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SmI_2-Promoted novel tandem elimination and coupling reactions of aliphatic imides with carbonyl compounds: application to the synthesis of *dl*-isoretronecanol

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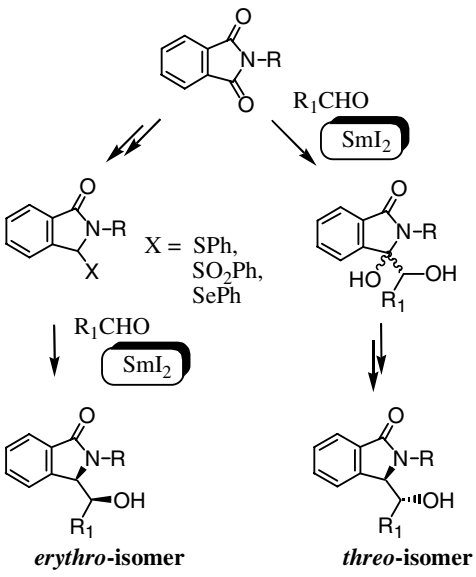
Abstract—Treatment of α-hetero-substituted cyclic imides with carbonyl compounds mediated by samarium(II) diiodide in the presence of HMPA was found to undergo novel tandem elimination and reductive coupling reactions to generate α-hydroxyalkylated imides in good to high yields. Stereochemistry of the coupling products was researched and the result that increasing the steric bulkiness of the N-substituents leads to an increase of *threo*-selectivity was observed. The mechanistic origins of this stereoselectivity are also briefly documented and the reaction was further applied to the convenient synthesis of a simple pyrrolizidine alkaloid, isoretronecanol.

Samarium(II) diiodide[1] 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 extremely *threo*-selective preparation of α-hydroxyalkylated aromatic lactams via the first pinacolic cross-coupling reaction between phthalimides and carbonyl compounds as shown in Scheme 1.[8] In addition, a reversibly *erythro*-selective method through SmI_2-mediated tandem elimination and coupling reactions of hetero-substituted aromatic lactams with carbonyl compounds was also developed.



Scheme 1.

These results demonstrate the mechanistically fascinating duality of aromatic lactam-employed coupling reactions for stereocontrolled carbon–carbon bond formation. Significant progress, thus, has been made in advancing the versatility of samarium(II) compounds, however, the lack of studies concerning the reactivity

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toward simple amides is surprising except in some special cases.[9] Especially no procedure starting with hetero-substituted aliphatic imides has appeared. This should be attributed to their low reactivity. Herein, we report our successful efforts for the development of a novel SmI_2-mediated tandem reaction of sulfur-substituted imides with carbonyl compounds, leading to the α-hydroxyalkylated products with *threo*-selectivity and its extensive application to the synthesis of a simple pyrrolizidine alkaloid, isoretronecanol.

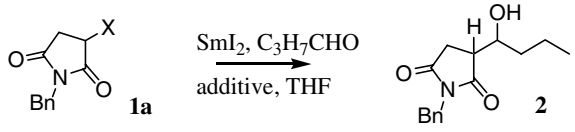
Initial experiments have been performed on a coupling reaction promoted by SmI_2 between *N*-benzyl α-, β-, or γ-phenylthio-substituted γ-lactams and butanal with a variety of additives such as HMPA, $CuCl_2$, $FeCl_3$, or NiI_2[6b,10] in expectation of new C–C bond formation.[11] The reactions, however, did not proceed under any conditions even in the use of excess SmI_2. Next, we examined the same type of reactions employing similar sulfur-substituted *N*-benzylsuccinimide derivative **1a**[12] prepared from maleimide with butanal, which, in turn, changed the results and gave the desired tandem desulfurization and coupling reaction products **2** (Table 1) but in unsatisfactory yield (entry 1) due to the formation of the aldehyde-self-coupling compounds. The use of additives, however, had a significant effect on the rate to give **2** (entries 2–4). After investigation of these reaction conditions, an expected enhancement was finally observed upon employing HMPA, which could effect these reactions strongly, leading to the coupling product **2** in 85% isolated yield (entry 5). The same beneficial result was again obtained in reaction with phenylsulfonylimide (entry 6). Furthermore, we were delighted to find that this procedure could be also applicable for the production of **2**[13] through replacement of the PhS leaving group to other sulfur-functions together with a change from the sulfur- to the seleno-substituent (entries 7–9). Although the reason why such unusual desulfurization and subsequent coupling reactions were observed only in the use of imides is not clarified at present, the presence of a nitrogen atom and two carbonyl groups in an aliphatic imide affecting the steric- and/or stereoelectronic effects would have a decisive role and indispensable for these reactions.

