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Lewis acid-promoted tandem desulfurization and hydroxylation of γ-phenylthio-substituted lactams: novel synthetic strategy of isoindolobenzazepine alkaloid, chilenine

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Abstract—Treatment of a variety of alicyclic and aromatic γ-phenylthio-substituted lactams with Lewis acids such as cuprous or cupric halides in aqueous solution at rt was found to undergo novel tandem desulfurization and hydroxylation reactions to generate γ-hydroxylated lactams without the ring-opened products in extremely high yields, respectively. This process was further applied to the total synthesis of an isoindolobenzazepine alkaloid, chilenine, by featuring the elaboration of the functionalized phthalimide derivative.

Due to their well documented and useful structural features for the synthesis of biologically active compounds, there has been increasing interest in the utilization of γ-phenylthio-substituted lactams as crucial and key intermediates. Thus, a number of efficient techniques to utilize such compounds have been accomplished and many advantageous reports have appeared for C–C bond formation, e.g. thionium/*N*-acyliminium ion cyclization cascade,[1a] Lewis acid-mediated allylation,[1b] intramolecular radical cyclization,[1c] direct replacement of the sulfur group by the alkyl function employing organo-zinc reagents,[1d] and successive alkylation–desulfurization sequence for the introduction of the alkyl side chain[1e] together with the well known desulfurization protocol.[1f,g] In this connection recent disclosures from this laboratory have demonstrated SmI_2-promoted tandem desulfurization and high *erythro*-selective coupling reactions of aromatic lactams with carbonyl compounds.[2] Although significant progress, thus, has been made in advancing the versatility of sulfur-substituted lactams, the lack of studies concerning the reactivity toward simple Lewis acids is surprising except the lactol type of compounds.[3] Herein we wish to report our successful efforts for the development of novel Lewis acid-mediated tandem reaction of phenylthio-substituted alicyclic and aromatic lactams in aqueous media, leading to the γ-hydroxylated products, whose process was further applied to the convenient total synthesis of isoindolobenzazepine natural product, chilenine.

Initial experiments have been performed on tandem desulfurization and hydroxylation reactions of simple γ-phenylthio-substituted alicyclic lactams **1** in the presence of a variety of Lewis acid-additives such as $MgBr_2$, $SmCl_3$, or $CeCl_3$ in aqueous solution (CH_3CN–H_2O = 9:1) at ambient temperature. The reactions, however, did not proceed under any conditions and recovered the starting material **1**. Next, we examined the same type of reactions employing another Lewis acids. The results from our survey are summarized in Table 1. Whereas the reactions with $FeCl_3$ and CuI gave the desired hydroxylated product **2**, but in low yield, respectively (entries 1, 2), use of CuCl or CuBr had a dramatic effect on the rate and smoothly brought about the target compound **2** in almost quantitative yields (entries 6–8) under these mild and readily available conditions. We were delighted to find that the same beneficial results were again obtained in reaction employing quaternary substituted phenylthiolactams containing aliphatic and aromatic alkyl side chains (entries 9,10) by replacement of the solvent system from CH_3CN–H_2O (9:1) to 1,4-dioxane–H_2O (2:1) without by-products such as ring-opened ketoamides derived from **2**.

As shown in Table 2, we further found that the use of β-substituted and α,β-disubstituted γ-phenylthiolactams **3** (entries 1, 2) as well as the aromatic one (entry 3) underwent convenient reactions to afford the corre-

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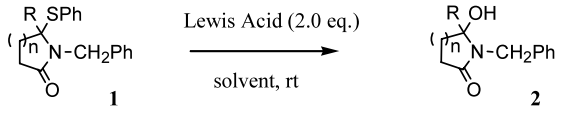
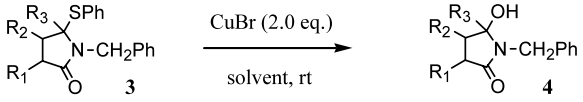
Table 1. Tandem desulfurization and hydroxylation reactions of γ-phenylthiolactams **1**



Entry	*n*	R	Lewis acid	Conditions[a]	Time (days)	Yield (%)[b]
1	1	H	$FeCl_3$	A	1	36
2	1	H	CuI	A	1	8
3	1	H	CAN	A	1	81
4	1	H	$CuBr_2$	A	1	65
5	1	H	$CuCl_2$	A	1	>99
6	1	H	CuCl	A	1	>99
7	1	H	CuBr	A	1	>99
8	2	H	CuBr	A	1	>99
9	1	$CH_3(CH_2)_3$	CuBr	B	0.1	84[c]
10	1	C_6H_5	CuBr	B	0.1	97[c]

[a] Conditions A performed in CH_3CN–H_2O (9:1) and conditions B performed in 1,4-dioxane-H_2O (2:1), respectively.
[b] Isolated yield.
[c] Reactions under conditions A gave the corresponding ring-opened ketoamides as a main product derived from the quaternary hydroxylactams **2** in 23% (R: butyl) and 53% (R: phenyl) yields, respectively.

