Sequenced Reactions with Samarium(II) Iodide. Sequential Intramolecular Reformatsky/Nucleophilic Acyl Substitution Reactions for the Synthesis of Medium-Sized Carbocycles

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Samarium(II) iodide was used to access eight- and nine-membered carbocycles via a domino reaction comprised of a Reformatsky reaction followed by a nucleophilic acyl substitution reaction. This method represents a general and efficient approach to a variety of highly functionalized, stereodefined carbocycles.

Introduction

Samarium(II) iodide (SmI_2) was introduced to the organic chemistry community as a reducing agent over 20 years ago.[1] Since that time it has become the reagent of choice for a variety of selective reactions.[2] Many of the earlier reports concentrated on the use of SmI_2 as a reductive coupling agent for a single transformation. However, it soon became apparent that this unique reagent could also be employed for a variety of sequential processes.[3] Further enhancing the scope of SmI_2 in any domino reaction is the ability to adjust the reactivity and/or selectivity of the process by varying different reaction parameters. For example, catalysts,[1,4] solvent effects,[5] or photochemical irradiation of the reaction mixture[6] can all be utilized to advantage in carrying out desired transformations. This ability to adjust the reaction conditions while using SmI_2 greatly facilitates its use for a variety of sequential processes (both radical and anionic) because the reductant can be selectively tuned for each individual step of a multistep process.

The development of efficient and novel approaches to medium-sized carbocycles is a worthy endeavor for organic chemists. Medium-sized carbocycles are incorporated into a variety of natural products either as isolated moieties or as part of a bicyclic or polycyclic framework.[7] Because of the well-known entropic and enthalpic factors associated with the formation of medium-sized rings, these carbon−carbon bond-forming reactions are considered quite challenging.[8] In fact, the number of general methods for preparing medium-sized carbocycles by cyclization or cycloaddition (annulation) reactions from acyclic precursors is relatively small.[7a,9] Methods that have been developed to access this type of carbon framework[10] include oxy-Cope rearrangements,[11] Wharton/Grob fragmentations,[12] metathesis reactions,[13] transition metal-catalyzed cycloaddition reactions,[14] and a variety of SmI_2 sequenced reactions.[3b,15]

On the basis of previous studies in our laboratories, an additional domino process leading to medium-sized rings was visualized. When SmI_2 is used as the promoter for an intramolecular Reformatsky reaction, the observed products are stereodefined lactones.[16] Because lactones

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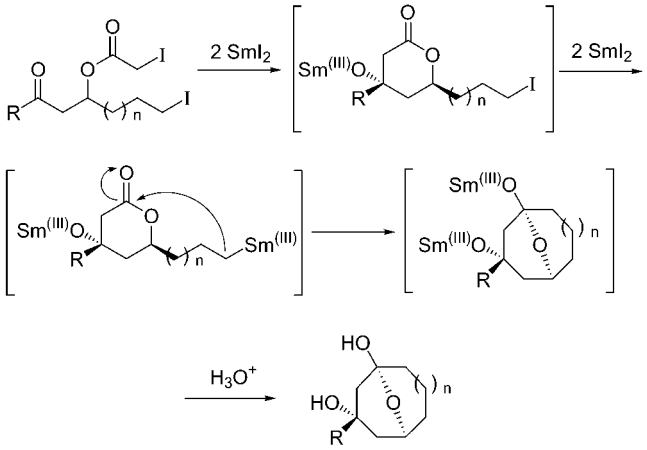
Scheme 1