As shown in Table 2, we further found that the use of aliphatic ketones as well as other aldehydes (entries 1–6) and sterically more demanded aromatic ketone (entry 7) also underwent fast reactions to afford the corresponding tandem desulfurization–coupling products **3** with moderate to high yields, respectively. Thus, this strategy will find convenient usage and proved to be a superior C–C bond formation method with cyclic imides accompanying the desulfurization reaction.

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,[14] we next examined the possibility of stereoselective tandem coupling reactions. As shown in Table 3, it will particularly be of interest to note that increasing the steric bulkiness of the N-substituents under these conditions led to an increase of the *threo*-selectivity (up to 84:16, indicated in entries 8 and 9).[15] We also found that the *threo*/*erythro* ratio of **2** was essentially independent of the leaving groups together with the reaction temperature[17] based on our supporting experiments.

In light of the above outcome, we turned our attention to the short and convenient synthesis of a biologically active pyrrolizidine alkaloid, isoretronecanol.[18] Treatment of the *N*-MPM imide **1c** (R = MPM) with 4-benzyloxybutanal in the presence of SmI_2 (3 equiv) as described in Scheme 2 afforded the hydroxyalkylated *threo*-imide **10** as a moderate diastereoselective product (*threo*/*erythro* = 56:19, isolated yields, respectively[19]). After TBS-protection of *threo*-**10**, this was submitted to reduction with $NaBH_4$ to give the hydroxylactam **11**, fortunately with complete chemoselectivity. Accompanying formation of the other regioisomer and the

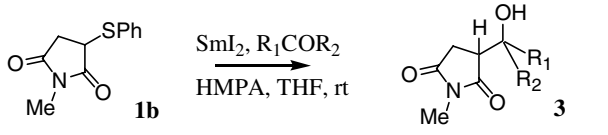
Table 1. Tandem desulfurization and coupling reactions of imides **1a**[a]



Entry	X	Additives (equiv)	Temp (°C)	Time (h)	Yield (%)[b]
1	PhS	—	rt	1	43
2	PhS	NiI_2 (0.01)	−20	3	48
3	PhS	*t*-BuOH (1.0)	−20	3	44
4	PhS	*t*-BuOH (1.0)	rt	1	65
5	PhS	HMPA (1.0)	rt	1	85
6	$PhSO_2$	HMPA (1.0)	rt	1	43
7	PhSe	HMPA (1.0)	rt	1	75
8	2-PyrS	HMPA (1.0)	rt	1	79
9	2-NaphthylS	HMPA (1.0)	rt	1	85

[a] All reactions employed 3.0 equiv of SmI_2 and 2.0 equiv of butanal, respectively.
[b] Isolated yield.

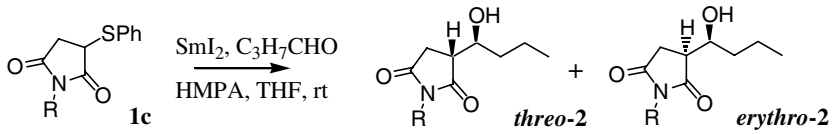
Table 2. Tandem desulfurization and coupling reactions of imides **1b**[a]



Entry	R_1	R_2	Time (h)	Yield (%)[b]
1	H	*n*-C_3H_7	1	82
2	H	*n*-C_6H_{13}	1	63
3	H	$(CH_3)_2CHCH_2$	1	66
4	H	$C_6H_5CH_2$	1	82
5	CH_3	CH_3	3	64
6	CH_3	CH_3CH_2	3	68
7	CH_3CH_2	CH_3CH_2	3	71
8	CH_3	C_6H_5	3	48

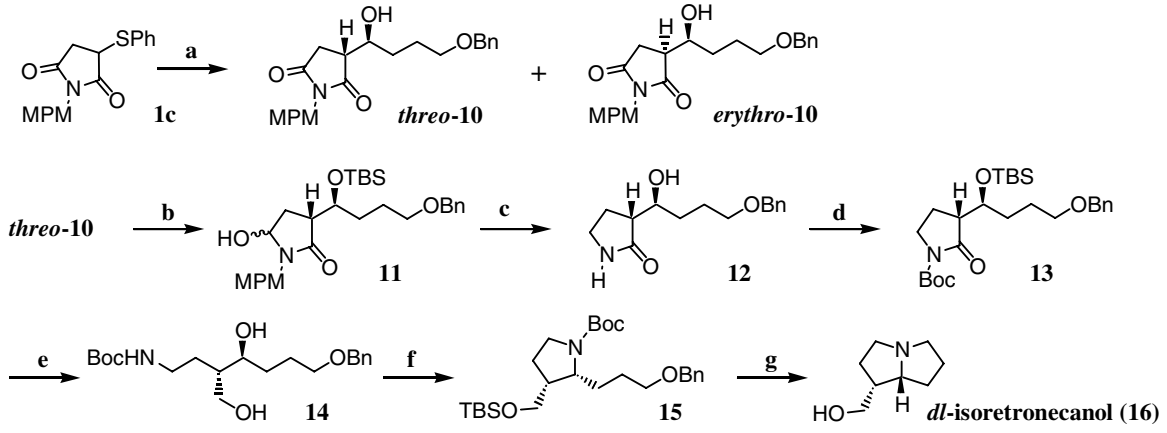
[a] All reactions employed 3.0 equiv of SmI_2, 2.0 equiv of carbonyl compounds, and 1.0 equiv of HMPA, respectively.
[b] Isolated yield.

