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A Ce(III)-catalyzed expeditious multicomponent stereoselective synthesis of 3-mercapto-2(1*H*)-pyridinones

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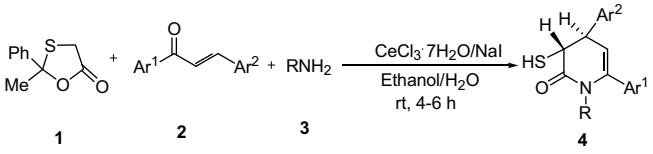
ABSTRACT

A novel Ce(III)-catalyzed, convenient, expeditious, and diastereoselective synthesis of 3-mercapto-2(1*H*)-pyridinones via one-pot, [3+2+1] three-component coupling reactions of chalcones, 2-methyl-2-phenyl-1,3-oxathiolan-5-one, and amines is reported. The synthesis involves sequential Michael addition, condensation, and ring transformation. Ambient temperature, operational simplicity, use of an environmentally clean catalyst, high yields, and diastereoselectivity are the key features of the present synthetic protocol.

The first synthesis of 3-mercapto-2(1*H*)-pyridinone was reported in 1996 starting from 2-aminopyridine via a number of steps.[1] However, until now there has been no report on the synthesis of hydrogenated and/or substituted analogues of 3-mercapto-2(1*H*)-pyridinone, which are the target molecules of the present investigation and desirable for expediting the synthesis of chemically and pharmacologically interesting azaphenoxathiines and related compounds.[2]

In general, multicomponent reactions (MCRs) are of significant academic, economic, and ecological interest because they address fundamental principles of synthetic efficiency and rational design. The development of novel MCRs has become an increasingly active area of research, that offers chemical scaffolds and combinatorial libraries in drug discovery efforts,[3–8] and has several advantages over conventional linear type syntheses.[9–13] Lewis acid-catalyzed multicomponent organic transformations are gaining increasing popularity due to their economic and ecological efficacy.[14] Ce(III)-derived Lewis acids have been used extensively in organic syntheses because of their water tolerance, non-toxicity, and ready availability at low cost.[15]

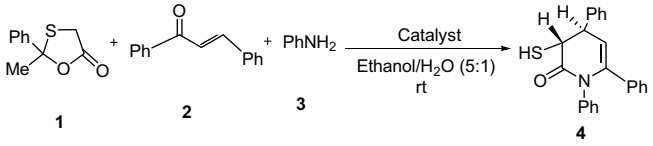
Heterocycles incorporating a 2(1*H*)-pyridinone framework constitute an extensively studied class of compounds owing to their diverse biological activities ranging from anti-HIV,[16] antibacterial,[17–19] and antifungal[20] to free radical scavenging.[21,22] Of these, cycloproxalamine (Loprox) is approved by the FDA as a broad spec-



1 2 3 4

Scheme 1. Three-component synthesis of **2** (1*H*)-pyridinones **4**.

Table 1
Screening of the Lewis acid-catalyst



1 2 3 4

Entry	Catalyst[a]	Time (h)	Yield[b] (%)	*anti*/*syn*[c]
1	$AlCl_3$	8	38	74:26
2	$TiCl_4$	7	45	84:16
3	$Ce_2(SO_4)_3$	6	60	86:14
4	$Ce_2(SO_4)_3{\cdot}8H_2O$/NaI (1:1)	7	73	90:10
5	$CeCl_3{\cdot}7H_2O$	7	67	87:13
6	$CeCl_3{\cdot}7H_2O$/NaI	6	88	95:5

[a] Catalyst loading was 20 mol %.
[b] Yield of isolated and purified products.
[c] As determined by ^1H NMR spectroscopy of the crude products.