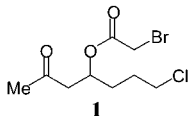
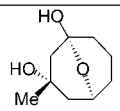
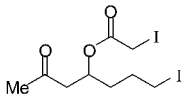
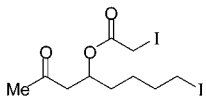
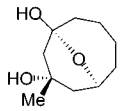
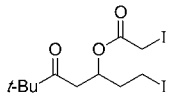
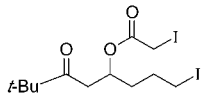
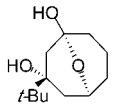
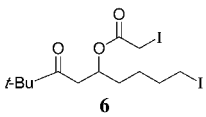
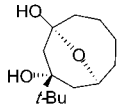
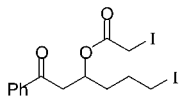
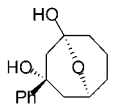
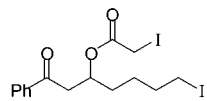
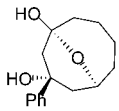
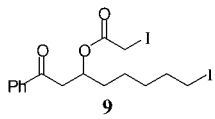
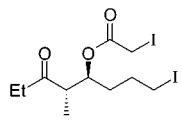
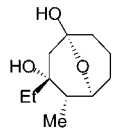
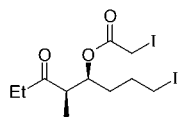
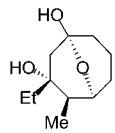
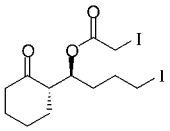
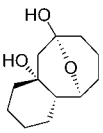
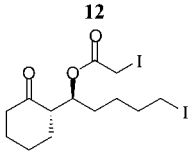
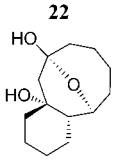


are substrates for SmI_2-promoted ring expansion reactions, the SmI_2-promoted Reformatsky reaction could be utilized as the initial component of a two-step sequence leading to medium-sized carbocycles. Thus, an intramolecular Reformatsky-type reaction followed by a nucleophilic acyl substitution reaction seemed likely to lead directly from acyclic substrates to highly functionalized, stereodefined eight- and nine-membered carbocycles. In the present contribution we outline the actualization of this novel combination of reactions resulting in the synthesis of an array of medium-sized carbocycles (Scheme 1).

Results and Discussion

To test the generality of the SmI_2-mediated sequential process a series of acyclic and cyclic substrates were synthesized and subjected to optimized reaction conditions. Compounds **1**−**3** and **5**−**13** (Table 1) were synthesized via an initial boron-catalyzed aldol reaction with the appropriate ketone and aldehyde (Scheme 2).[17] The resulting β-hydroxy ketones were treated with bromoacetyl bromide in the presence of pyridine at 0 °C to provide the bromoacetate derivatives. These acetates were subjected to sodium iodide in boiling acetone to give the desired diiodides via a double Finkelstein reaction. Because of the sensitivity of 3-chloropropanal, in the case of substrate **4** the aldol reaction was carried out using 3-((*tert*-butyldimethylsilyl)oxy)propanal.[18] The resulting aldol product was then deprotected using TBAF to give the diol which was selectively mesylated at the primary

Table 1. Sequential Reformatsky/Nucleophilic Acyl Substitution Reactions Mediated by Samarium(II) Iodide

entry	substrate	product	(%) isolated yield
1	 **1**	 **14**	39
2	 **2**	**14**	90
3	 **3**	 **15**	76
4	 **4**	-	-[a]
5	 **5**	 **16**	84
6	 **6**	 **17**	76
7	 **7**	 **18**	70
8	 **8**	 **19**	63
9	 **9**	-	-[a]
10	 **10**	 **20**	70[b]
11	 **11**	 **21**	58[c]
12	 **12**	 **22**	85
13	 **13**	 **23**	69

[a] Complex mixture. [b] Isolated as a 32:1 mixture of diastereomers. [c] Isolated as an 8.6:1 mixture of diastereomers.

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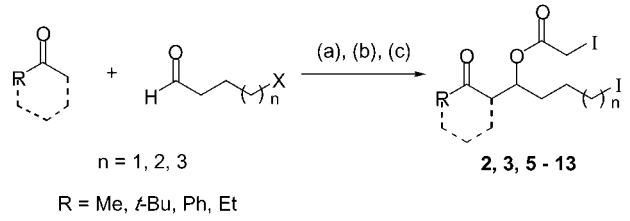
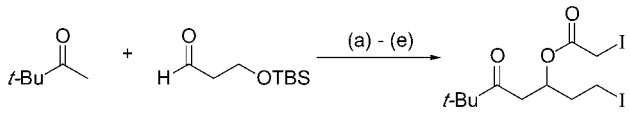
Scheme 2[a]



[a] Key: (a) $(C_6H_{11})_2BCl$, NEt_3, or $(Bu)_2BOTf$, Hunig's base; (b) bromoacetyl bromide, pyr; (c) NaI.

