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SmI_2-promoted tandem desulfurization and reductive coupling reactions of aromatic lactams with carbonyl compounds

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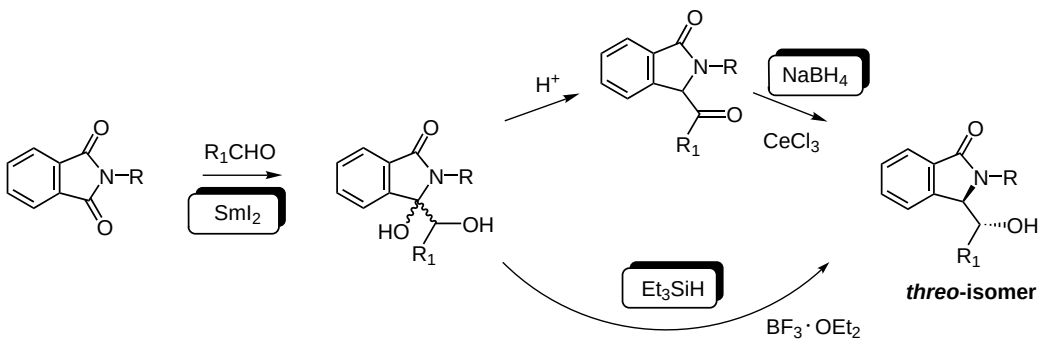
Abstract—Treatment of sulfur-substituted aromatic lactams with carbonyl compounds in the presence of samarium(II) diiodide was found to undergo novel tandem desulfurization and reductive coupling reactions to generate α-hydroxyalkylated lactams in high yield. Stereochemistry of the coupling products was researched and the results that decreasing the steric bulkiness of the *N*-substituents as well as raising the reaction temperature leads to an increase of the *erythro*-selectivity were observed. The mechanistic origins of this stereoselectivity are also briefly documented. © 2001 Elsevier Science Ltd. All rights reserved.

Since its introduction by Kagan and co-workers[1] SmI_2 has been extensively investigated as a powerful electron donor able to promote a wide range of reductions and coupling reactions.[2] Its use in synthesis has been especially advantageous for ring closure reactions and C–C bond formation such as hydroxyl-directed addition of carbonyl to C=C double bond and stereocontrolled intramolecular pinacol reactions.[2k,3] The reactions of acid chlorides[4] and acid anhydrides[5] with this reagent have also been researched. In addition, intramolecular and intermolecular Barbier-type reactions with haloalkanes toward the carbonyl group of ketones[6] and imides[7] have been reported. In this connection recent disclosures from this laboratory have demonstrated the first pinacolic cross-coupling reaction between phthalimides and carbonyl compounds and its application to two types of complete *threo*-selective reactions; $CeCl_3$-mediated reduction after dehydration of the coupling products is the first and the second one is direct Lewis acid-promoted deoxygenation of the coupling substrates with Et_3SiH as shown in Scheme 1.[8] Although significant progress, thus, has been made in advancing the versatility of samarium(II) compounds, the lack of studies concerning the reactivity toward simple amides is surprising except in some special cases.[9] This should be attributed to their low reactivity. Herein we report our successful efforts for the development of novel SmI_2-mediated tandem reaction of sulfur-substituted aromatic lactams with carbonyl compounds, leading to the α-hydroxyalkylated products with *erythro*-selectivity.

Initial experiments have been performed on a coupling reaction promoted by SmI_2 between γ-hydroxy-,



Scheme 1.

Keywords: SmI_2; desulfurization; coupling reaction; lactam.