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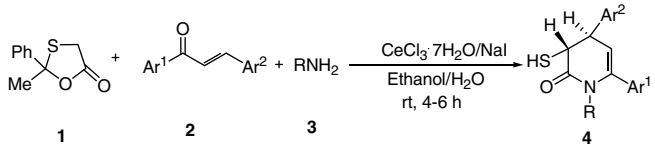
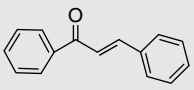
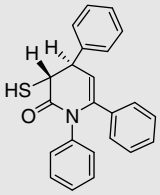
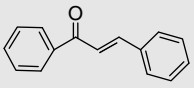
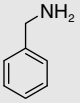
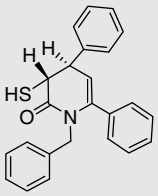
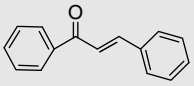
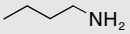
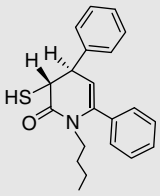
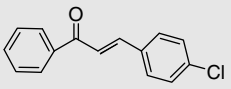
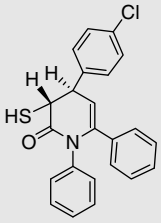
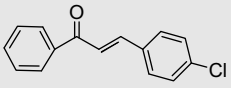
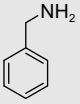
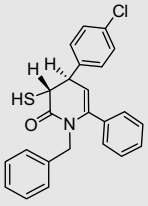
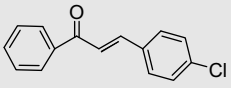
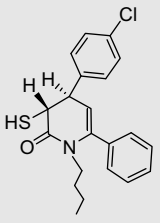
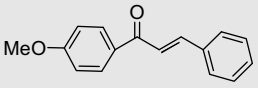
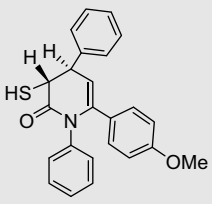
Table 2
Lewis acid-catalyzed stereoselective synthesis of 3-mercapto-2(1*H*)-pyridinones at room temperature

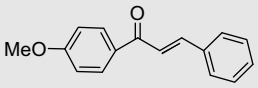
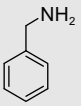
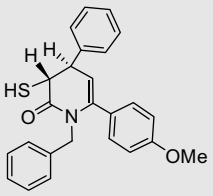
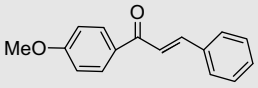
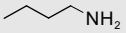
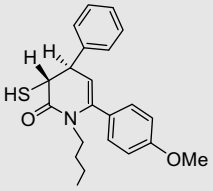
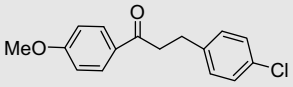
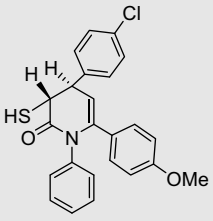
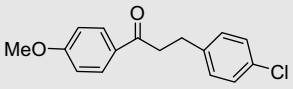
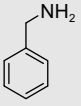
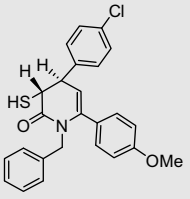
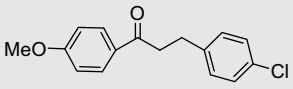
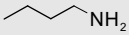
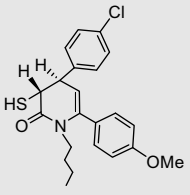


1 2 3 4

Entry	Chalcone **1**	Amine **3**	Product **4**	Yield[a,b] (%) (time[c] h)	*anti*/*syn*[d]
1				88 (6)	95:5
2				89 (5)	94:6
3				80 (4)	93:7
4				89 (6)	96:4
5				91 (5)	95:5
6				81 (4)	93:7
7				85 (6)	94:6

(*continued on next page*)

Table 2 (*continued*)

Entry	Chalcone **1**	Amine **3**	Product **4**	Yield[a,b] (%) (time[c] h)	*anti*/*syn*[d]
8				84 (5)	96:4
9				78 (5)	94:6
10				86 (6)	97:3
11				82 (5)	93:7
12				79 (5)	94:6

[a] Yield of isolated and purified products.
[b] All compounds gave C, H, and N analyses ±0.38% and satisfactory spectral (^{1}H NMR, ^{13}C NMR, and EIMS) data.
[c] Stirring time at room temperature.
[d] As determined by ^{1}H NMR of the crude products.