Table 3. Stereoselective tandem desulfurization and coupling reactions of imides **1c**[a]



Entry	R (compound)	Time (h)	Yield (%)[b]	*threo*/*erythro*[c]
1	H	1	5	50:50
2	Me (**1b**)	1	82	65:35
3	Bn (**1a**)	1	87	71:29
4	MPM	1	76	64:36[d]
5	Ph	1	85	73:27
6	1-Naphthyl	2	59	72:28
7	$(m\text{-Bu}^t)_2$Ph	2	41	73:27
8	$CHPh_2$	2	59	84:16
9	$(p\text{-Bu}^t)$Ph	2	67	84:16

[a] All reactions employed 3.0 equiv of SmI_2, 2.0 equiv of butanal, and 1.0 equiv of HMPA, respectively.
[b] Isolated yield.
[c] Determined by ^1H NMR.
[d] Isolated ratio.



Scheme 2. Reagents and conditions: (a) $BnO(CH_2)_3CHO$, SmI_2, HMPA, THF; 56% (*threo*-**10**), 19% (*erythro*-**10**); (b) **1**, TBSCl, imidazole, DMF; 98%; **2**, $NaBH_4$, MeOH; quant.; (c) **1**, Et_3SiH, BF_3OEt_2, CH_2Cl_2, −40 °C; 82%; **2**, CAN, CH_3CN–H_2O (9:1); 98%; (d) **1**, TBSCl, imidazole, DMF; 90%; **2**, $(Boc)_2O$, DMAP, Et_3N, CH_2Cl_2; 99%; (e) **1**, $NaBH_4$, MeOH; quant.; **2**, Bu_4NF, THF; quant.; (f) **1**, TBSCl, Et_3N, CH_2Cl_2; 91%; **2**, MsCl, Et_3N, CH_2Cl_2; **3**, *t*-BuOK, THF; 82% (two steps); (g) **1**, H_2, Pd/C, EtOH; 94%; **2**, MsCl, Et_3N, CH_2Cl_2; **3**, TFA, CH_2Cl_2, 0 °C; 70% (two steps).

ring-opened amide alcohol was not observed. Then, **11** was readily effected by BF_3OEt_2-promoted deoxygenation with Et_3SiH followed by removal of the *N*-MPM group with cerium ammonium nitrate (CAN), leading to the *N*-H lactam **12** in 79% yield (four steps). For the purpose of the construction of a pyrrolizidine ring system, reduction of the *N*-Boc lactam **13** derived from **12** through protection of the two functional groups was performed to give the acyclic alcohol **14**, which was, in turn, reacted subsequently under cyclization conditions after chemoselective TBS-protection of the primary alcohol to provide the pyrrolidine **15** with the desired stereochemistry in 66% yield (seven steps from **12**). Finally, **15** thus obtained was submitted to successive reactions of debenzylation, mesylation, and TFA-induced Boc-deprotection followed by simultaneous cyclization of the resulting pyrrolidine intermediate to complete the synthesis of *dl*-isoretronecanol (**16**).[18]

In conclusion, we have developed synthetically useful tandem SmI_2-mediated elimination and reductive coupling reactions between α-hetero-substituted aliphatic imides and carbonyl compounds with satisfactory diastereoselectivity.

This procedure found an application in the new synthetic opportunity for biologically important pyrrolizidine and/or indolizidine alkaloids. Current efforts to expand the scope of the synthetic application to more complexed natural products such as a recently isolated amphorogynine family[20] are in progress.

