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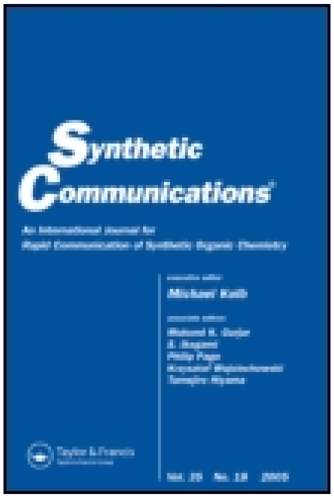

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A New Entry for the Preparation of Substituted Aromatic Carbonyl Compounds Mediated by Samarium(II) Iodide

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ABSTRACT

A new route to substituted aromatic lactones and lactams via SmI_2-promoted desulfurization is described. Direct replacement of the phenylthio substituent by hydroxyalkylated groups featuring the novel accessible process for the construction of continuous quaternary carbon centers could be accomplished when the same type of reactions was undertaken with carbonyl compounds in the presence of SmI_2.

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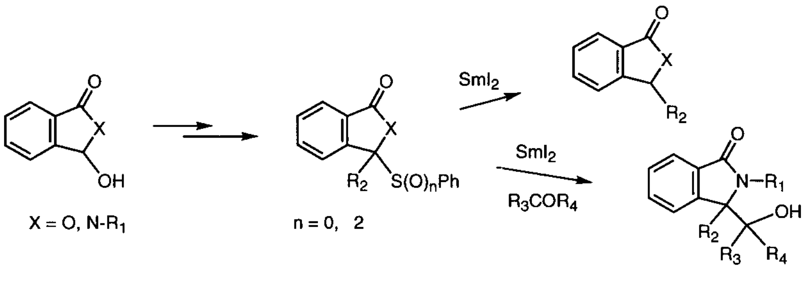
INTRODUCTION

During the past 10 years, many studies have been devoted to reactivity of Samarium(II) species[1] with a variety of carbonyl compounds (aldehydes, ketones, esters,[2] acid chlorides,[3] and acid anhydrides[4]) for ring closure and/or C–C bond formation reactions. In addition, intramolecular and intermolecular Barbier-type reactions with haloalkanes toward the carbonyl group of ketones[5] and imides[6] 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.[7] 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.[8] This low reactivity sometimes permits some selective transformations, for example Barbier-type reaction with amide ketones[9] or selective side chain introduction onto small peptides mediated by SmI_2.[10] Herein we wish to report our new successful entry for the preparation of substituted aromatic lactones and lactams via desulfurization mediated by SmI_2, and the coupling reactions with carbonyl compounds[11] under mild conditions, leading to the continuous quaternary α-hydroxyalkylated lactams (Sch. 1), since little effort with SmI_2 has been made for the utilization to desulfurization reactions.

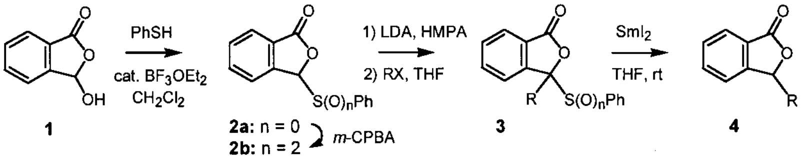


Scheme 1.

RESULTS AND DISCUSSION

Experiments have been initially performed on SmI_2-promoted desulfurization reaction employing γ-alkyl substituted derivatives **3** obtained from alkylation of sulfur-containing phthalides **2**.[12] The results from our survey are summarized in Table 1. To begin with, treatment of allylated phenylsulfonyl- or phenylthio-phthalide **3** with 2.0 equiv. of SmI_2 at ambient temperature provided the desired desulfurized product **4** but in low yield, respectively (Entries 1,6) together with the recovered starting material. The use of 3 equiv. of this reagent (Entries 2,7) or the presence of an additive such as HMPA (Entries 3,8) or *t*-BuOH (Entries 4,9) had an effect on the rate to some extent, giving **4** in moderate yield (up to 42%) within 5 min. Finally, we found that the use of excess SmI_2 (Entries 10,11) could effect these reactions in reasonable yield (up to 68%) without by products.

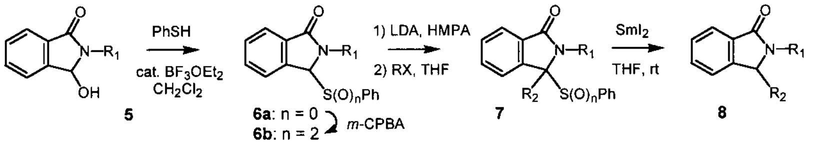
Table 1. SmI_2-promoted desulfurization reaction of lactones (**3**) after alkylation of (**2**).



