Vinylogous Intramolecular Nucleophilic Acyl Substitution Reactions Mediated by Samarium(II) Iodide

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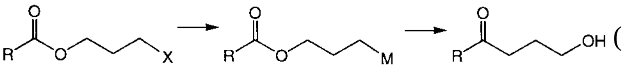
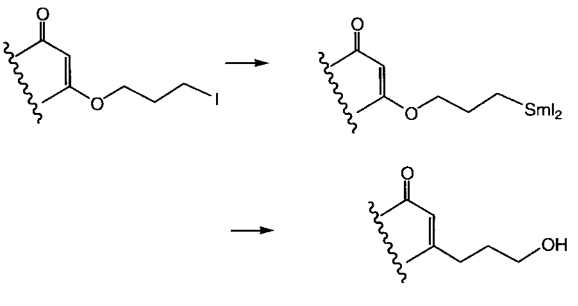
Intramolecular acyl substitution (INAS) reactions (Eq. 1) could be useful for providing synthetically valuable compounds such as 4-hydroxy ketones. This could be utilized as an facile route to ketones with remotely located stereogenic centers. The main conceivable difficulties associated with devising successful INAS reactions are the necessity of having reactive nucleophiles in the presence of an ester electrophile, which have to be compatible with the hydroxy ketones produced by the reactions.



(1)

Organolanthanides are known to meet the requirements for successful INAS reactions. Organosamarium reagents appeared to be especially well suited to the criteria required.[1] In fact, Molander and Shakya have studied the samarium(II) iodide-promoted INAS reactions of substituted 3-iodopropyl carboxylates.[2] In the presence of iron(III) catalysts, various esters have been converted to 4-hydroxy ketone derivatives in good yields. A variety of chiral compounds possessing a 1,4-, 1,5-, or 1,6-relationship between the two stereogenic centers have been efficiently prepared. The transformation is, however, only limited to 3-iodoproyl carboxylates. 4-iodobutyl carboxylates underwent an INAS reaction followed by a Meerwein-Ponndorf-Verley redox reaction.[3] This sequential process has been proven to a facile route to prepare chiral, nonracemic δ-hydroxy ketones.

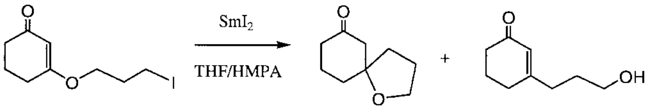
In order to expand the utility of the above mentioned samarium(II) iodide-promoted INAS reactions, we decided to investigate a vinylogous version of the INAS reactions illustrated by the following equation (Eq. 2). The starting 3-(3-iodopropoxy)-2-alkenones are expected to proceed via an initial Michael addition followed by a ring opening due to the β-elimination. In fact, the intramolecular conjugated addition of an alkyl iodide to an α,β-unsaturated carbonyl system has been investigated by Molander and Harris.[4] They have successfully utilized this samarium(II) iodide-promoted conjugated addition to prepare variety of carbocycles. We believe that the samarium(II) iodide-promoted vinylogous INAS reactions should expand the utility of samarium(II) iodide-promoted reactions by providing an opportunity to control the stereocenters which are located farther apart. It would also help us to understand the behavior and the property of the organosamarium species.



(2)

The required substrates, 3-(3-iodopropoxy)-2-cycloalkenones were synthesized in a straightforward way, that is, heating 1,3-cycloalkanediones at reflux with the corresponding 3-iodopropanols in the presence of p-TsOH in benzene.

We initially investigated the feasibility of this reaction with an α,β-unsaturated cyclic ketone **1**. The iodoketone **1** was subjected to samarium(II) iodide in THF in the presence of HMPA. In this case the anticipated product **3** was formed as a major product. However, formation of the spiro product **2** was also observed.[5,6]

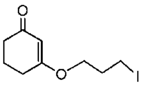
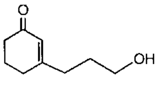
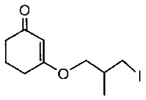
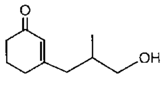
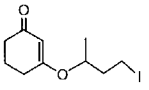
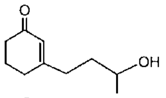
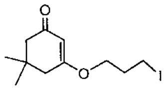
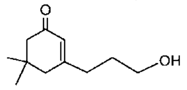
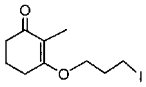
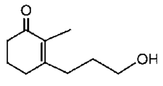
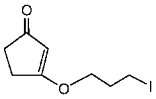
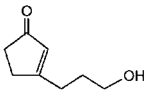
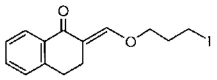
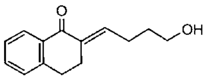


