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Samarium-mediated intramolecular cross-couplings of an α,β-unsaturated *N*-acylpyrrole

Katherine R. Law, Christopher S. P. McErlean *

School of Chemistry, The University of Sydney, New South Wales 2006, Australia

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ABSTRACT

The first example of an α,β-unsaturated *N*-acylpyrrole undergoing a SmI_2-mediated cyclization is reported. In contrast to other unsaturated units, the intermediate samarium enolate readily engages in aldol-type reactions, necessitating careful control of the reaction conditions.

The *trans*, *syn*, *trans*-fused polycyclic ether architecture of the marine ladder toxins (Fig. 1) has stimulated a variety of strategies for their construction.[1,2] Nakata was the first to recognize the power of the SmI_2-mediated intramolecular carbonyl-ene cyclization for the reiterative synthesis of polyether units.[3–7] In Nakata's model (Scheme 1) the coordinated samarium(II) reduced the aldehyde to give the ketyl radical anion **4**, which subsequently underwent an intramolecular radical addition onto an α,β-unsaturated ester to form a cyclic ether **5** with the desired relative stereochemistry. Our continuing interest in the *N*-acylpyrrole[8] functional group led us to investigate whether the SmI_2-mediated protocol might be amenable to an α,β-unsaturated *N*-acylpyrrole system.[9–11]

While α,β-unsaturated esters and ketones have been employed in SmI_2-mediated cyclizations,[12–14] the use of α,β-unsaturated amides is less well documented and to date, has been restricted to lactams.[9]

N-Acylpyrroles generally have reactivity closer to a ketone than to the corresponding amide.[9] The product of hydride addition to the *N*-acylpyrrole is a tetrahedral pyrrolic carbinol that is usually stable toward isolation and purification.[15,16] Treatment of the carbinol with bases or heating, results in elimination of the pyrrole unit and production of an aldehyde. Therefore we anticipated that an α,β-unsaturated *N*-acylpyrrole could be employed as a masked aldehyde in the SmI_2-mediated cyclization. Despite these promising attributes, to the best of our knowledge, no studies of the compatibility or reactivity of α,β-unsaturated *N*-acylpyrrole units with SmI_2 have been reported. The outcomes of our investigation of the SmI_2-mediated intramolecular ring-closing reaction are described in this Letter.

The synthesis of a suitable substrate to test the applicability of the SmI_2-mediated protocol is shown in Scheme 2. Deoxy-D-ribose (**6**) was treated with propanedithiol and benzaldehyde dimethyl acetal to give the dithiane **8**. Conjugate addition of this compound onto *N*-propiolpyrrole **9** and removal of the dithiane unit revealed the desired aldehyde **11**. We have previously demonstrated that this molecule can undergo a completely stereoselective Stetter reaction to generate the cyclic ketone,[10] but the samarium-mediated process has the potential to deliver the alcohol **12** directly, circumventing the need for a separate reduction.

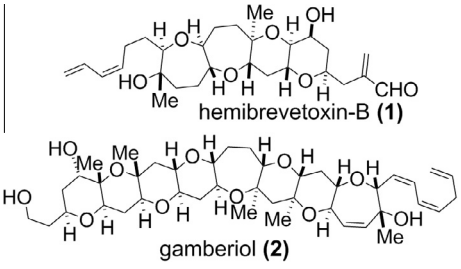

Figure 1. Representative marine ladder toxins.

* Corresponding author. Tel.: +61 2 9351 3970; fax: +61 2 9351 3329.
E-mail address: christopher.mcerlean@sydney.edu.au (C.S.P. McErlean).

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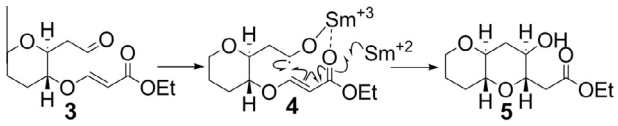
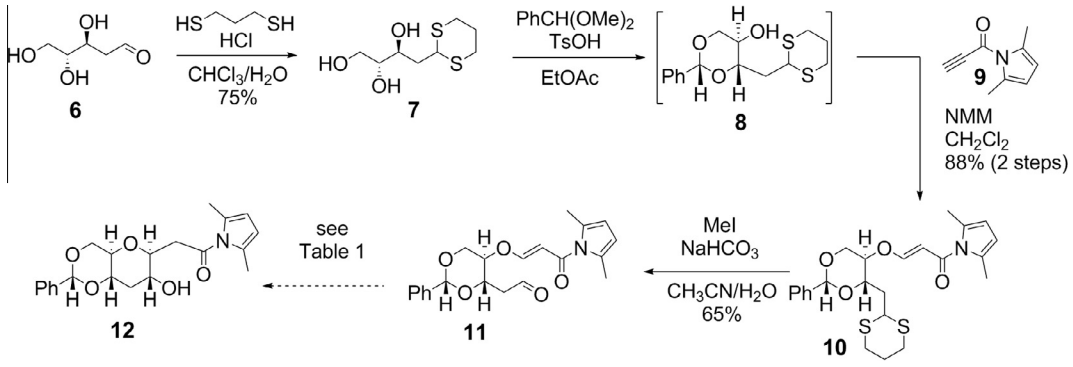


Scheme 1. Nakata's SmI_2 cyclization involving an enoate.