Scheme 3[a]



[a] Key: (a) $(C_6H_{11})_2BCl$, NEt_3; (b) TBAF; (c) MsCl, NEt_3; (d) bromoacetyl bromide, pyr; (e) NaI.

alcohol. The secondary alcohol was then acetylated with bromoacetyl bromide, and the resulting compound was subjected to the standard Finkelstein conditions to afford the desired substrate **4** for the sequential protocol (Scheme 3).

Initial optimization studies involved bromoacetate **1**. We postulated that the attenuated reactivity of the alkyl chloride would allow the desired SmI_2-promoted Reformatsky reaction to occur selectively, and only with photochemical irradiation[6] would the SmI_2 be activated enough to reduce the chloride and undergo the desired nucleophilic acyl substitution reaction. As can be seen from Table 1, entry 1, addition of substrate **1** to a solution of SmI_2 in the presence of 2% NiI_2[4b] followed by irradiation gave the desired medium-sized carbocycle in a yield of only 39%. The use of other additives such as $Fe(DBM)_3$[4a] or LiCl[4c] instead of NiI_2 failed to improve the yield of the reaction.

During the first phase of our studies, 2.5 equiv of SmI_2 was used to convert **1** cleanly and nearly quantitatively to the intermediate (chloropropyl)-β-hydroxyvalerolactone product. Subsequently, TLC was utilized to monitor the reaction, wherein the lactone could be observed because it was more polar than the starting material but less polar than the final product. Using this analytical technique revealed that the initial Reformatsky reaction was indeed proceeding smoothly. Thus, the low yield of the overall process was attributed to an ineffective nucleophilic acyl substitution. In an effort to improve the global yield of the transformation, substrate **1** was converted to substrate **2** via a simple Finkelstein reaction. Thus, the more easily reduced alkyl iodide was expected to improve the nucleophilic acyl substitution component of the two-step transformation.[15c] Addition of the diiodide **2** to a solution of SmI_2 containing 2% NiI_2 at −78 °C generated the intermediate lactone in situ. Upon warming of the solution to room temperature, an alkylsamarium species was generated by reaction of SmI_2 with the alkyl iodide. This species reacted via a nucleophilic acyl substitution reaction with the lactone generated in the previous step to provide the observed medium-sized carbocycle in 90% yield as a single diastereomer after isolation by silica gel chromatography. The relative stereochemistry was assigned by comparison to products **16** and **19** (vide infra).

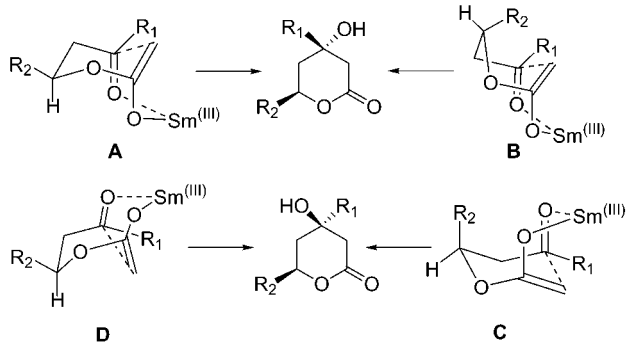


Figure 1. Empirical transition structure models for the SmI_2-promoted cyclization of β-haloacetoxy ketones.

