Samarium(II) Iodide-Promoted Vinylogous Intramolecular Nucleophilic Acyl Substitution Reactions of β-Alkoxyacrylates

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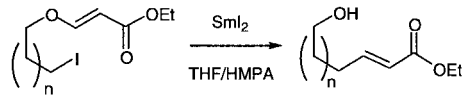
Received May 31, 2001

Keywords : Samarium(II) iodide, Intramolecular nucleophilic acyl substitution, Organosamarium, β-Alkoxyacrylates.

Recently, we reported a vinylogous intramolecular nucleophilic acyl substitution (INAS) reaction of 3-(3-iodopropoxy)-2-alkenones.[1] Although these types of transformations could be useful for providing 6-hydroxyalkenones, there have been limitations. First, substrates of the reactions, 3-(3-iodopropoxy)-2-alkenones considered were limited to those with cyclic structures, that is, all of the compounds were derived mainly from 1,3-cycloalkanediones. The more serious limitation was that this vinylogous INAS reaction was successful only for 3-(3-iodopropoxy)-2-alkenones. Therefore, we turned our attention to find more general substrates to overcome these limitations and decided to investigate the vinylogous INAS reactions of β-alkoxyacrylates shown below (Eq. 1).



(1)

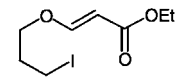
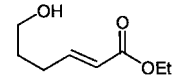
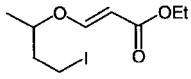
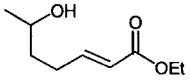
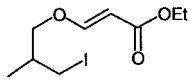
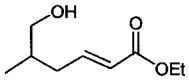
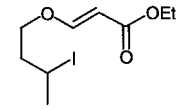
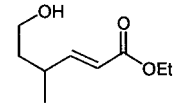
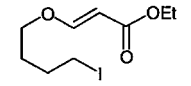
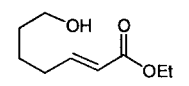
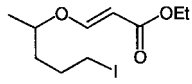
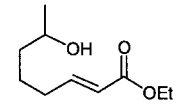
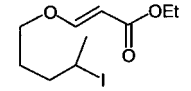
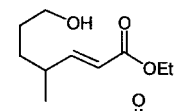
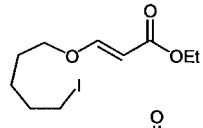
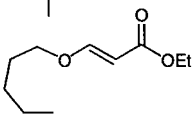
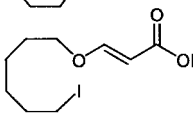
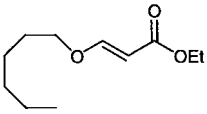
Radical chemistry of the β-alkoxyacrylates derivatives has already attracted much attention.[2] There are also needs to develop tin-free radical routes for replacing many useful radical processes.[3,4] Samarium(II) iodide-mediated reactions could be, in principle, an alternative to meet the requirements.[5,6] During the course of the study, samarium(II) iodide-induced reductive intramolecular cyclization of aldehydes and β-alkoxyacrylates appeared.[7] However, samarium(II) iodide-mediated intramolecular cyclization of alkyl iodides and β-alkoxyacrylates has not been studied yet. Herein, we report the behavior of the organosamarium species derived from alkyl iodides in the presence of β-alkoxyacrylate moiety represented by Eq. (1).

The required substrates, β-(ω-iodoalkoxy)acrylic acid esters were prepared by the procedures reported in the literature *via* the reaction of the corresponding iodo alcohols with ethyl propiolate in the presence of *N*-methylmorpholine.[2(a)] β-(ω-iodoalkoxy)acrylates, thus prepared were treated with samarium(II) iodide in THF-HMPA at 0 °C. The reactions proceeded smoothly under this condition to provide the intramolecular INAS reaction products, that is, ω-hydroxy-α,β-unsaturated esters in reasonable yields in the presence of excess amount of samarium(II) iodide (6 equiv).[8] Use of additives such as Fe(III) or Ni(II) salts did not provide the desired products. The best yields were obtained also at 0 °C in THF-HMPA. The results are summarized in Table 1.