Entry	n	R	Yield of **3** (%)[a]	SmI_2 (equiv.)	Additives (equiv.)	Yield of **4** (%)[a]
1	2	$CH_2{=}CHCH_2$	85	2.0	—	6
2	2	$CH_2{=}CHCH_2$	—	3.0	—	20
3	2	$CH_2{=}CHCH_2$	—	3.0	HMPA (3.0)	24
4	2	$CH_2{=}CHCH_2$	—	3.0	*t*-BuOH (1.0)	42
5	2	$CH_2{=}CHCH_2$	—	5.0	—	42
6	0	$CH_2{=}CHCH_2$	64	2.0	—	11
7	0	$CH_2{=}CHCH_2$	—	3.0	—	38
8	0	$CH_2{=}CHCH_2$	—	3.0	HMPA (3.0)	38
9	0	$CH_2{=}CHCH_2$	—	3.0	*t*-BuOH (1.0)	42
10	0	$CH_2{=}CHCH_2$	—	5.0	—	61
11	0	$CH_2{=}CHCH_2$	—	10.0	—	68
12	0	CH_3	92	5.0	—	32
13	0	CH_2Ph	90	5.0	—	37

[a] Isolated yield.

Table 2. SmI_2-promoted desulfurization reaction of lactams (**7**) after alkylation of (**6**).



Entry	n	R_1	R_2	Yield of **7** (%)[a]	SmI_2 (equiv.)	Additives (equiv.)	Yield of **8** (%)[a]
1	2	CH_2Ph	$CH_2{=}CHCH_2$	78	2.0	—	19
2	2	CH_2Ph	$CH_2{=}CHCH_2$	—	3.0	—	17
3	0	CH_2Ph	$CH_2{=}CHCH_2$	96	2.0	—	12
4	0	CH_2Ph	$CH_2{=}CHCH_2$	—	3.0	—	52
5	0	CH_2Ph	$CH_2{=}CHCH_2$	—	3.0	HMPA (3.0)	73
6	0	CH_2Ph	CH_3	96	3.0	HMPA (3.0)	53
7	0	CH_2Ph	CH_3	—	3.0	*t*-BuOH (1.0)	43
8	0	CH_2Ph	CH_3	—	3.0	HMPA (3.0)	72
9	0	CH_2Ph	CH_3	—	5.0	HMPA (3.0)	88
10	0	CH_2Ph	CH_2Ph	92	3.0	HMPA (3.0)	73
11	0	CH_2Ph	CH_2Ph	—	5.0	HMPA (3.0)	90
12	0	CH_3	$CH_2{=}CHCH_2$	96	5.0	HMPA (3.0)	93
13	0	CH_3	CH_3	92	5.0	HMPA (3.0)	84
14	0	CH_3	CH_2Ph	95	5.0	HMPA (3.0)	89

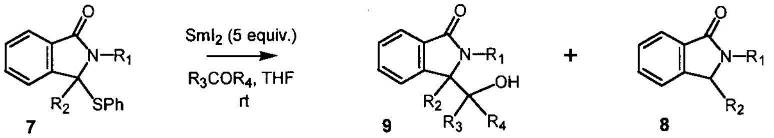
[a] Isolated yield.

Next, we examined the same type of reactions by the use of sulfur-substituted lactams **7** prepared from **5** in a similar manner as described above. As shown in Table 2, the reactions with allylated *N*-benzyl phenylsulfonyl lactam did not proceed in satisfactory yield when a small excess of SmI_2 were again used (Entries 1,2), whereas the desulfurization reactions of phenylthio derivative changed the results and rapidly brought about the desired product **8** in 52% yield under the same reaction conditions along with the starting lactam (Entry 4). The further beneficial result was obtained in reaction employing HMPA as an additive (Entry 5) to afford **8** in 73% isolated yield. Furthermore, it became apparent that this procedure was applicable for the production of a wide range of lactams through replacement of the γ-substituents together with a change of the *N*-functional groups. Especially, we were delighted to find that 5 equiv. of this reagent in the presence of HMPA (3.0 equiv.) effect these reactions in excellent yield (up to 93%) to provide various types of γ- and *N*-substituted lactams **8** (Entries 9,11–14).

Although an in-depth mechanistic investigation of the above experiments was not pursued, a tentative explanation of these results could be possible. Thus, the presence of the nitrogen atom in the substrate would stabilize the Sm(III) species obtained from subsequent reduction of the desulfurization-derived benzyl radical with the excess equiv. of SmI_2.

As a further illustration of the scope of the above outcome, we turned our attention to the construction of the quaternary carbon center via direct replacement of the sulfur substrate to alkyl groups. The reactions of lactam **7** with haloalkane did not proceed under any conditions even in the use of excess SmI_2. When **7** was, however, in turn treated with butanal (3.0 equiv.) in the presence of SmI_2 as shown in Table 3 (Entry 1), it afforded the desired coupling product **9** with the crucial hydroxyalkylated quaternary carbon center (41%) accompanying the formation of the normal desulfurized compound **8** (51%). It will be of interest to note that enhancement of the yield was observed upon employing the sterically more hindered ketones (up to 71%), leading to the various types of coupling products containing the continuous quaternary carbon centers (Entries 2,3,5,6).