The diastereoselectivity of this sequential process has its origins in the initial SmI_2-promoted Reformatsky reaction.[16] The diastereoselectivity in the SmI_2-promoted Reformatsky reaction is believed to result from the formation of a highly organized reaction intermediate by coordination of the oxophilic Sm(III) species to the carbonyl of the ketone starting material. The usual Zimmerman−Traxler chair transition structures must be adjusted for this particular transformation because of the bicyclic nature of the transition structures.[19] Using this modified paradigm, boat transition structures (**B** and **D**, Figure 1) are higher in energy than the chair transition structures (**A** and **C**) because of the usual unfavorable interactions associated with the former. Additionally, conformational analyses have established that *Z* ester rotamers are substantially favored over the corresponding *E* ester rotamers.[20] If this preference asserted itself in the transition state of the intramolecular Reformatsky reaction, involvement of the chair transition structures would be even more favored. Finally, all equatorial **A** is more stable than **C**, accounting for the observed sense of diastereoselection.

Increasing the carbon chain length by one methylene unit (Table 1, entry 3) by using 5-bromopentenal[17b] as the aldehyde in the initial aldol reaction provided the desired nine-membered carbocycle **15** as a single diastereomer in 76% yield. Varying the ketone used in the aldol reaction to either acetophenone or pinacolone provided a range of different substrates that underwent the SmI_2-promoted tandem sequence to afford both eight- and nine-membered carbocycles in good yields as single diastereomers (Table 1, entries 5−8). The relative stereochemistry of compounds **16** and **19** was determined by X-ray crystallography. The sense of diastereoselection observed is consistent with a chair transition structure in the initial Reformatsky reaction as outlined above.

When the SmI_2-promoted sequential process was attempted with substrate **4**, the desired seven-membered ring carbocycle was not observed and only a complex mixture was obtained (Table 1, entry 4). It seems likely in this case that the strain engendered in creating a bicyclo[3.2.1] intermediate upon attack of the organosamarium at the mildly electrophilic lactone cannot be overcome, and side reactions result. Attempted formation

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of a 10-membered carbocycle via substrate **9** served to demonstrate another limitation of the method. This time entropic effects were presumably to blame. Again a complex mixture of products was generated (Table 1, entry 9).

The *threo* substrate **10** was synthesized using the standard aldol protocol employing dicyclohexylboron chloride and triethylamine to afford the desired aldol product in 68% yield as a 10:1 mixture of anti and syn isomers.[21] To obtain *erythro* substrate **11**, reversal of the aldol selectivity was realized by carrying out the reaction using dibutylboryl triflate and Hunig's base which provided the aldol product in 66% yield as an 8:1 mixture of syn and anti isomers.[22] Both of these mixtures of aldol products were elaborated to the desired substrates (**10** and **11**) for the sequential process via the standard sequence of reactions described previously. When these substrates were exposed to the SmI_2-promoted reaction conditions (excess SmI_2 and 2% NiI_2), they both reacted smoothly to afford the desired eight-membered carbocycles in moderate yields as mixtures of diastereomers (Table 1, entries 10 and 11). The attenuation of diastereoselectivity in the initial Reformatsky reaction for the *erythro* isomer has been observed previously.[16]

The final class of substrates studied were those in which a ring was already incorporated into the initial structure. It was anticipated that these substrates would provide stereodefined bicyclic products after the SmI_2-promoted sequential process. Substrates **12** and **13** were both synthesized according to the standard sequence of reactions outlined previously. The aldol reactions were carried out using cyclopentylhexylboron triflate[21b] to give the desired aldol products as a mixture of *threo* and *erythro* isomers. A simple recrystallization from Et_2O/*n*-pentane gave exclusively the *threo* isomers. The structure of the *threo* aldol product from cyclohexanone and 4-chlorobutanal was confirmed by X-ray cystallography. When these substrates were exposed to the SmI_2 reaction conditions, they both gave the expected bicyclic products in good yields, and only one diastereomer was observed in each case (Table 1, entry 12 and 13). The relative stereochemistry of product **23** was confirmed by X-ray crystallography.

Conclusion

A samarium(II) iodide-promoted sequential cyclization protocol has been developed that provides an efficient approach to the synthesis of functionalized medium-sized carbocycles. This method involves the samarium(II) iodide-promoted Reformatsky reaction followed by a nucleophilic acyl substitution reaction to afford stereodefined medium-sized carbocycles with high yields under mild conditions.