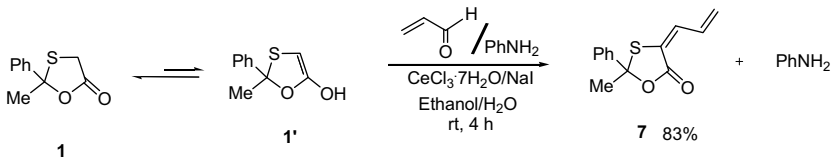
trum antifungal drug and is presently in clinical use for the treatment of various skin diseases.[23] Polysubstituted 2(1*H*)-pyridinones are of special interest due to their anxiolytic activity with improved side effect profiles.[24] In addition, dihydro and tetrahydro derivatives of 2(1*H*)-pyridinone have been applied as scaffolds for the construction of constrained amino acids.[25–28]

To date, the combinatorial preparation of pyridine and pyridinones was achieved via the synthesis of dihydropyridines (Hanztsch condensation).[29–34] However, even this route sets severe constraints on the substitution patterns of the pyridine and their derivatives. Indeed, compounds prepared by this method incorporate an acyl group and a carbonyl group at the 3 and 5 positions. In view of the above points and our efforts to develop new one-pot stereoselective cyclization processes,[35] we herein report an original and practical stereocontrolled synthetic route to hithertho unknown 3-mercapto-2(1*H*)-pyridinones **4** (Scheme 1).

For this purpose, we utilized the mercaptoacetyl transfer agent 2-methyl-2-phenyl-1,3-oxathiolan-5-one **1**[35e] which leads to heteroannulation and is the cornerstone of the present synthesis. As regards the choice of catalyst, we tested several Lewis acid-catalysts, and among these, the best result was obtained with $CeCl_3{\cdot}7H_2O$/NaI (1:1) (Table 1, entry 6). This is in conformity with the earlier observation that the catalytic activity of $CeCl_3{\cdot}7H_2O$ increases dramatically in the presence of an iodide source, such as NaI,[36] owing to the formation of a complex which exhibits stronger Lewis acid character than $CeCl_3{\cdot}7H_2O$. The optimum catalyst loading for $CeCl_3{\cdot}7H_2O$/NaI was found to be 20 mol %. A decrease in the catalyst amount decreased both the yields and the diastereoselectivity considerably.

We next examined the effect of solvents on the present three-component coupling reaction and found that among EtOH, MeCN, CH_2Cl_2, EtOH/H_2O (5:1), MeCN/H_2O (5:1), and H_2O, EtOH/H_2O (5:1) was the best solvent system in terms of the yield as well as diastereoselectivity. It was noted that a higher reaction temperature, for example, in a refluxing solvent instead of at rt, led to decreased diastereoselectivity without any appreciable effect on the yield.

In order to investigate the substrate scope of the reaction, different α,β-unsaturated ketones (chalcones) were reacted with various amines under the optimized reaction conditions. The yields

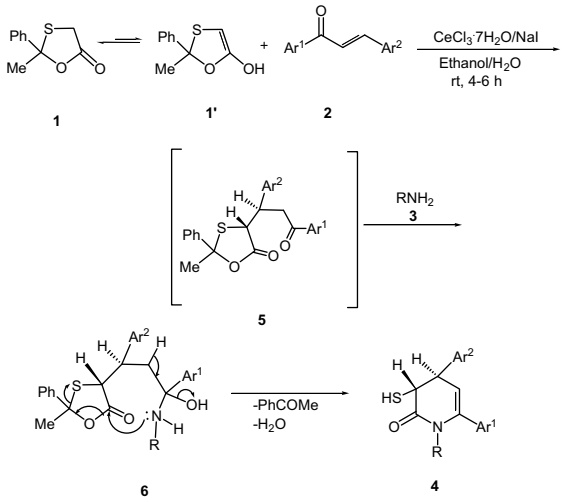


Scheme 2. Reaction of acrolein with **1**.