1 **2** **3**

The amount of the spiro product **2** in yields varied with runs from 15 to 45%. In order to optimize the yield of **3,** the addition of additives other than HMPA was investigated. Effects of the reaction temperature and reaction time on yields in the presence of HMPA have also been tested. As a result, the best combined yield was obtained at 0 °C with 30-min reaction time. HMPA has been found to be essential for optimizing the yield. Use of other additives such as $Fe(DBM)_3$ and NiI_2 did not produce the desired products, although Fe(III)[1,7] and Ni(II) salts[4,8] have been reported to be good for the generation of organosamarium reagents. Finally we were pleased to find that with excess amounts of samarium(II) iodide (6 equiv, 0 °C) the reaction proceeded cleanly and produced the desired hydroxy ketone **3** (73%) without formation of the spiro product **2**. This reaction condition was, therefore, employed for all of the substrates in this study. The results of the INAS reaction on various 3-(3-iodopropoxy)-2-alkenones are summarized in Table 1.[9]

In cases of the iodoenones with methyl substituents on the tether (entry 2 and 3) the corresponding 6-hydroxyenone compounds were produced. The iodoenone derived from dimedone (entry 4) also proceeded without any difficulty. Even the substrate with a methyl group at α-position of the cyclic enone system did not pose a problem (entry 5). Effect of the ring size of the enones was also examined. The

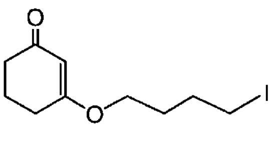
Table 1. Vinylogous INAS reaction promoted by samarium(II) iodide[a]

Entry	Substrate	Product	Yield (%)
1			73
2			76
3			75
4			66
5			72
6			79
7			68

[a] All the reactions were carried out in THF-HMPA for 30 min at 0 °C; 6 equiv of SmI_2 were used.

iodoenone derived from 1,3-cyclopentendione has been converted to the corresponding 6-hydroxyenone in good yield (entry 6). To test the general utility of the reaction, an iodoenone with exocyclic double bond was prepared. The anticipated vinylogous INAS reaction occurred smoothly (entry 7), and this result illustrates the feasibility of applying this type of reaction to more general substrates.

A reaction with unsaturated enones with an elongated tether chain was also investigated. Thus, 3-(4-iodobutoxy)-2-cyclohexenone (**4**) was subjected to the conditions described above. However, this resulted only in decomposition of the material to give a mixture of compounds. None of the expected vinylogous INAS reaction products were observed.



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In summary, we have investigated the samarium(II) iodide-promoted intramolecular vinylogous INAS reactions of 3-(3-iodopropoxy)-2-alkenones. The reactions proceeded smoothly with excess of samarium(II) iodide in THF-HMPA. These examples have extended the utility of the simple nucleophilic acyl substitution reaction mediated by samarium(II) iodide and could provide an easy access to 1,6-difunctionalized compounds.

Acknowlegment. We thank the Korea Science and Engineering Foundation for support (98-0501-04-01-3) of this research.

References

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5. The structure of the 3-(3-hydroxypropyl)cyclohex-2-one (**3**) was unambiguously identified by comparing it with the authentic sample which was prepared according to the method reported in the literature: (a) Godleski, S. A.; Valpey, Rr. S. *J. Org. Chem.* **1982**, *47*, 383. (b) Becker, D.; Harel, Z.; Nagler, M.; Gillon, A. *J. Org. Chem*. **1982**, *47*, 3297. (c) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamija, Y. *J. Am. Chem. Soc*. **1989**, *111*, 4392. (d) Crimmins, M. T.; Dedopoulou, D. *Synth. Commun*. **1992**, *22*, 1953.
6. The spiro compound **2** was also identified by spectroscopic method and comparing with the ^{1}H and ^{13}C NMR, and DEPT data with those reported in the literature. Middleton, D. S.; Simpkins, N. S. *Tetrahedron* **1990**, *46*, 545.
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9. Typical Procedure: **3-(3-Hydroxypropyl)cyclohex-2-enone**. 3-(3-Iodopropoxy)cyclohex-2-enone (200 mg, 0.71 mmol) in THF (2.0 mL) was added dropwise to a solution of SmI_2 (4.3 mmol) in THF/HMPA (10% v/v) at 0 °C under nitrogen atmosphere. After stirring for 30 min at 0 °C, the reaction mixture was quenched with Rochells salt solution.[10] Extraction with dichloromethane, drying ($MgSO_4$), and concentration followed by flash chromatography provided the desired hydroxyketone as a colorless oil (80 mg, 73%). **^{1}H NMR (300 MHz, $CDCl_3$)** δ 1.71-1.80 (m, 2H, $-CH_2CH_2OH$), 1.96-2.02 (m, 2H, $C(O)CH_2CH_2-$), 2.28-2.37 (m, 6H, $=C-CH_2CH_2-$, $C(O)CH_2CH_2CH_2C-$), 3.67 (t, 2H, $-CH_2OH$, J = 6.3 Hz), 5.88 (s, 1H, $(O)CCH=C$). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 23.0 ($C(O)CH_2CH_2-$), 30.1 ($-CH_2CH_2OH$, $-CH_2CH_2C-$), 34.6 ($=C-CH_2CH_2-$), 37.6 ($C(O)CH_2CH_2-$), 62.4 ($-CH_2OH$), 126.0 ($C(O)CH=C$), 168.51 ($CH=C-CH_2$), 200.4 ($C(O)CH=C$).
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