Experimental Section

General Procedures. ^1H and ^{13}C NMR were recorded at 500 and 125 MHz for proton and carbon, respectively. $CDCl_3$ was employed as the solvent unless stated otherwise, and residual $CHCl_3$ was applied as an internal standard ($\delta = 7.27$ ppm) for ^1H spectra while the $CDCl_3$ signal served as internal standard ($\delta = 77.23$ ppm) for ^{13}C spectra. Standard flash chromatography procedures were followed using 32−63 mm silica gel.[23] Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled immediately prior to use from sodium benzophenone ketyl under Ar. Samarium metal was 99.9% and −40 mesh. CH_2I_2 was distilled under Ar and stored over copper granules. NiI_2 powder was 99.999%. Standard benchtop techniques were employed for handling air-sensitive reagents,[24] and all air-sensitive reactions were carried out under N_2.

General Procedure for the Synthesis of *β*-Hydroxy Ketones. 7-Chloro-4-hydroxyheptan-2-one. To a solution of acetone (1.06 g, 18.30 mmol) in 35 mL of Et_2O was added dicyclohexylboron chloride (4.48 g, 21.12 mmol) at 0 °C, followed by the dropwise addition of NEt_3 (2.85 g, 28.15 mmol). The resulting white suspension was stirred at 0 °C for 3.5 h. The suspension was then cooled to −78 °C, and a solution of 4-chlorobutanal (1.50 g, 14.08 mmol) in 15 mL of Et_2O was added over 5 min. The reaction mixture was stirred at −78 °C for 2 h and then stored in a freezer at −30 °C for 12 h. The reaction mixture was then quenched with pH 7 buffer and methanol and cooled to 0 °C, and 30 mL of H_2O_2 (30% v/v) was added dropwise. The mixture was stirred at 0 °C for 1 h and then diluted with 100 mL of H_2O. The aqueous layer was extracted with CH_2Cl_2, and the organic extracts were combined and washed with brine and then dried with $MgSO_4$. Flash chromatography (30% EtOAc/petroleum ether) yielded 1.56 g (67%) of the title compound as a colorless oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 4.09−4.04 (m, 1H), 3.63−3.54 (m, 2H), 3.11 (d, J = 3.0 Hz, 1H), 2.65 (dd, J = 17.9, 2.7 Hz, 1H), 2.56 (dd, J = 17.9, 9.0 Hz, 1H), 2.18 (s, 3H), 2.01−1.94 (m, 1H), 1.88−1.82 (m, 1H), 1.61−1.56 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 210.0, 66.9, 50.1, 45.2, 33.5, 30.9, 28.8; IR (film) ν_{max} 3436, 1712 cm^{-1}; HRMS (CI^+) calcd for $(M + H)^+$ $C_7H_{14}O_2Cl$ 165.0682, found 165.0690.

General Procedure for the Acetylation of *β*-Hydroxy Ketones with Bromoacetyl Bromide. 4-(Bromoacetyloxy)-7-chloroheptan-2-one (1). To a solution of 7-chloro-4-hydroxyheptan-2-one (1.00 g, 6.07 mmol) in 30 mL of anhydrous CH_2Cl_2 at 0 °C was added pyridine (0.96 g, 12.15 mmol) followed by bromoacetyl bromide (1.84 g, 9.11 mmol). The resulting suspension was stirred for 2 h at 0 °C and then quenched with 40 mL of 1 N HCl. The mixture was extracted with CH_2Cl_2. The organic extracts were combined and washed with brine and then dried with $MgSO_4$. Flash chromatography (20% EtOAc/petroleum ether) yielded 1.53 g (88%) of the title compound as a colorless oil (**1**): ^1H NMR ($CDCl_3$, 500 MHz) δ 5.36−5.31 (m, 1H), 3.79 (s, 2H), 3.56 (t, J = 6.1 Hz, 2H), 2.84 (dd, J = 17.0, 7.0 Hz, 1H), 2.66 (dd, J = 17.7, 5.6 Hz, 1H), 2.18 (s, 3H), 1.87−1.74 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 204.9, 166.7, 71.4, 47.3, 44.4, 31.3, 30.5, 28.1, 25.7; IR (film) ν_{max} 1732, 1716 cm^{-1}; HRMS (CI^+) calcd for $(M + H)^+$ $C_9H_{15}O_3ClBr$ 284.9893, found 284.9895.

