Triethylamine-Catalyzed Synthesis of Oxazepine from Maleamic Acids

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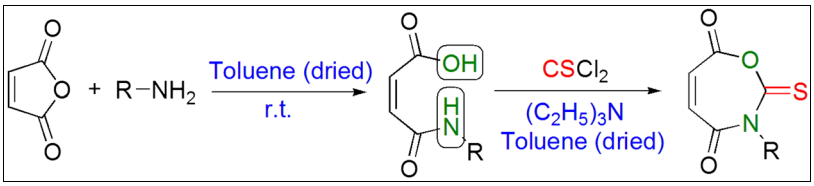

2-Thioxo-1,3-oxazepine-4,7-dione compounds were obtained via triethylamine-catalyzed condensation of maleamic acids with thiophosgene under anhydrous conditions. This method features relatively a simple methodology, use of inexpensive reagents, convenient operating conditions and high yields.

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INTRODUCTION

Seven-membered ring systems containing two heteroatoms oxazepines (N and O) and their aryl-annelated (benzoxazepines) and structural analogues diazepines (N and N) and thiazepines (N and S) occupy an important place in the realm of synthetic organic chemistry, as they account for a significant portion of widely prescribed azepine-based drugs possessing/showing manifold biological activities like antidepressant [1], anticonvulsant [2], antiviral [3], antimicrobial [4], antifungal [5], anticancer [6], antithrombotic [7], antihistamines [8], nonnarcotic analgesic [9], sedatives, and hypnotics [10]. They are also active in the treatment of Alzheimer's disease and type 2 diabetes [11]. They act as inhibitors of several enzymes like glycosidase [12], kinase [13] and nitric oxide synthases [14], angiotensin-converting enzyme [15], HIV-1 integrase [16], and HIV-1 reverse transcriptase [17] and also inhibit several targets such as cannabinoid-1 receptor [18], squalene synthase [19], 5-HT_{1A} receptor [20], progesterone receptor [21], histamine H_2, and gastrin receptor [22]. They are active constituents of a series of new potent bradykinin agonists [23]. Some of these compounds have also shown activity as endogenous natriuretic factors [24] and also induce apoptosis in MCF-7 cells [25] and myeloma cells [26]. Because of a wide range of physiological properties, synthetic manipulations on these molecules have been an area of current interest.

A considerable number of methods toward the formation of oxazepine ring have been reported in recent years via the Baylis–Hillman reaction [27], by the cyclization of propenamides with 2-aminophenol [28], by the reaction of nitrosonaphthol with TNT [29], a phosphine-mediated tandem reaction of ynones with 2-azido alcohols [30], intermolecular amidoalkylation reaction [31], using the benzotriazole methodology [32], scandium- or copper-triflate-catalyzed acylaminoalkylation of α-methoxyisoindolones [33], from imines by their acylation and further cyclization [34], and one-pot multicomponent reaction of 2-aminophenols, Meldrum's acid and isocyanides [35]. The use of microwave irradiation has also been employed [36].

However, above-reported methods suffer from drawbacks like prolonged reaction times and complex methodology and frequently have low yields. Thus, despite the great success in the synthesis of oxazepine derivatives, a convenient and efficient way to form the oxazepine ring is still preferred owing to its utmost importance as pharmaceutical drugs and active substances in biological systems.

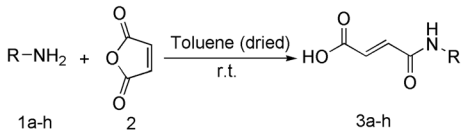
RESULTS AND DISCUSSION

In the present study, 2-thioxo-1,3-oxazepine-4,7-diones have been efficiently synthesized by the triethylamine-catalyzed condensation of maleamic acids with thiophosgene under anhydrous conditions. The nucleophilic attack of O and N of maleamic acid moiety onto thiophosgene, followed by elimination, leads to 2-thioxo-1,3-oxazepine-4,7-dione as the cyclized product. This method relatively features a low catalyst loading, use of inexpensive reagents, convenient operating conditions and high yields.

In the first step, the maleamic acids were obtained by adopting a procedure similar to that reported in literature [37]. For this purpose, a variety of amines 1a–h (1 mmol) was treated with maleic anhydride 2 (1 mmol) in sodium-dried toluene (5 mL) at room temperature (Scheme 1) to afford the corresponding maleamic acids 3a–h (Table 1).