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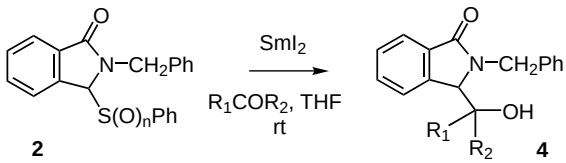
phenylthio-, or phenylsulfonyl-substituted phthalides and iodobutane with a variety of additives such as HMPA, $CuCl_2$, $FeCl_3$, or NiI_2[6b,10] in expectation of new C–C bond formation.[11] The reactions, however, did not proceed under any conditions even in the use of excess SmI_2. Next, we examined the same type of reactions employing similarly sulfur-substituted *N*-benzyllactams **2**[12] prepared from imides **1** (Table 1) and iodobutane, which, in turn, changed the results and unexpectedly gave the desulfurized lactam alone in high yield (up to 89%) without coupling adducts.

With the above desulfurization method in hand, we researched the tandem reaction followed by C–C bond formation of **2** employing more reactive aldehyde than haloalkane. The results from our survey are summarized in Table 1. To begin with, treatment of *N*-benzylphenylthiolactam **2a** with heptanal in the presence of 2 equiv. of SmI_2 at ambient temperature for 1 h rapidly provided the desired tandem reaction products **3** but in low yield (entry 1) due to the formation of the aldehyde-self-coupling compounds. The use of excess SmI_2 (3 equiv.), however, had a dramatic effect on the rate, giving **3** in 86% isolated yield within 5 min (entry 3). The same beneficial results were again obtained in reaction employing the phenylsulfonyllactam **2b** (80% in entry 4). We were delighted to find that 5 equiv. of this reagent (entry 5) could effect these reactions in excellent yield (98%) without byproducts except the aldehyde-dimerized substances. This procedure is also applicable for the production of a wide range of α-hydroxyalkylated lactams through replacement of the *N*-benzyl group by the larger diphenylmethyl (entry 7) or the smaller methyl functions (entries 8–13) together with a change from the sulfur- to the seleno-substituent in **2** (entry 6). Although the reason why such unusual desulfurization and subsequent coupling reactions were observed in the use of lactams is not clarified at present, the presence of a nitrogen atom in the substrate has a decisive role and is indispensable for these reactions.

We further found that the use of both aliphatic (entries 1–4 shown in Table 2) and sterically more hindered aromatic ketones (entries 5 and 6) also underwent fast reactions (5 min) to afford the corresponding desulfurized coupling products with good to high yields in

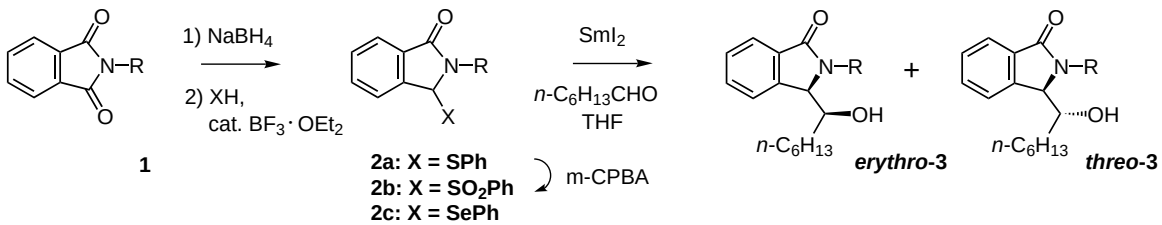
Table 2. SmI_2-promoted[a] tandem reactions of lactams **2** with ketones[a]



Entry	*n*	R_1	R_2	Yield (%)[b]
1	0	CH_3	CH_3	50
2	2	CH_3	CH_3	85
3	0	CH_3	*n*-C_3H_7	71
4	2	CH_3	*n*-C_3H_7	79
5	0	CH_3	Ph	72
6	2	CH_3	Ph	85

[a] Reactions employed 3 equiv. of SmI_2 and ketones, respectively.
[b] Isolated yield.

