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Development of a tandem cyclization mediated by samarium(II) iodide: sequential intramolecular conjugate addition/nucleophilic acyl substitution

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Abstract—The development of a one-pot tandem intramolecular conjugate addition/nucleophilic acyl substitution using samarium(II) iodide is reported. The reaction relies on the reagent's unique ability to mediate both radical and anionic pathways, which are likely integral to the mechanism of this transformation. The tricyclic hemiacetal product was formed in good yield, with excellent diastereoselectivity, and its structure was verified by X-ray crystallographic analysis.

Since the initial report by Kagan, samarium diiodide has been shown to be a versatile reducing agent in organic chemistry.[1] This one-electron reductant has been shown to mediate a variety of transformations.[2–8] Interestingly, although there exist a number of tandem reactions mediated by samarium diiodide, only a few fully utilize this reagent's unique ability to mediate both radical and anionic processes.[5,9,10]

Samarium diiodide has been shown to mediate the conjugate addition of alkyl halides onto a variety of α,β-unsaturated systems.[11,12] Furthermore, this reagent has also proven to be a suitable reductant for intramolecular nucleophilic acyl substitutions.[13,14] Given the unique ability of SmI_2 to mediate either radical or anionic pathways, we envisioned a tandem ring forming reaction that would capitalize on this reactivity. This proposed novel tandem process is shown in Figure 1. After initial dissociative electron transfer, the resulting radical would undergo a facile conjugate addition. It has been shown previously that similar reactions proceeded stereoselectively forming the *syn* isomer exclusively.[12] After a second reduction by SmI_2, the samarium enolate should be protonated by an alcoholic additive present in solution to provide an intermediate halo lactone. Following two additional reductions by SmI_2, the organosamarium intermediate (**1**) would cyclize to yield the desired tricyclic hemiacetal (**2**). Realization of this method could potentially be utilized to construct a variety of tricyclic acetals, including epimeric analogues of the carotene sesquiterpene class of natural products.[15]

This tandem process presents two primary challenges. The first is deleterious side reactions, which could be minimized by modulating the reactivity of one halide (i.e. X, Fig. 1). The second challenge is protonation of the enolate that results from conjugate addition without quenching the intermediate organosamarium (**1**). Selection of an appropriate alcoholic additive and careful temperature control may ameliorate this issue.

In order to examine the effect of the halide on the tandem process, compounds **3**, **4**, and **5** were synthesized.[16] Our initial efforts focused on the conditions previously reported and utilized unsaturated lactones **3** and **4**.[12] Unfortunately, when **3** was exposed to the conditions shown below (Table 1), no product was seen after visible light irradiation.[17–20] The more reactive alkyl bromide **4** also failed, providing only small amounts of the desired product. However, when **5** was exposed to SmI_2, **2** was formed in 32% as a single diastereomer.

Since the selective quenching of the intermediate enolate was crucial to the success of this reaction, a survey of alcoholic additives was undertaken (Table 1). A variety of different protic additives were examined. Eventually, it was determined that 1 equiv of MeOH was optimal

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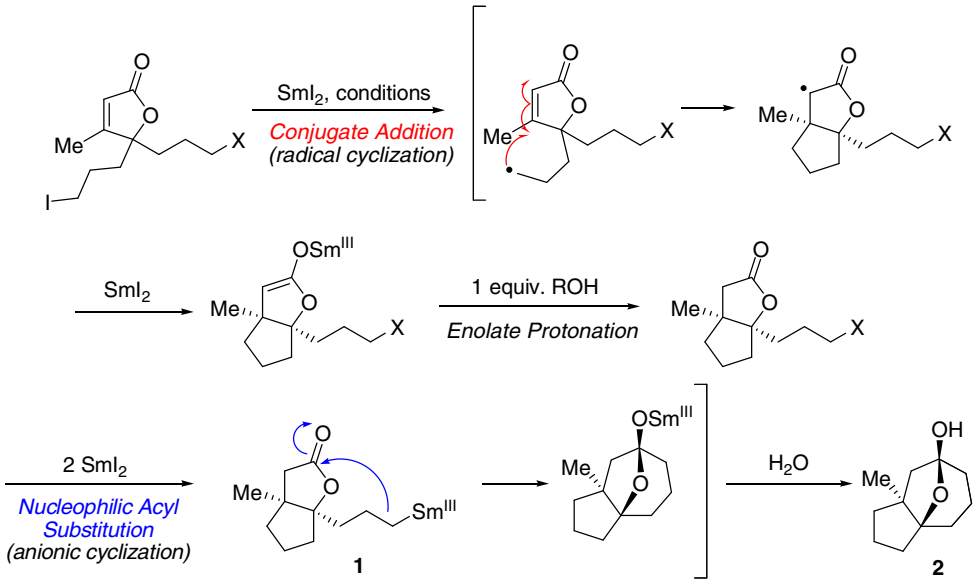
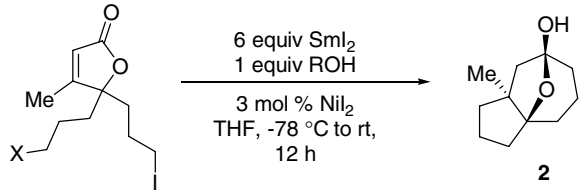


Figure 1. Proposed tandem cyclization mediated by SmI_2.