General Procedure for the Finkelstein Reaction. 7-Iodo-4-(iodoacetyloxy)heptan-2-one (2). To a solution of **1** (1.00 g, 3.50 mmol) in 30 mL of acetone was added NaI (2.62 g, 17.51 mmol). The solution was heated at reflux for 16 h and cooled to room temperature, and 50 mL of water was added. The aqueous phase was extracted with CH_2Cl_2 (3 × 35 mL). The organic extracts were combined and washed with brine and then dried with $MgSO_4$. Purification by flash chromatography (20% EtOAc/petroleum ether) afforded 1.33 g (89%) of **2** as a pale yellow oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 5.31−5.28 (m, 1H), 3.65 (ABq, ν_{AB} = 11.9 Hz, J = 10.2 Hz, 2H), 3.22−3.18 (m, 2H), 2.81 (dd, J = 16.9, 6.9 Hz, 1H), 2.64 (dd, J = 16.9, 5.7 Hz, 1H), 2.18 (s, 3H), 1.92−1.87 (m, 2H), 1.81−1.71 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 204.9, 168.4, 70.9, 47.4, 34.9, 30.7, 29.1, 6.0, −5.3; IR (film) ν_{max} 1734, 1717 cm^{-1}; HRMS (CI^+) calcd for $(M + Na)^+$ $C_9H_{14}O_3I_2Na$ 446.8930, found 446.8947.

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General Procedure for the Sequenced Reactions Using Samarium(II) Iodide. Samarium metal (0.88 g, 5.85 mmol) was added under a flow of N_2 to an oven-dried flask. A 50 mL volume of THF was added, the suspension was cooled to 0 °C, and CH_2I_2 (1.34 g, 5.0 mmol) was added. The mixture was stirred at room temperature for 4 h, and NiI_2 (2% mol) was added. After being stirred for 5 min, the deep-blue solution was cooled to −78 °C and the substrate (1 mmol) in 10 mL of THF was added over 5 min. After the initial starting material was consumed (TLC or GC analysis), the reaction mixture was warmed to room temperature and stirred for 12 h. The resultant solution was quenched with a saturated aqueous solution of Rochelle's salt (potassium sodium tartrate) and extracted with Et_2O. The organic extracts were combined and washed with 30 mL of brine and dried over $MgSO_4$.

(1*R,3*S**,5*R**)-3-Hydroxy-3-methyl-9-oxabicyclo[3.3.1]-nonan-1-ol (14).** This was prepared from **2** (424 mg, 1.0 mmol) according to the general procedure described above to afford, after flash chromatography (50% EtOAc/petroleum ether), **14** (155 mg, 90%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.58 (br s, 1H), 4.50−4.48 (m, 1H), 3.93 (br s, 1H), 2.07−1.96 (m, 2H), 1.85 (d, part of ABq, J = 14.9 Hz, 1H), 1.73−1.64 (m, 4H), 1.52−1.47 (m, 1H), 1.32 (dd, J = 13.9, 4.5 Hz, 1H), 1.25−1.22 (m, 1H), 1.20 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 95.5, 70.1, 69.6, 47.6, 38.1 (2C), 29.8, 28.3, 16.8; IR (film) ν_{max} 3468 cm^{-1}; HRMS (CI$^+$) calcd for $(M + H)^+$ $C_9H_{17}O_3$ 173.1178, found 173.1184.

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Supporting Information Available: Full experimental details, ^{1}H and ^{13}C NMR spectra for all compounds, and X-ray structural data for **16**, **19**, and **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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