In the performed reaction, the desired products usually precipitated from the reaction mixtures after the reaction mixture was cooled to below the room temperature. The obtained precipitates were recrystallized out of ethanol,

Scheme 1



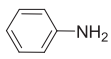
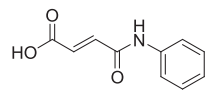
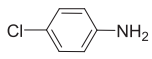
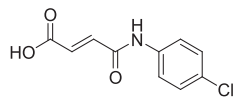
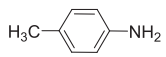
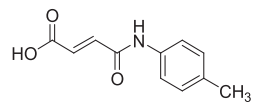
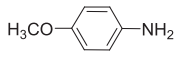
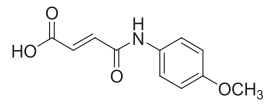
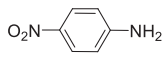
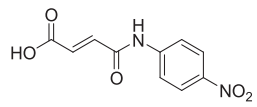
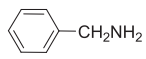
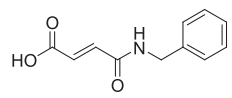
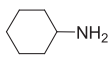
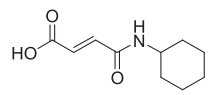
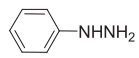
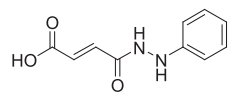
1a, 3a: R = C_6H_5
1b, 3b: R = 4-Cl-C_6H_4
1c, 3c: R = 4-CH_3-C_6H_4
1d, 3d: R = 4-OCH_3-C_6H_4
1e, 3e: R = 4-NO_2-C_6H_4
1f, 3f: R = -CH_2-C_6H_5
1g, 3g: R = C_6H_{11}
1h, 3h: R = -NH-C_6H_5

and the physical data (mp, IR, NMR) of the known compounds were found to be identical with those reported in literature [37,38].

The maleamic acids thus synthesized were initially air-dried and then well-dried in a vacuum desiccator for 2–3 days under anhydrous calcium chloride and phosphorus pentachloride mixture before using them for the next step. In the next step, the ice-cold solution of well-dried maleamic acid of aniline 1 mmol (Table 1, entry 1) in 5 mL dry toluene was topped with 1 equiv triethylamine, followed by dropwise addition of solution of thiophosgene (1 mmol thiophosgene in 5 mL dry toluene) with constant stirring for 15 min. Stirring was continued for a further 3 h. After that, the cooling bath was removed, and the reaction mixture was kept overnight at room temperature. The reaction mixture was separated using diethyl ether and washed with aqueous sodium hydrogen carbonate

Table 1

Synthesis of maleamic acids.[a]

Entry	Amine	Product	Yield[b] (%)
1			94
2			92
3			90
4			92
5			88
6			94
7			96
8			90

[a]Reaction conditions: amine (1 mmol), maleic anhydride (1 mmol), sodium-dried toluene (5 mL), room temperature.
[b]Isolated yields after recrystallization.

solution to neutralize any residual thiophosgene and to wash out the triethylamine hydrochloride salt that formed during the reaction. Further workup and purification by column chromatography afforded the cyclized product 2-thioxo-1,3-oxazepine-4,7-diones in low yields of 41% (Scheme 2).

In an effort to improve the yield, the quantities of triethylamine catalyst were varied, and results are summarized in Table 2. Use of 2.2 equiv of catalyst per equivalent of reactant afforded the product in 72% yield. This may be attributed to 2 equiv of catalyst required to remove two proton equivalents from N–H and O–H of the maleamic acid. Further increase did not show much improvement in the yield.

After screening the reaction for catalyst loading, the reaction was performed in different solvents to further study the effect of a solvent and improve the yield (Table 3). Maximum yields were obtained in either toluene or chloroform as a solvent.

After establishing the optimized conditions, the various synthesized maleamic acid precursors were used to synthesize a variety of 2-thioxo-1,3-oxazepine-4,7-diones (Table 4).

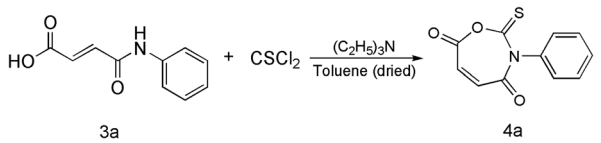
The products were identified by IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectral techniques. Absence of O–H and N–H stretch in their IR spectra and peaks corresponding to acidic protons (COOH and NH) in their NMR spectra confirmed the formation of cyclized product from corresponding maleamic acid. Their mass spectra results further supported this fact (Table 4).