Table 1. SmI_2-promoted tandem reactions of lactams **2** with aldehyde[a]



Entry	X	R	SmI_2 (equiv.)	Temp. (°C)	Yield (%)[b]	*erythro*/*threo*[c]
1	SPh	CH_2Ph	2.0	rt	22	–
2	SO_2Ph	CH_2Ph	2.0	rt	42	–
3	SPh	CH_2Ph	3.0	rt	86	83/17
4	SO_2Ph	CH_2Ph	3.0	rt	80	79/21
5	SO_2Ph	CH_2Ph	5.0	rt	98	79/21
6	SePh	CH_2Ph	3.0	rt	58	–
7	SPh	$CHPh_2$	3.0	rt	39	55/45[d]
8	SPh	CH_3	3.0	−20	63	76/24[d]
9	SO_2Ph	CH_3	3.0	−20	69	68/32[d]
10	SPh	CH_3	3.0	0	71	82/18[d]
11	SO_2Ph	CH_3	3.0	0	73	84/16[d]
12	SPh	CH_3	3.0	rt	69	92/8[d]
13	SO_2Ph	CH_3	3.0	rt	90	92/8[d]

[a] All reactions employed 3.0 equiv. of heptanal.
[b] Isolated yield.
[c] Isolated ratio after chromatographic separation unless otherwise indicated and stereochemistry determined according to our preceding report.[8]
[d] Determined by ^1H NMR.

contrast to the fact that direct SmI_2-promoted reaction of phthalimides with ketones did not provide any desired coupling adduct.[8] This strategy will find convenient usage and proved to be a superior C–C bond formation method accompanying the desulfurization reaction.

In addition to the development of novel tandem reaction described here, we investigated the stereochemistry of these products, since the stereodefined construction of *threo*- or *erythro*-heterocyclic moieties with a hydroxyl-containing side chain attracts considerable attention due to their presence in the framework of natural products.[13]

It will particularly be of interest to note that decreasing the steric bulkiness of the *N*-substituents as well as raising the reaction temperature[14] up to rt led to an increase of the *erythro*-selectivity (from 55:45 to 92:8 as shown in Table 1) contrary to our previous *threo*-selective results[8] and the *erythro*/*threo* ratio of **3** is essentially independent of the leaving groups. The observed reverse stereochemical outcome of these reactions can be explained by consideration using the six-membered SmI_2-chelation models A and B[7b] containing nitrogen lone-paired electrons (Fig. 1). In the thermodynamically stable former the reaction progressed through coupling of the radical produced by desulfurization with a carbonyl compound from the same face of the smaller *N*-methyl group and SmI_2, avoiding the mutual steric repulsion between *N*- and aldehyde-alkyl groups. On the other hand, the fact that the steric bulkiness of the *N*-substituents and raising the reaction temperature affect the *erythro*-selectivity reversibly can be ascribed to the attack of the radical present in the other six-membered conformational isomer (Model B) on the carbonyl group, in which the *N*-larger functions prefer to be equatorial. In this case coupling reactions resulted in a decrease of the *erythro*-selectivity, since the aldehyde-alkyl group constituting the chelation structure could occupy both sides.

In conclusion, we have developed synthetically useful tandem SmI_2-mediated desulfurization and reductive coupling reactions that employ commercially available reagents. In addition, the success of these reversibly *erythro*-selective reactions together with our previous *threo*-selective results demonstrates the mechanistically fascinating duality of the lactam-employed coupling reactions for controlled carbon–carbon bond formation. Current efforts to expand the scope of coupling partners with this method as well as to elucidate the thermodynamic behavior and detailed mechanism of the reaction are in progress.

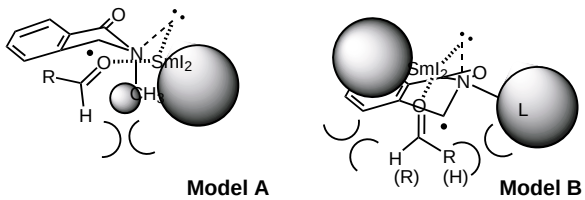


Figure 1. Potential stereocontrol elements.

Acknowledgements

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