave no imine formation despite prolonged reaction times (entry 4). The corresponding butyrolactam derived imines could also be prepared in similar yields as judged by crude ^{1}H NMR; however, the volatility of these products lowered the yields dramatically.

Direct generation of alkyllithiums from alkyl iodides is critical for our projected total synthesis of gymnodimine (**1**) involving coupling of iodide **3b** and lactam **4a**. Bailey and co-workers reported that use of Et_2O as solvent for halogen−metal exchange affords good yields of alkyllithiums from alkyl iodides with minimal competing elimination reactions.[13] Treatment of the model alkyl iodide **13** with 2.1 equiv of *t*-BuLi in Et_2O at −78 °C, followed by addition of the silyllactam **16** generated in situ in DME, gave imine **9a** in good yield (Scheme 2). In a similar manner, treatment of the lactam **8** under similar conditions gave a 63% yield of imine **10e**.

To apply this process to more complex substrates such as lactam **4b** projected for our gymnodimine synthesis, lower reaction temperatures are preferable to avoid any side reactions due to the organolithium reagents. Thus, a temperature study of the alkyllithium addition was performed to determine the lowest reaction temperature that could be employed without compromising conversion. As shown in Table 2, a reaction temperature of 0 °C seems optimal for this transformation. Addition of an alkyllithium to the *N*-silyl lactam **16** occurs readily at 25 °C (Table 2). At 0 °C, the reaction was 50% complete after 4 h and 90% complete after 8 h. However, no reaction occurred at −20 °C even after 8 h.

Table 2. Effect of Temperature on Yield of Imine **10b** Derived from *n*-BuLi Addition to Silyl Lactam **16**[a]

temp (°C)	time (h)	% conversion[b]
−20	8	NR
0	4	50
0	8	90
25	2	70

[a] A solution of **8** was treated with *n*-BuLi and TMSOTf at −78 °C, and then *n*-BuLi was added after the mixture warmed to −20 °C. The solution was then stirred for the times and at the temperatures indicated. [b] The percent conversions are estimated on the basis of ^{1}H NMR (300 MHz) analysis of the crude reaction mixtures.

We noted that the α,α-dimethyl cyclic imines synthesized in this study were remarkably stable, even though imines in general are known to undergo hydrolysis quite readily.[14] We found that imine **10e** does not hydrolyze to the ketoamine

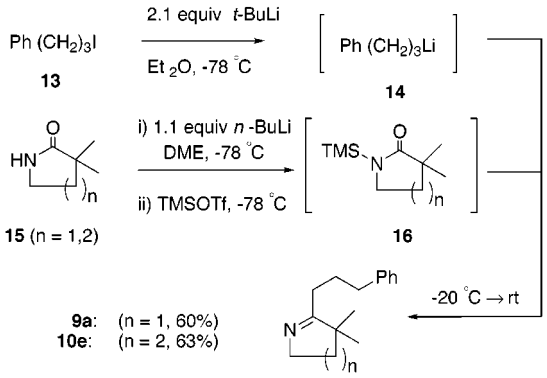
(11) Stonehouse, J.; Adell, P.; Keeler, J.; Shaka, A. J. *J. Am. Chem. Soc.* **1994**, *116*, 6037−6038

(12) (a) Smith, M. B. *Organic Synthesis*; McGraw-Hill: New York, 1994. (b) Schlosser, M. *J. Organomet. Chem.* **1967**, *8*, 9−16.

(13) Bailey, W. F.; Punzalan, E. R. *J. Org. Chem.* **1990**, *55*, 5404−5406.

(14) (a) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley-Interscience: New York, 1992. (b) For kinetic and mechanistic studies on Schiff base hydrolysis, see: Cordes, E. H.; Jencks, W. P. *J. Am. Chem. Soc.* **1962**, *84*, 832−837.

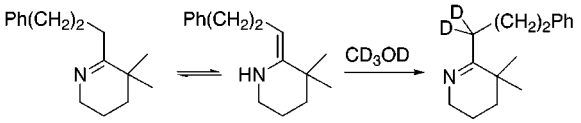
Scheme 2



after stirring in 1 N HCl/THF (1:1) or 1 N NaOH/ THF (1:1) solution for 12 h at 25 °C. Likewise, stirring imine **10e** in 6 N HCl/THF (1:1) or 3 N NaOH/EtOH for 6 h at 25 °C led to no apparent hydrolysis. This is consistent with our finding that even highly reactive organolithiums must be deaggregated with DME to promote nucleophilic addition to *N*-silyl α,α-dimethyllactams.

The stability of these imines raises questions regarding their exact role in gymnodimine and related toxins. The results presented herein and the stability of these imine-containing toxins suggests that the mechanism of action does not involve formation of a covalent bond via nucleophilic addition to the imine. However, as previously observed by Yasumoto[1a] during isolation of gymnodimine, not unexpectedly, these imines are in equilibrium with their enamine tautomers as evidenced by complete incorporation of deuterium at the exocyclic methylene carbon after prolonged exposure to CD_3OD. We also found complete deuterium incorporation at the exocyclic methylene carbon of imine **10e** after ~6 h in CD_3OD at 25 °C to afford **19** presumably via enamine **18** (Scheme 3). Considering the requirement of the imine for toxicity,[3b] it is tempting to speculate that these α-quaternary substituted imines serve as latent nucleophiles

Scheme 3



as a result of their masked enamine character. Thus, Nature may have devised a way to protect an otherwise readily hydrolyzed functionality that has latent nucleophilic character.

In summary, we have developed a convenient one-pot procedure for preparation of cyclic imines from sterically hindered lactams building on the work of Hua. Use of DME as solvent was crucial to promote alkyllithium addition to α,α-dimethylated lactams. Overall, the procedure described herein allows a direct coupling of alkyliodides and lactams and is thus applicable to our projected fragment coupling toward gymnodimine. Currently, we are applying this procedure to the coupling of tetrahydrofuran **3b** and lactam **4a** en route to gymnodimine.

Acknowledgment. We thank the NIH (GM 52964-06) and Zeneca Pharmaceuticals for support of these investigations. D.R. is an Alfred P. Sloan Fellow and a Camille-Henry Dreyfus Teacher-Scholar. Mass spectral analyses were performed at the Texas A&M Center for Characterization using instruments acquired by generous funding from the NSF (CHE-8705697) and the TAMU Board of Regents Research Program.

Supporting Information Available: General experimental procedures for α-dialkylation and imine synthesis; complete characterization data including ^1H and ^{13}C NMR spectra for compounds **7**−**9**, **10b**, **10e**, and **19**. This material is available free of charge via the Internet at http://pubs.acs.org

OL0155081