In the ^{1}H-NMR spectrum of 2,3-dihydro-3-(4-chlorophenyl)-2-thioxo-1,3-oxazepine-4,7-dione (Table 4, entry 2), two doublets at δ 6.30 and δ 6.61, respectively, were observed for cis protons C_5–H and C_6–H with coupling constants $J = 7.28$ Hz for each proton. Aromatic protons appeared as two doublets at δ 7.16 and δ 7.54 as per para substitution pattern with coupling constants $J = 8.56$ Hz for each proton. In the ^{13}C-NMR spectrum, carbonyl carbons of lactam and lactone moiety appeared at δ 166.96 and δ 171.37, respectively. A signal at δ 178.03 was assigned to C═S carbon. Rest of the carbons appeared in the aromatic region at δ 126.98–136.17.

This method holds good to a broad range of aromatic amines bearing electron donating as well as electron-withdrawing groups, including cyclohexylamine and phenylhydrazine even (Table 4, entry 7 and 8). The phenylhydrazine afforded the corresponding product but with a somewhat low yield (Table 4, entry 8); however, in the case of cyclohexylamine, the yield was comparable with that of other aromatic amines (Table 4, entry 7).

In summary, we have synthesized a number of oxazepine derivatives by the condensation of maleamic acids with thiophosgene under base catalytic conditions. This method is effective with a variety of amines. The attractive features of this protocol are simplicity of the experimental procedure, use of inexpensive reagents, convenient operating conditions, and high yields. Further studies to replace thiophosgene with environment-friendly dialkyl carbonates are being investigated and will be discussed in the near future.

Scheme 2



3a 4a

Table 2

Effect of catalyst loading for thiocarbonylation of maleamic acid of aniline **3a** (Table 1, entry 1) with thiophosgene.[a]

Entry	Catalyst equiv per equiv of **3a**	Solvent	Yield[b] of **4a** (%)
1	—	Toluene	22
2	1	Toluene	41
3	2	Toluene	63
4	2.2	Toluene	72
5	2.5	Toluene	74

[a]Reaction conditions: maleamic acid of aniline **3a** (1 mmol), dry toluene (5 mL), thiophosgene solution (1 mmol in 5 mL dry toluene).
[b]Isolated yield.

Table 3

Thiocarbonylation of maleamic acid of aniline (Table 1, entry 1) with thiophosgene in different solvents.[a]

Entry	Solvent	Catalyst (equiv)	Yield[b] of **4a** (%)
1	Toluene	2.2	72
2	Dichloromethane	2.2	67
3	Chloroform	2.2	70
4	Tetrahydrofuran	2.2	59

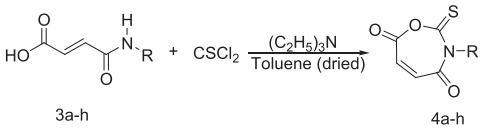
[a]Reaction conditions: maleamic acid of aniline 3a (1 mmol), triethylamine (2.2 equiv), thiophosgene solution (1 mmol in 5 mL solvent).
[b]Isolated yield.

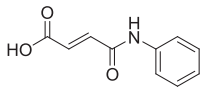
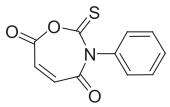
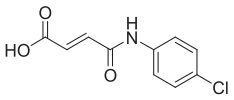
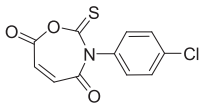
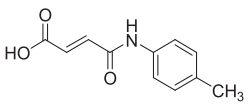
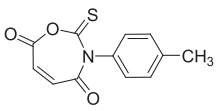
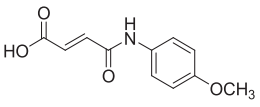
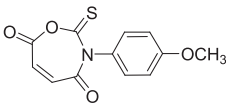
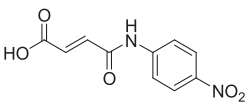
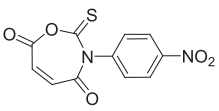
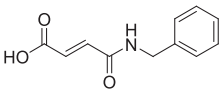
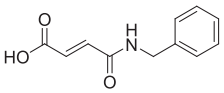
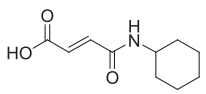
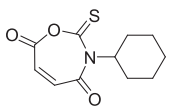
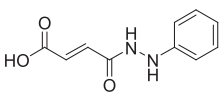
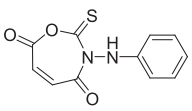
EXPERIMENTAL