Acknowledgments

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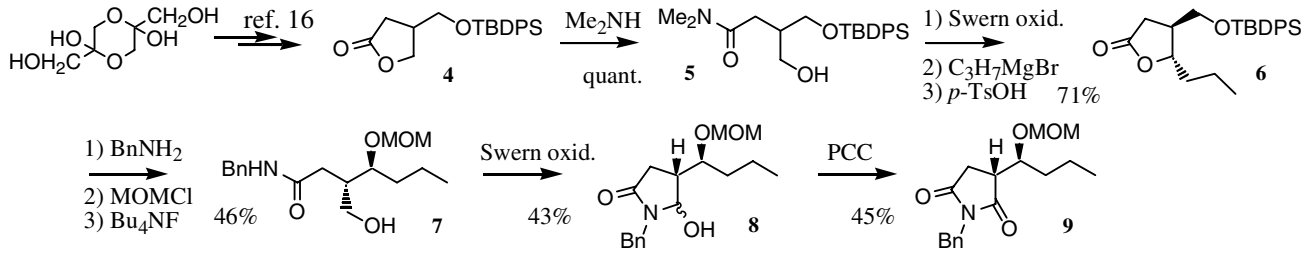
12. We have recently communicated the result that treatment of unsubstituted simple lactams with aldehydes in the presence of SmI_2 undergoes a novel N–C(hetero)-coupling reaction instead of the pinacolic-type one to generate N-α-hydroxyalkylated products, which could be applied to the synthesis of some biologically active indolizidine natural products.[9e]
13. We could not prepare the hydroxyalkylated imide **2** from direct coupling reaction of *N*-benzylsuccinimide with butanal in the presence of base (cf. Lozzi, L.; Ricci, A.; Taddei, M. *J. Org. Chem.* **1984**, *49*, 3408).
14. For examples, see: (a) Rieser, M. J.; Kozlowski, J. F.; Wood, K. V.; McLaughlin, J. L. *Tetrahedron Lett.* **1991**, *32*, 1137; (b) Baussanne, I.; Schwardt, O.; Royer, J.; Pichon, M.; Figadère, B.; Cavé, A. *Tetrahedron Lett.* **1997**, *38*, 2259; (c) Capon, R. J.; Barrow, R. A.; Rochfort, S.; Jobling, M.; Skene, C.; Lacey, E.; Gill, J. H.; Friedel, T.; Wadsworth, D. *Tetrahedron* **1998**, *54*, 2227.
15. Relative *threo*/*erythro* stereochemistry of **2** obtained was unambiguously proved after MOM-protection by comparing its spectral data with those of the synthesized compound **9** elaborated through crucial manipulations from the lactone **4** according to our previous reports[16] as shown below:



The other compounds were also estimated to have the same stereochemistry based on the similarity of its spectral data to those of *threo*-**2** (R = Bn).

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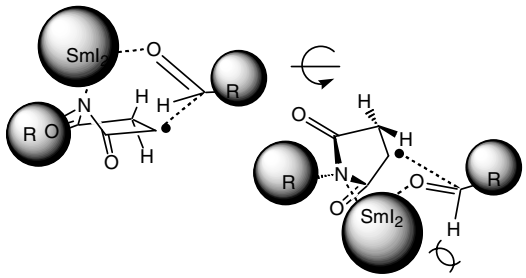
17. The observed stereochemical outcome of these reactions can be explained by consideration using six-membered SmI_2-chelation model containing nitrogen lone-paired electrons as described below. In the thermodynamically stable form in which the larger N-substituent would occupy the equatorial position, the reaction progressed through coupling of the radical produced by desulfurization with a carbonyl compound. In this case the attack of the radical present in the chelation model occurred from the face avoiding the mutual steric repulsion between SmI_2 and an aldehyde-alkyl group. In addition, the alkyl function would also prefer to be equatorial resulting in an increase of the *threo*-selectivity. Additional studies on the precise mechanistic origin of these reactions are in progress.



18. For recent examples of the synthesis of isoretronecanol, see: (a) Bertrand, S.; Hoffmann, N.; Pete, J.-P. *Eur. J. Org. Chem.* **2000**, 2227; (b) David, O.; Blot, J.; Bellec, C.; Fargeau-Bellassoued, M.-C.; Haviari, G.; Celerier, J.-P.; Lhommet, G.; Gramain, J.-C.; Gardette, D. *J. Org. Chem.* **1999**, *64*, 3122; (c) Konno, H.; Kishi, M.; Hiroya, K.; Ogasawara, K. *Heterocycles* **1998**, *49*, 33; (d) Knight, D. W.; Share, A. C.; Gallagher, P. T. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2089.

19. Whereas the major *threo*-isomer **10** only was employed for further synthetic sequence in this communication, minor *erythro*-**10** could be also taken advantage of the synthesis of the other stereoisomeric natural alkaloid, trachelanthamidine (laburnine).[18]

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