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Diastereoselective synthesis of *trans*-3,5-disubstituted dihydrofuran-2(3*H*)-ones via SmI_2-mediated reductive coupling of 2-alkylacrylates of *N*,*N*-diisopropyl-2-hydroxybenzamide with aldehydes

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ABSTRACT

Samarium(II) diiodide has been used to mediate reductive coupling reactions of aldehydes with a variety of substituted acrylates, in both achiral and chiral forms, for accessing substituted dihydrofuran-2(3*H*)-ones (γ-butyrolactones). Two major issues, concerning with self-dimerization of α-non-branched aliphatic aldehydes and low diastereoselectivity of the products, render limited application of the reductive coupling protocol in total synthesis of natural products. We report here on a novel type of substituted acrylates derived from the 2-amido arenols (HO-Ar^{am}) such as *N*,*N*-diisopropyl-2-hydroxybenzamide. The acrylates of HO-Ar^{am} enable: (a) preferential conjugate reduction of the acrylates than carbonyl reduction of aliphatic aldehydes, leading to diminished aldehyde self-dimerization; and (b) organization of an eight-membered ring among the amide carbonyl oxygen atom and samarium(III) to form a 7/8-bicyclic transition state, resulting in highly diastereoselective protonation of the samarium(III) enolate intermediate. Examples of synthesis of *trans*-3,5-disubstituted dihydrofuran-2(3*H*)-ones from 2-alkylacrylates of HO-Ar^{am} and aliphatic aldehydes are provided.

1. Introduction

Samarium(II) diiodide (SmI_2, Kagan's reagent) has been widely used as an efficient reductant in facilitating various organic transformations.[1] One major utility of the SmI_2-mediated reactions is the reductive couplings for carbon–carbon bond formation. Although the intramolecular reductive couplings mediated by SmI_2 have enjoyed applications in total synthesis of natural products,[1e,g,k] the intermolecular reductive cross-coupling of carbonyl compounds with conjugate alkenes using SmI_2 remains challenging.[1m] In 1986, Fukuzawa[2] and Inanaga[3] independently reported the cross-coupling reactions of substituted acrylates **1** and **3** with aldehydes in the presence of SmI_2 and an alcohol (as the proton source) to afford substituted dihydrofuran-2(3*H*)-ones (γ-butyrolactones) **2a**,**b** and **4a**,**b** in 70–75% yields (Scheme 1). However, the diastereoselectivity of the products varies from 70:30 to 95:5 in terms of the structures of both acrylates and aldehydes. In 1997, Fukuzawa and co-workers[4] reported the first enantioselective reductive coupling reaction of the *N*-methylephedrine-derived chiral crotonate **5a** with aliphatic aldehydes to produce chiral dihydrofuran-2(3*H*)-ones **6** in both high *cis*:*trans* ratios and high enantioselectivity (93–97% ee) (Scheme 2). However, the product yields as estimated by GC analysis are moderate (57–74%). Procter and co-workers[5] disclosed the Wang resin-bound chiral crotonate **5b** and the fluorous-tagged chiral crotonate **5c** for the reductive coupling reactions with aliphatic aldehydes, obtaining the products **6** in both high *cis*:*trans* ratios and high enantioselectivities (88–99% ee) albeit in low to moderate isolated yields (43–82%). In our previous work,[7a] we developed a novel class of chiral crotonate **5d**, which was derived from the atropisomeric 2-hydroxy-8-methoxy-1-naphthamide.[7b] The SmI_2-mediated reductive coupling of **5d** with aliphatic aldehydes gave the chiral products **6** in good *cis*:*trans* ratios (72:28–91:9) and high enantioselectivities (97–99%). Moreover, the isolated product yields of 81–90% are much higher than those obtained with the crotonates **5a**–**c**.