Table 2. Tandem desulfurization and hydroxylation reactions of functionalized γ-phenylthiolactams **3**



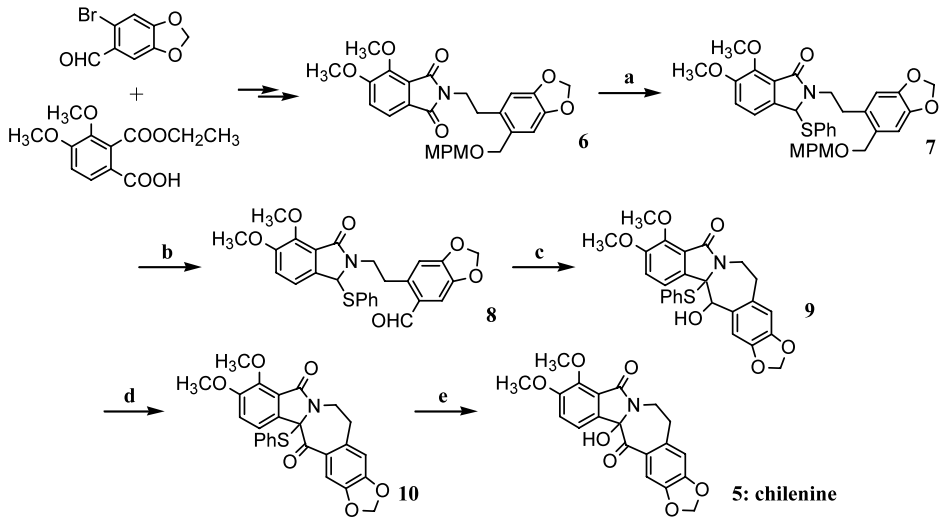
Entry	R_1	R_2	R_3	Conditions[a]	Time (days)	Yield (%)[b]
1	H	OBn	H	A	3	>99[d]
2	OBn	OBn[c]	H	A	1	>99[d]
3	-C_6H_4-		H	A	1	98
4	H	OBn	$CH_3(CH_2)_3$	B	1	92[d]
5	H	OBn	C_6H_5	B	1	90[d]
6	OBn	OBn[c]	$CH_3(CH_2)_3$	B	1	86[d]
7	OBn	OBn[c]	C_6H_5	B	1	98[d]
8	-C_6H_4-		$CH_3(CH_2)_3$	A	0.1	>99
9	-C_6H_4-		C_6H_5	A	0.1	>99

[a] Conditions A performed in CH_3CN–H_2O (9:1) and conditions B performed in 1,4-dioxane–H_2O (4:1), respectively.
[b] Isolated yield.
[c] *d.l*-Tartaric acid-derived lactam **3** was used.
[d] Unfortunately, these reactions resulted in the almost non-stereoselective formation of **4** except the case of entry 1, which indicated the moderate *trans*-selectivity (*cis*:*trans* (to the β-OBn group) = 16:84, isolated ratio).

sponding desulfurized hydroxylactams in quite high yields, respectively. In addition, it will be particularly of interest to note that a variety of both sterically more hindered and unstable quaternary hydroxy-substituted lactams **4** with β- or α,β-disubstituents[4a–f] could be obtained again under these conditions (entries 4–9) irrespective of their structures.

Thus, this procedure is applicable for the production of a wide range of γ-hydroxylated lactam derivatives and provides an easily accessible alternative to the existing synthetic method of these types of compounds, since, to the best of our knowledge, one approach to the direct preparation of γ-hydroxylactams **2** or **4** through nucleophilic addition of organometallic reagents to cyclic imides has been demonstrated.[4]

In light of the above outcome, we turned our attention to the development of novel and convenient synthetic method of isoindolobenzazepine alkaloid, chilenine (**5**),[5] whose structure incorporating the 3*H*-3-benzazepine moiety and equally an isoindolinone ring system is architecturally sophisticated and possesses the real and potential biological properties.[6] As summarized in Scheme 1, the functionalized imide **6** obtained from 3,4-dimethoxy-2-ethoxycarbonylbenzoic acid and bromopiperonal based on our reported method,[6f] was reduced with DIBAL-H[7] at low temperature to provide the hydroxylactam intermediate, which was quickly treated with thiophenol under acidic conditions, leading to the phenylthiolactam **7** in 61% yield (two steps) regioselectively (96:4, determined by ^1H NMR). When the deprotection of the MPM-group in **7** was performed by the use of DDQ, the desired aldehyde



Scheme 1. *Reagents and conditions*: (a) **1**, DIBAL-H, THF, −78°C; **2**, PhSH, BF_3OEt_2, CH_2Cl_2; 61% (two steps); (b) DDQ, CH_2Cl_2–H_2O (10:1); 97%; (c) LiHMDS, HMPA, THF, −78 to 0°C; 65%; (d) TPAP, NMO, CH_2Cl_2; 78%; (e) CuBr, CH_3CN–H_2O (1:1); 83%.

derivative **8** could be obtained directly. This was successively effected by intramolecular cyclization reaction under basic conditions to provide the corresponding product **9** possessing the benzazepine structure. Although the oxidation of the hydroxyl function in **9** with PCC or Swern-oxidation reagents gave inseparable mixtures, use of TPAP (tetrapropylammonium perruthenate)[8] in the presence of NMO brought about the desired ketone **10** in satisfactory yield without the sulfur-oxidized compound. Finally, **10** was subjected to the tandem desulfurization and hydroxylation reactions with CuBr in aqueous media at ambient temperature to complete the total synthesis of chilenine **5** in 83% isolated yield. The spectral data of synthesized **5** were completely identical with those of the reported natural substance.[5a]

In summary, we have disclosed herein the instructive example of the Lewis acid-mediated tandem reaction of desulfurization and hydroxylation in aqueous solution, whose process found application in the novel synthetic strategy of a structurally sophisticated and biologically important isoindolobenzazepine alkaloid and will be widely applicable to the synthesis of other fused alkaloidal natural products such as new antitumor antibiotics, UCS 1025 series[9] containing a quaternary hydroxyl group α to the nitrogen.

Acknowledgements

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