and diastereoselectivities were consistently good (Table 2), the highest yield being 91% (Table 2, entry 5) and the best trans diastereoselectivity being 97% (Table 2, entry 10). However, in the case of α,β-unsaturated aldehydes such as acrolein, the reaction suffered from regiochemical restriction caused by competing 1,2- versus 1,4-addition and in this case, alkenylidene **7** was isolated in 83% yield (Scheme 2).

The present optimized synthesis involves stirring of a mixture of 1,3-oxathiolan-5-one **1**, chalcone **2**, amine **3**, and $CeCl_3{\cdot}7H_2O$/NaI in EtOH/H_2O (5:1) at room temperature for 4-6 h to afford **2** (1*H*)-pyridinone **4** in 78–91% yields with 93–97% diastereoselectivity in favor of the trans isomer as determined by ^{1}H NMR spectroscopy (Table 2).[37] In the trans isomer protons 3-H and 4-H are axial as indicated by their coupling constants ($J_{3,4}$ = 9.8 Hz, J_{trans}). The trans stereochemistry of **4** was also supported by the absence of any appreciable NOE between 3-H and 4-H. The diastereomeric ratios in the crude isolates were checked by ^{1}H NMR to note any inadvertent alteration of these ratios during subsequent purification. The transition state leading to the formation of Michael adducts **5** adopts the most stable *anti*-conformation about the ensuing C–C bond. Thus, **5** are formed with high *anti*-diastereoselectivity, which is also retained in 3-mercapto-2(1*H*)-pyridinones **4** as the chiral carbons of **5** incorporated in products **4** are not involved in any bond breaking/formation (Scheme 3).

The formation of **4** may tentatively be rationalized by the conjugate addition of 1,3-oxathiolan-5-one **1** to chalcone **2** followed by condensation of the resulting Michael adduct **5** with amine **3** and ring transformation to afford the final product **4** (Scheme 3). This presumption is supported by the observation that Michael adduct **5** could be isolated in 83% yield when the reaction of **1** and **2** was performed in the absence of amine **3**, and that **5** could be converted into **4** in quantitative yield on treatment with amine **3** under the same reaction conditions. Once adducts **5** are formed, there is no chemoselectivity problem in their condensation reaction with amines **3** because the attack of **3** on the acyclic C=O followed by that on the cyclic C=O (Scheme 3) or vice versa would lead to the same products **4**, which we have obtained. It is noteworthy that acetophenone, which was used to activate mercaptoacetic acid to give the mercaptoacetylating agent **1**, was removed during the reaction yielding **4** without requiring any additional deprotection step.



Scheme 3. A plausible mechanism for the formation of **4**.

In summary, we have developed a novel Ce(III)-catalyzed three-component diastereoselective protocol for the synthesis of various potentially pharmacologically useful 3-mercapto-2(1*H*)-pyridinones. This one-pot synthesis is operationally simple, high yielding, and is performed at room temperature utilizing readily available starting materials, and may find application in organic synthesis.

Acknowledgment

We sincerely thank SAIF, CDRI, Lucknow, for providing microanalyses and spectra.