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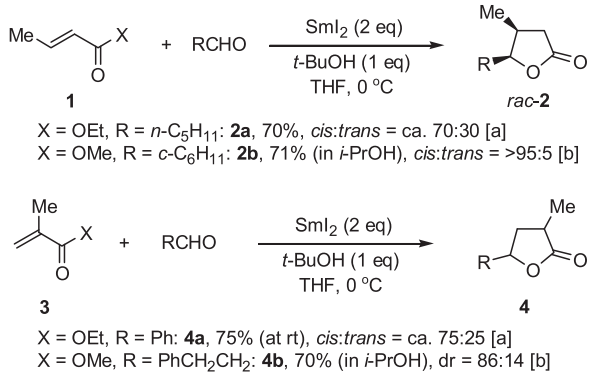
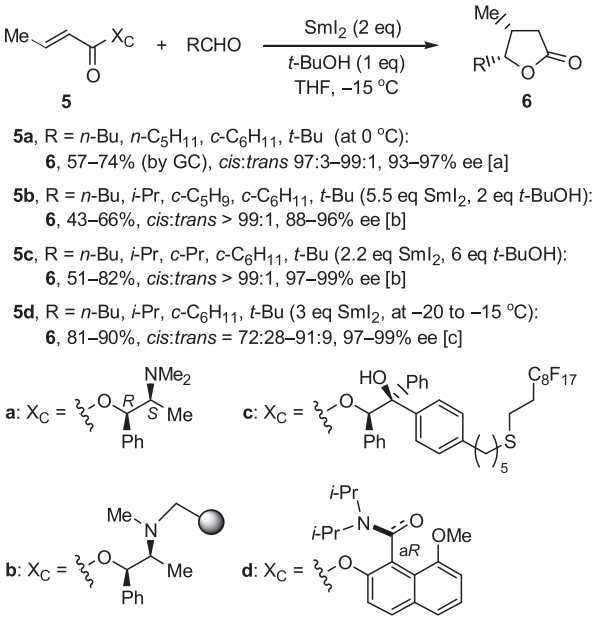
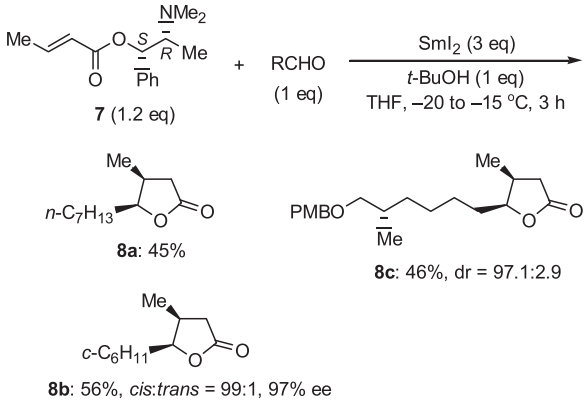


Scheme 1. SmI_2-mediated reductive coupling of the substituted acrylates **1** and **3** with aldehydes reported by Fukuzawa [a; Ref. 2] and Inanaga [b; Ref. 3].



Scheme 2. Reductive coupling of the chiral crotonates **5** with aldehydes reported by Fukuzawa [a; Ref. 4], Procter [b; Refs. 5 and 6], and Dai [c; Ref. 7].

Low product yields are the drawback for accessing the chiral *cis*-4,5-disubstituted dihydrofuran-2(3*H*)-ones **6** from the *N*-methylephedrine-derived chiral crotonate **5a** and it hampered general applications of this highly enantioselective reaction. In our effort in synthesis of the 2,3,5-trisubstituted tetrahydrofuran fragment[8] of amphidinolide T family of congeners, the chiral compound **8c** was prepared from the reductive coupling of the *N*-methylephedrine-derived chiral crotonate **7** with the corresponding α-non-branched aldehyde in 46% isolated yield on a 3 mmol scale under the optimized conditions (Scheme 3). Similarly, the reaction of **7** with *n*-octanal furnished the product **8a** in 45% isolated yield. When cyclohexanecarboxaldehyde was used, the product **8b** was formed in a slightly higher yield (56%). We found that the main byproduct in the reductive coupling reaction of α-non-branched aliphatic aldehydes with **7** was the dimers of the aldehyde. The undesired dimerization pathway might be suppressed for the ketyl radical generated from α-branched aliphatic aldehydes. In order to address both issues of low product yield and low stereoselectivity associated with SmI_2-mediated reductive coupling of substituted acrylates with aliphatic aldehydes, we have introduced a novel class of substituted acrylates derived from the 2-amido arenols (HO-Ar^{am}) such as *N*,*N*-diisopropyl-2-hydroxybenzamide. We report here on the