Table 1. Optimization of the tandem conjugate addition/nucleophilic acyl substitution mediated by samarium(II) iodide



X = Cl, **3**
X = Br, **4**
X = I, **5**

X	ROH	Isolated yield of **2** (%)
Cl	*t*-BuOH	0
Br	*t*-BuOH	Trace
Br	MeOH	8
I	*t*-BuOH	32
I	CF_3CH_2OH	0
I	$MeOCH_2OH$	27
I	MeOH	43
I	3 equiv MeOH	Trace
I	None	0
I	MeOH	67[a]

[a] After warming to −20 °C, the temperature was maintained for 2.5 d.

for this system. In addition to screening protic additives, the effect of temperature was also investigated. Maintaining the reaction at −20 °C (rather than warming to rt) delivered **2** in 67% yield. Under these conditions, the competing quench of the alkyl organosamarium intermediate (**1**) was avoided. The product of this tandem cyclization protocol, **2**, was verified by X-ray crystallographic analysis (Fig. 2).

This optimized method (6 equiv SmI_2, 3 mol % NiI_2, 1 equiv of MeOH, −78 to −20 °C) appears to be applicable to other unsaturated lactones (Table 2).[21]

It is important to note that when the reaction was carried out in the presence of excess MeOH (see Table 1), only trace amounts of **2** were formed. The major product from this reaction was **8** (44% yield, Scheme 1),

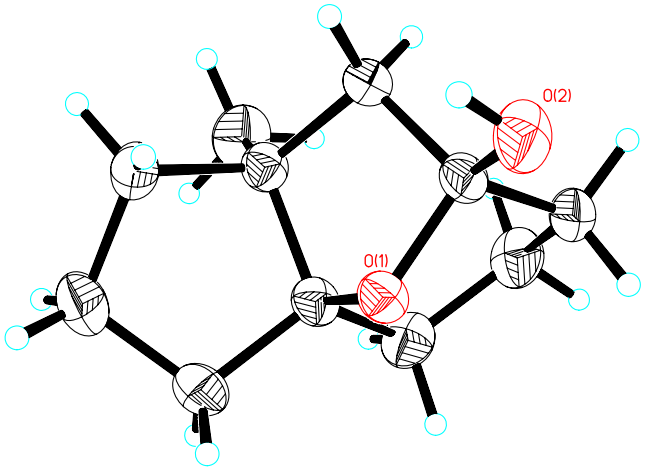
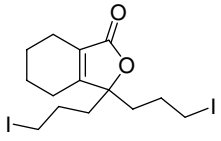
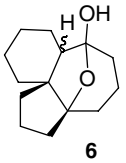
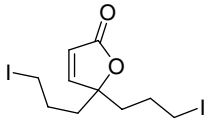
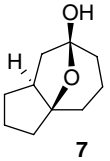
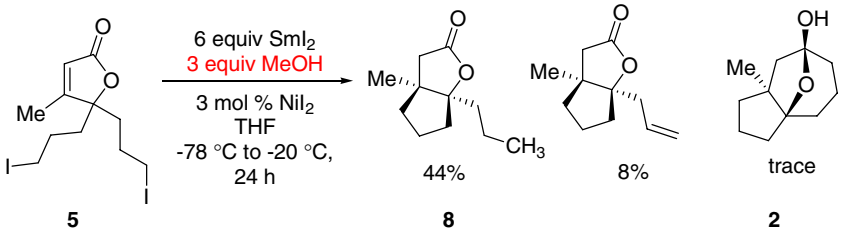


Figure 2. X-ray crystal structure of **2**.

Table 2. SmI_2-mediated tandem conjugate addition/nucleophilic acyl substitution

Substrate	Product	Yield (%)
	 **6**	45
	 **7**	37



Scheme 1.

which is derived from conjugate addition followed by reduction, rather than nucleophilic acyl substitution. The formation of **6** in the presence of excess protic additive, along with other observations reported in the literature,[11,12] supports the notion of sequential radical and anionic cyclizations.

We have reported the first example of a one-pot tandem conjugate addition/nucleophilic acyl substitution mediated by samarium diiodide.[22] The reaction is unique since it proceeds through both radical and anionic cyclization. Furthermore, the process provides rapid entry to complex tricyclic hemiacetals from relatively simple precursors in sequential steps.

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Supplementary data

The supplementary data include synthetic procedures for the synthesis of **3**, **4**, and **5** (including ^{1}H and ^{13}C NMR data), analytical data for **6** and **7**, and the X-ray data for **2**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.06.146.

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20. The reaction was followed by TLC. Once the conjugate addition was complete, the mixture was irradiated with visible light for 12 h. This resulted in a complex mixture of nonpolar products.
21. These substrates were synthesized from 1,7-dichloroheptan-4-one based on procedures that were reported previously (see Ref. 12).
22. Optimized procedure for **2**: To a 250 mL Schlenk flask was added 0.950 g (6.0 mmol) of samarium metal. This metal was flame-dried under vacuum and allowed to cool to rt under nitrogen. Dry THF (60 mL) was added, and the suspension was cooled to 0 °C. CH_2I_2 (1.57 g, 0.475 mL, 6.0 mmol) was added, and the mixture was warmed to rt. After stirring in the dark for 3 h, a dark blue solution was obtained. This solution was then cooled to −78 °C where NiI_2 (0.050 g, 0.16 mmol) was added under a stream of nitrogen. A solution of **5** (0.434 g, 1.0 mmol) and MeOH (0.041 mL, 1.0 mmol) in 10 mL of THF was then added dropwise. The solution was slowly allowed to warm to −20 °C (over 5 h) and was then maintained at that temperature for 2.5 d. After that time, the blue solution was quenched with 25 mL of a saturated aqueous solution of Rochelle's salt. After stirring for 3 h at rt, the mixture was extracted with EtOAc. The combined extracts were dried and concentrated to provide an oil, which was purified by column chromatography (12.5–40% EA/Hex) to yield 0.122 g of **2** (67%) as oil that slowly crystallized.