References and notes

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37. *General procedure for the synthesis of 3-mercapto-2(1H)-pyridinones* **4**: A mixture of 1,3-oxathiolan-5-one (5 mmol), chalcone **2** (5 mmol), aromatic amine **3** (5 mmol), $CeCl_3{\cdot}7H_2O$ (1 mmol), and NaI (1 mmol) in ethanol (25 mL) was stirred at room temperature for 4–6 h. After completion of the reaction, as indicated by TLC (hexane/EtOAc, 8:2, v/v), the solvent was evaporated under reduced pressure and the residue thus obtained was extracted with ether (3 × 15 mL). The extract was evaporated to leave a crude product which was recrystallized from ethanol to afford a diastereomeric mixture (>93:<7; in the crude products the ratio was >95:<5 as indicated by ^{1}H NMR spectroscopy). The product on second recrystallization from ethanol furnished analytically pure pale yellow crystals of a single diastereomer **4**, which was assigned the trans stereochemistry on the basis of ^{1}H NMR spectra. Physical data of representative compounds: (Table 2, entry 1): Pale yellow crystals. yield 88%, mp 168–169 °C. IR (KBr) ν_{max} 3010, 2588, 1677, 1620, 1602, 1512, 1288, 749, 703 cm^{-1}. ^{1}H NMR (400 MHz; DMSO-d_6 + D_2O) δ: 3.92 (d, 1H, J = 9.8 Hz, 3-H), 4.04 (dd, 1H, J = 9.8 Hz, 5.8 Hz, 4-H), 5.91 (d, 1H, J = 5.8 Hz, 5-H), 7.12–7.80 (m, 15H$_{arom}$). ^{13}C NMR (100 MHz; DMSO-d_6 D_2O), δ: 39.3, 46.4, 114.2, 125.8, 126.7, 127.5, 128.3, 129.2, 130.3, 131.2, 131.9, 132.8, 133.5, 134.3, 135.4, 143.0, 167.1. EIMS (m/z): 357. Anal. Calcd For $C_{23}H_{19}NOS$: C, 77.28; H, 5.36; N, 3.92. Found: C, 76.94; H, 5.12; N, 4.23 (Table 2, entry 4). Pale yellow liquid, yield 89%, mp 186–188 °C. IR (KBr) ν_{max} 3014, 2590, 1679, 1625, 1598, 1512, 1283, 856 cm^{-1}. ^{1}H NMR (400 MHz; DMSO-d_6 + D_2O) 3.95 (d, 1H, J = 9.8 Hz, 3-H), 4.06 (dd, 1H, J = 9.8, 5.8 Hz, 4-H) 5.92 (d, 1H, J = 5.8 Hz, 5-H), 7.11–7.85 (m, 14H$_{arom}$). ^{13}C NMR (100 MHz; DMSO-d_6 + D_2O) δ: 39.5, 46.5, 114.4, 125.9, 126.8, 127.5, 128.4, 129.3, 130.2, 131.1, 131.9, 132.9, 133.7, 134.5, 135.4, 143.2, 167.2. EIMS (m/z): 391. Anal. Calcd for $C_{23}H_{18}ClNOS$: C, 70.49; H, 4.63; N, 3.57. Found: C, 70.81; H, 4.94; N, 3.90 (Table 2, entry 7). Pale yellow crystals, yield 85%, mp 175–177 °C. IR (KBr) ν_{max} 3010, 2585, 1672, 1623, 1600, 1515, 1280,852 cm^{-1}. ^{1}H NMR (400 MHz; DMSO-d_6 + D_2O) δ: 3.81 (s, 3H, OMe), 3.90 (d, 1H, J = 9.8 Hz, 3-H), 4.01 (dd, 1H, J = 9.8, 5.8 Hz, 4-H), 5.86 (d, 1H, J = 5.8 Hz, 5-H), 7.10–7.81 (m, 14H$_{arom}$). ^{13}C NMR (100 MHz; DMSO-d_6 + D_2O) δ: 39.2, 46.2, 54.8, 114.1, 125.7, 126.9, 127.6, 128.4, 129.2, 130.1, 131.3, 132.0, 132.9, 133.7, 134.8, 135.6, 143.1, 167.0. EIMS (m/z): 387. Anal. Calcd for $C_{24}H_{21}NO_2S$: C, 74.39; H, 5.46; N, 3.61. Found: C, 74.76; H, 5.15; N, 3.30.