Scheme 3. Reductive coupling of **7** with aldehydes reported by Dai.

results of the highly diastereoselective synthesis of *trans*-3,5-disubstituted dihydrofuran-2(3*H*)-ones.

2. Results and discussion

In our previous work, as mentioned in Scheme 2, the reactions of the chiral 1-amido-2-naphthol-derived crotonate **5d** with aliphatic aldehydes afforded higher product yields. We attributed the results to the electron-withdrawing nature of the 1-amido-2-naphthol moiety,[9] which might favor for conjugate reduction of the crotonate over carbonyl reduction of the aldehyde. Consequently, the undesired self-dimerization of the aldehyde partner via the ketyl radical could be minimized. Therefore, we envisioned that the crotonate **11** derived from a simpler 2-amido arenol, i.e., *N*,*N*-diisopropyl-2-hydroxybenzamide (**10**) should be a useful substrate for the synthesis of racemic *cis*-5-alkyl-4-methyldihydrofuran-2(3*H*)-ones *rac*-**2a**,**c**–**e** (Scheme 4). Starting from salicylic acid (**9**), the 2-amido phenol **10** was prepared in 85% overall yield by treating **9** in refluxing $SOCl_2$ and subsequent amidation of the resultant acyl chloride with *i*-Pr_2NH in PhMe at 80 °C. Reaction of **10** with crotonoyl chloride in the presence of Et_3N and catalytic DMAP in PhMe at 70 °C for 12 h furnished the crotonate **11** in 86% yield. Three aliphatic α-non-branched aldehydes, *n*-hexanal, $TBDPSOCH_2CH_2CHO$, and $PMBOCH_2CH_2CHO$, were subjected to the SmI_2-mediated reductive coupling with **11** to afford the products *rac*-**2a**, *rac*-**2c**, and *rac*-**2d** in 85%, 74%, and 75% yields, respectively, and in diastereomeric ratios of 87:13–95:5. For comparison purpose, we repeated the reductive coupling of ethyl crotonate (**1**, *X*=OEt) with *n*-hexanal (Scheme 1).[2] Under our conditions,[8] the product *rac*-**2a** was isolated in 41% yield and in a *cis*:*trans* ratio of 84:16 along with the dimer byproducts **12a** (34%; dr=81:19) (Scheme 4). These results are different from those as originally reported by Fukuzawa in Scheme 1.[2] Also, the product yields of *rac*-**2a**,**c**,**d** obtained from **11** are much better than the yields for the chiral compounds **6** and **8a**–**c** synthesized from the chiral crotonates **5a**–**c** and **7** derived from *N*-methylephedrine and the related 1,2-amino alcohol or 1,2-diol (Schemes 2 and 3).[4–6,8] Therefore, it can be concluded that the undesired dimerization of the aliphatic α-non-branched aldehydes in the SmI_2-mediated reductive coupling reactions could be minimized or suppressed by using the crotonate **11** derived from the 2-amido arenol **10** via preferential conjugate reduction of the crotonate **11**. Another piece of evidence was obtained from the reductive coupling of cyclopropanecarboxaldehyde with **11**. The expected product, *cis*-5-cyclopropyl-4-methyldihydrofuran-2(3*H*)-one (*rac*-**2e**),[6] was formed in 80% isolated yield as a 90:10 mixture of *cis* and *trans*