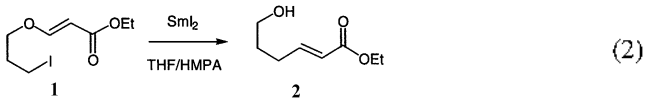
As shown in entry 1, ethyl 3-(3-iodopropoxy)acrylate underwent the INAS reaction smoothly to give the corresponding ω-hydroxy-α,β-unsaturated ester in 75% yield. With a methyl substituent at the carbon next to propoxy oxygen (entry 2) or at the other carbon (entry 3), the reactions occurred without any difficulty. These results are, in general, similar to those previously obtained from the INAS reactions of 3-(3-iodopropoxy)-2-cycloalkenones. The substrates we have used here are, however, more general to be employed in the general synthetic sequences, and should be more useful. Furthermore, these reactions were found to have enhanced generality in scope, that is, these successfully provided the corresponding esters not only from 3-(3-iodopropoxy)acrylates but also 3-(4-iodopropoxy)acrylates. Therefore, it was possible to introduce hydroxyl functionality at 6- or 7-position of ω-hydroxy-α,β-unsaturated esters. Thus, 3-(4-iodobutoxy)-acylates also underwent the INAS reactions under the same conditions to offer the corresponding ethyl 7-hydroxy-2-alkenoates (entries 5 and 6). This makes rather clear difference from the previously reported case, in which 3-(4-iodobutoxy)-2-cyclohexenone did not give any expected vinylogous INAS reaction product.[1]

Investigation with ethyl 3-(3-iodopropoxy)acrylate (**1**) revealed that ethyl 7-hydroxy-2-hexenonate (**2**) was formed in THF in the presence of HMPA (Eq. 2). The best yield of **2** was obtained when 6 equiv of samarium(II) iodide was used. In the case that less amount of samarium(II) iodide was used the yield of the product was reduced. For example, only 58% yield of the product was obtained with 2.8 equiv of samarium(II) iodide. However, when ethyl 3-(3-iodo-1-methylpropoxy)acrylate (**3**) was subjected to the same condition, the expected vinylogous INAS reaction product **4** as well as the corresponding cyclic product **5** was isolated with less than 6 equiv of samarium(II) iodide (Eq. 3). Thus, with 2.8 equiv of samarium(II) iodide, the cyclic product **5** and the INAS product **4** were obtained in 16 and 30% yields, respectively. When less or more samarium(II) iodide was used, the yield of the cyclic product decreased.[10] Another interesting feature in the reactions shown in Table 1 is the behavior of the secondary iodides, that is, the substrates having a methyl substituent at the carbon bearing an iodine (entries 4 and 7). These secondary iodides also provided the corresponding INAS reaction products.

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

Entry	Substrate	Product	Yield (%)
1			75
2			91
3			82
4			68
5			75
6			76
7			32
8			50
9			50

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



Increasing length of the tether in alkoxy group of the substrates (entries 8 and 9) prohibited the INAS reactions. In these cases, only reduction of iodides was observed.

Thus, samarium(II) iodide-promoted INAS reactions were successfully achieved with β-(ω-iodoalkoxy)acrylates. These results provided a potentially useful way to provide 1,6- as well as 1,7-difuntionalized compounds.

Acknowledgment. This work was financially supported by the Center for Molecular Design and Synthesis (CMDS), KAIST.

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8. Typical Procedure: **Ethyl 6-hydroxy-2-hexenoate (2)**. Ethyl 3-(3-iodopropoxy)acrylate (**1**) (60 mg, 0.20 mmol) in THF (2.0 mL) was added dropwise to a solution of SmI_2 (1.2 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 Rochell's salt solution.[9] Extraction with dichloromethane, drying ($MgSO_4$), and concentration followed by flash chromatography provided the desired hydroxyester **2** as a pale yellowish oil (25 mg, 75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.96 (dt, 1H, J = 15.6 Hz, J = 7.0 Hz, C*H*–CHCOOEt), 5.78 (d, 1H, J = 15.6 Hz, -CH–C*H*COOEt), 4.12 (q, 2H, J = 7.1 Hz, -OCH_2-CH_3), 3.61 (t, 2H, J = 6.4 Hz, -CH_2OH), 2.24 (m, 2H, -C*H*$_2$CH=CH-), 1.66 (m, 2H, -CH_2CH_2OH), 1.22 (t, 3H, J = 7.1 Hz, -CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2 (-$CO_2CH_2CH_3$), 154.1 (-CH_2CH=CH-), 120.4 (-CH_2CH=CH-), 60.9 (-CH_2OH), 59.6 (-OCH_2CH_3), 31.2 (-CH_2CH_2OH), 28.8 (-CH_2CH=CH-), 14.7 (-CH_2CH_3).
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10. The stereochemistry of the cyclic product was found to be *cis*. Identification was achieved according to the method reported:[3(b)] The product **5** was reduced ($LiAlH_4$) and acetylated to prepare 2-(2'-acetoxyethyl)-5-methyltetrahydrofuran. The methyl doublet of the product appears at δ 1.23 (in the ^{1}H NMR spectrum) which is identical to the value reported for the *cis*-2-(2'-acetoxyethyl)-5-methyltetrahydrofuran.