Under Nakata's optimized conditions (Table 1, entry 1),[3] (2.2 equiv of both SmI_2 and MeOH) we did observe formation of the desired cyclized product **12**, but it was the minor product alongside the dimeric compound **15** (Scheme 3). Surprisingly, conducting the reaction at higher dilution (entries 2 and 3) or lower temperature (entries 4 and 5) did not circumvent formation of dimeric compounds **14** and **15**. As depicted in Scheme 3, it was apparent that aldehyde **11** underwent SmI_2 induced cyclization to give the samarium enolate **13**. In contrast to results obtained using ester or ketone substrates in SmI_2-mediated processes, the samarium enolate **13** rapidly engaged in an aldol-reaction with another molecule of starting material **11** (Scheme 3). As both the isolated dimeric products **14** and **15** existed as single stereoisomers, we postulate that the aldol process must be under chelation control, although we were unable to definitively assign the relative stereochemistry at the stereocentres linking the two units. Attempts to competitively protonate the initially generated samarium enolate **13** before it could undergo aldol-coupling were unsuccessful. The reaction was immune to the acidity of the alcohol employed, with the relatively acidic trifluoroethanol and the less acidic *tert*-butanol giving similar outcomes to methanol (Table 1, entries 6 and 7). Inverting the order of addition by adding the aldehyde to a solution of SmI_2 was the logical strategy, but the isolation of the compound **15** was worrisome as it suggested a possible competing mechanism. Two modes of SmI_2-mediated ring-closure have been documented.[17] Nakata suggested aldehyde reduction to give the ketyl radical anion **4** (Scheme 1),[3,7] but the initial step

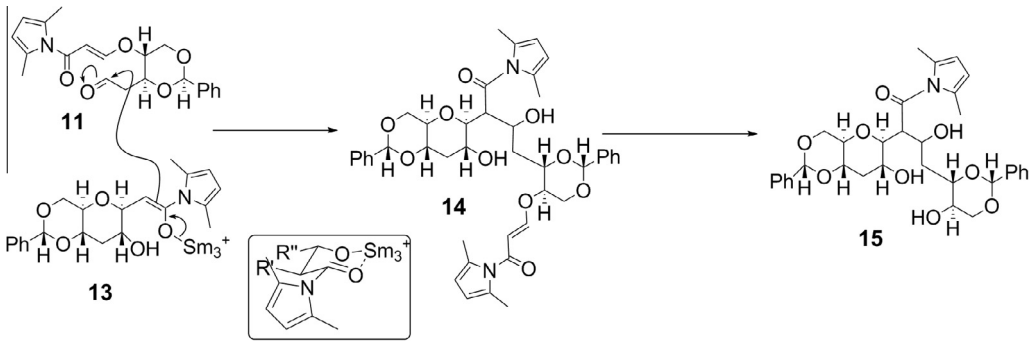


Scheme 2. Synthesis of compound **11**.

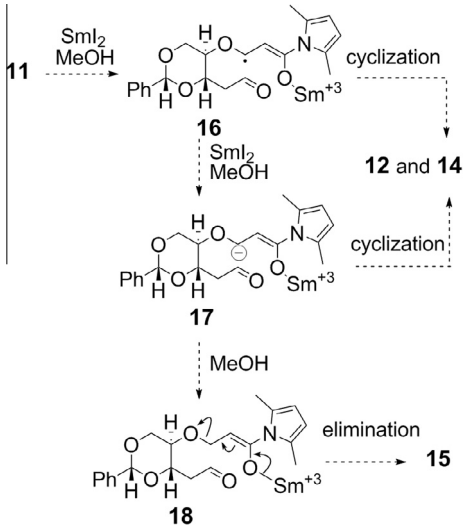
Table 1
Optimization of the SmI_2-mediated cyclization

Entry	Conc. (M)	Temp. (°C)	Equiv. SmI_2 (equiv MeOH)	**12**[a] (%)	**14**[a] (%)	**15**[a] (%)
1	0.1	0	2.2 (2.2)	18	—	34
2	0.05	0	2.2 (2.2)	29	5	20
3	0.01	0	2.2 (2.2)	24	39	—
4	0.05	−78, 0	2.2 (2.2)	40	14	—
5	0.01	−78, 0	2.2 (2.2)	44	18	—
6	0.1	0	2.2 (2.2 CF_3CH_2OH)	37	-	34
7	0.1	0	2.2 (2.2 *t*-BuOH)	25	—	34
8	0.05	0	2.5 (10)	67	—	—
9	0.01	0	2.5 (10)	88	—	—

[a] Isolated yield after chromatography.



Scheme 3. Formation of compounds **14** and **15**.



Scheme 4. Plausible pathways to compounds **12**, **14** and **15**.

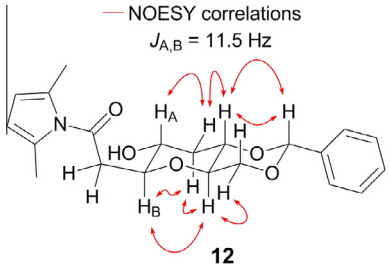


Figure 2. Stereochemistry of cyclized product **12**.