Table 3. SmI_2-promoted coupling reactions of substituted lactams (**7**) with carbonyl compounds.[a]



Entry	R_1	R_2	R_3	R_4	Yield of **9** (%)[b]	Yield of **8** (%)[b]
1	CH_2Ph	CH_3	n-C_3H_1	H	41	51
2	CH_2Ph	CH_3	CH_3	CH_3	62	33
3	CH_3	CH_2Ph	CH_3	CH_3	47	51
4	CH_3	CH_3	n-C_3H_1	H	33	66
5	CH_3	CH_3	CH_3	CH_3	71	25
6	CH_3	CH_3	CH_3	n-C_3H_1	61	34

[a] All reactions employed 3.0 equiv. of carbonyl compounds.
[b] Isolated yield.

In summary, we have achieved a short and easily accessible entry not only for the preparation of a variety of substituted aromatic carbonyl compounds but also for the development of the coupling reaction with several carbonyl compounds via desulfurization mediated by SmI_2, leading to the continuous quaternary α-hydroxyalkylated lactams. This procedure will find more convenient alternative to existing desulfurization reactions and proved to be a superior quaternary C–C bond formation method.

EXPERIMENTAL

Typical experimental conditions (Entry 5 in Table 3). To a deep-blue THF (5 mL) solution prepared from Samarium metal powder (0.228 g, 1.53 mmol) and diiodomethane (0.393 g, 1.474 mmol) under Ar was added a solution of *N*-methyl-3-methyl-3-phenylthiophthalimidine (0.079 g, 0.295 mmol) and acetone (0.051 g, 0.885 mmol) in THF (1 mL) at 0°C. After the mixture was stirred for 1 h at room temperature, it was poured into a dilute HCl (4 mL) and extracted with ethyl acetate. The product was chromatographed after evaporation (eluted with hexane-ethyl acetate (1:1)) to give *N*-methyl-3-methyl-3-(1-methyl-1-hydroxyethyl)phthalimidine (0.046 g, 0.21 mmol) in 71% and *N*-methyl-3-methylphthalimidine (0.012 g, 0.074 mmol) in 25% yields, respectively.

***N*-benzyl-3-methyl-3-(1-hydroxybutyl)phthalimidine (Entry 1 in Table 3).** IR (thin film) 3255, 1661, 766, 701 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.62–0.96 (t, $J = 6.6$ Hz, 3H), 0.96–1.62 (m, 4H), 1.42 (s, 3H), 3.71 (br, 1H), 4.01 (t, $J = 6.6$ Hz, 1H), 4.83 (s, 2H), 7.05–7.62 (m, 8H), 7.71–8.13 (m, 1H). Anal. calcd. for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.75; H, 7.42; N, 4.39.

***N*-benzyl-3-methyl-3-(1-methyl-1-hydroxyethyl)phthalimidine (Entry 2 in Table 3).** IR (thin film) 3266, 1656, 760, 705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (s, 3H), 1.35 (s, 3H), 1.51 (s, 3H), 2.12 (br, 1H), 4.98 (s, 2H), 7.11–7.68 (m, 8H), 7.75–7.82 (m, 1H). Anal. calcd. for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.29; H, 7.11; N, 4.71.

***N*-methyl-3-benzyl-3-(1-methyl-1-hydroxyethyl)phthalimidine (Entry 3 in Table 3).** IR (thin film) 3286, 1672, 756, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.01 (s, 3H), 1.33 (s, 3H), 2.38 (br, 1H), 3.20 (s, 3H), 3.48, 3.53 (2s, 2H), 7.48–7.05 (m, 5H), 7.15–7.81 (m, 4H). Anal. calcd. for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.38; H, 7.09; N, 4.66.

***N*-methyl-3-methyl-3-(1-hydroxybutyl)phthalimidine (Entry 4 in Table 3).** IR (thin film) 3266, 1655, 746, 703 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.59–0.93 (t, $J = 6.6$ Hz, 3H), 0.96–1.75 (m, 4H), 1.36, 1.45 (2s, 3H), 2.49 (br, 1H), 2.88, 3.01 (2s, 3H), 3.71 (br, 1H), 4.05 (t, $J = 5.6$ Hz, 1H), 7.15–7.56 (m, 3H), 7.61–7.94 (m, 1H). Anal. calcd. for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.94; H, 8.19; N, 6.13.

***N*-methyl-3-methyl-3-(1-methyl-1-hydroxyethyl)phthalimidine (Entry 5 in Table 3).** IR (thin film) 3250, 1668, 756, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (s, 3H), 1.18 (s, 3H), 1.50 (s, 3H), 2.62 (br, 1H), 3.07 (s, 3H), 7.03–7.50 (m, 3H), 7.60–7.92 (m, 1H). Anal. calcd. for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.40; H, 7.79; N, 6.31.

***N*-methyl-3-methyl-3-(1-methyl-1-hydroxybutyl)phthalimidine (Entry 6 in Table 3).** IR (thin film) 3286, 1659, 766, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.55–0.85 (t, $J = 6.6$ Hz, 3H), 0.96–1.45 (m, 4H), 0.85, 1.18 (2s, 3H), 1.50 (s, 3H), 2.45 (br, 1H), 3.03 (s, 3H), 7.15–7.61 (m, 3H), 7.61–7.91 (m, 1H). Anal. calcd. for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.96; H, 8.47; N, 5.71.

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