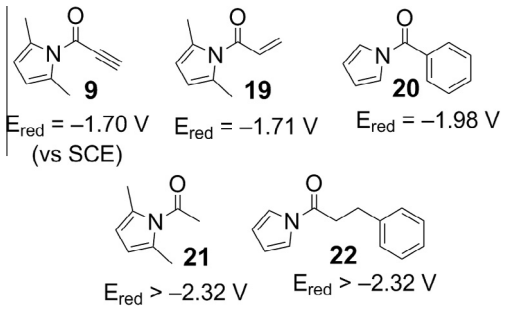


Figure 3. Reduction potentials of *N*-acylpyrroles **9** and **19**–**22**.

of the reaction may in fact be the samarium(II) reduction of the unsaturated system to give **16** or **17** (Scheme 4),[18] which could undergo radical or anionic addition to the pendant aldehyde. Protonation of **17** prior to ring-closure would give the samarium enolate **18**, which can undergo elimination. If this proved to be the case, inverse addition would exacerbate the problem, and *N*-acylpyrroles would not be suitable substrates for SmI_2-mediated cyclizations.

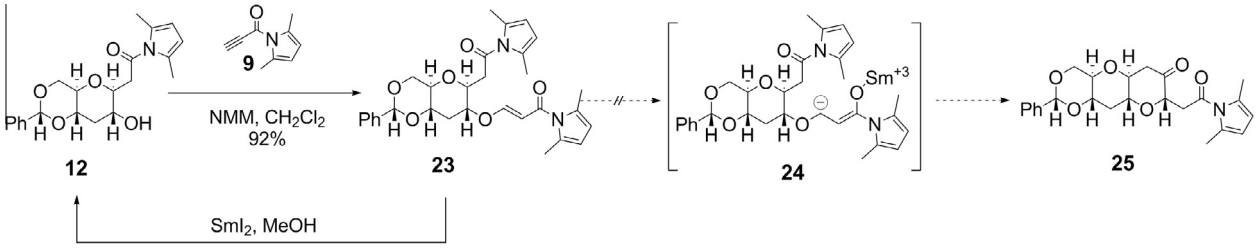
Pleasingly, the slow addition of aldehyde **11** into the SmI_2 mixture and competitive protonation with a tenfold excess of MeOH, gave the desired compound **12** in excellent yields as a single stereoisomer (Table 1, entry 8). The yield of the transformation could be further increased at higher dilution (entry 9). NMR analysis of the isolated compound **12** demonstrated key through-space interactions that are diagnostic of the *trans*, *syn*, *trans* stereochemical arrangement of the newly formed tetrahydropyran (Fig. 2).

Additionally, we hypothesized that if the mechanism depicted in Scheme 4 was operational, then the aldehyde unit of compounds **16** and **17** could be replaced with a functional group that has similar reactivity toward nucleophiles, i.e., with an *N*-acylpyrrole, and the SmI_2-mediated cyclization would still operate. The redox potentials of SmI_2-additive mixtures vary from −0.89 to −1.79 V depending on the identity of the additive.[19–23] We therefore measured the reduction potentials of the *N*-acylpyrroles **9** and **19**–**22** shown in Figure 3. This confirmed that SmI_2–MeOH mixtures would have sufficient reducing power to react with α,β-unsaturated *N*-acylpyrroles (**9**, **19**–**22**), while saturated *N*-acylpyrroles (**21** and **22**) would require a more powerful reductant.

As shown in Scheme 5, the product of the previous SmI_2-mediated ring-closure **12** underwent Michael addition onto *N*-propiolpyrrole **9** to give compound **23** in high yields. This molecule contained both an α,β-unsaturated *N*-acylpyrrole and a saturated *N*-acylpyrrole. Chemoselective reduction of the unsaturated *N*-acylpyrrole would produce **24**, which could undergo cyclization onto the pendant saturated *N*-acylpyrrole.[24]

When compound **21** was subjected to the action of SmI_2 and MeOH, no ring-closed product was observed. Isolation of the eliminated product **12** confirmed that the α,β-unsaturated *N*-acylpyrrole unit was reduced under the reaction conditions, but did not undergo intramolecular radical or anionic addition to the pendant *N*-acylpyrrole. This outcome is consistent with the SmI_2-mediated carbonyl-ene cyclization onto α,β-unsaturated *N*-acylpyrrole **11** proceeding by initial reduction of the aldehyde unit.

In summary, we have shown that an α,β-unsaturated *N*-acylpyrrole is a suitable substrate for SmI_2-mediated reductive cyclization to give a *trans*, *syn*, *trans*-fused tetrahydropyran. In contrast to previously reported reductive cyclizations using unsaturated esters and ketones, the intermediate samarium enolate **13** readily engages in aldol-type reactions, so inverse addition is mandatory. The application of this transformation to the construction of polycyclic ethers is underway in our laboratory.



Scheme 5. Attempted ring-closure of compound **23**.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.06.010.

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