General. Melting points reported are uncorrected. ^{1}H-NMR spectra were recorded on a 400-MHz spectrometer (Bruker, Fallanden, Switzerland) in $CDCl_3$ solution, and the chemical shifts are reported in parts per million (δ) relative to internal standard TMS (0 ppm). The coupling constants (J) are reported in Hertz (Hz). ^{13}C-NMR spectra were obtained at 100 MHz and referenced to the internal solvent signals (central peak is 77.00 $CDCl_3$). Mass spectra were recorded on a Thermo Scientific LTQ-XL LCMS (Waltham, MA). IR spectra were recorded on a Perkin Elmer RX I FTIR Spectrophotometer (Buckinghamshire, England). TLC plates were coated with silica gel G suspended in methanol–chloroform. Elemental analysis was carried out using an Elementar vario MICRO cube CHNS

Table 4

Synthesis of 2-thioxo-1,3-oxazepine-4,7-diones.[a]



Entry	Maleamic acid	Product	Yield[b] (%)	*m/z*
1			72	233
2			67	267, 269[c]
3			70	247
4			68	263
5			63	278
6			74	247
7			66	239
8			56	248

[a]Reaction conditions: maleamic acid (1 mmol), dry toluene (5 mL), triethylamine (2.2 equiv), thiophosgene solution (1 mmol in 5 mL dry toluene).
[b]Isolated yield.
[c]Molecular ion peaks M and M+2.

analyzer. All reactions were carried out under an inert nitrogen atmosphere in oven-dried glassware. Purification of compounds was done with column chromatography over silica gel using hexane-ethyl acetate mixture as the eluent.

General procedure for the synthesis of 2-thioxo-1,3-oxazepine-4,7-diones. A flask surrounded by ice-water bath was charged with 1 mmol well-dried maleamic acid of aniline (Table 1, entry 1), followed by 5 mL dry toluene

and 2.2 equiv triethylamine. The solution became clear. A solution of thiophosgene (1 mmol) in dry toluene (5 mL) was added to it slowly with constant stirring for 15 min. There was a little foaming. The stirring was continued for a further 3 h. After that, the cooling bath was removed, and the reaction mixture was kept overnight at room temperature. On the next day, the reaction mixture was separated using diethyl ether and washed with aqueous sodium hydrogen carbonate solution to neutralize any residual thiophosgene and to wash out the triethylamine hydrochloride salt that formed during the reaction. The ether layer was dried over sodium sulfate, filtered, and reduced on a rotary evaporator. Further purification by column chromatography provided the cyclized product 2-thioxo-1,3-oxazepine-4,7-diones in good to excellent yields.

The Spectral data for all products are provided as follows:

2,3-Dihydro-3-phenyl-2-thioxo-1,3-oxazepine-4,7-dione (Table 4, entry 1). ^{1}H-NMR (DMSO-d_6, 400 MHz, ppm): $\delta = 6.31$ (d, 1H, $J = 7.36$ Hz), 6.61 (d, 1H, $J = 7.36$ Hz), 7.04 (m, 1H), 7.21 (m, 2H), 7.64 (m, 2H); ^{13}C-NMR (DMSO-d_6, 125 MHz, ppm): $\delta = 127.11$, 128.74, 131.56, 132.32, 133.91, 135.53, 166.78, 171.24, (C═O), 177.83 (C═S); IR (υ cm^{-1}, $CHCl_3$): 1715 (C═O of lactam), 1678 (C═O of lactone), 1155 (C═S); MS: *m/z*: 233 $[M]^+$. *Anal*. Calcd for $C_{11}H_7NO_3S$: C, 56.64; H, 3.02; N, 6.01; S, 13.75. Found: C, 56.23; H, 2.98; N, 5.95; S, 13.64.

2,3-Dihydro-3-(4-chlorophenyl)-2-thioxo-1,3-oxazepine-4,7-dione (Table 4, entry 2). ^{1}H-NMR (DMSO-d_6, 400 MHz, ppm): $\delta = 6.30$ (d, 1H, $J = 7.28$ Hz), 6.61 (d, 1H, $J = 7.28$ Hz), 7.16 (d, 2H, $J = 8.56$ Hz), 7.54 (d, 2H, $J = 8.56$ Hz); ^{13}C-NMR (DMSO-d_6, 125 MHz, ppm): $\delta = 126.98$, 128.19, 130.92, 132.86, 133.69, 136.17, 166.96, 171.37, (C═O), 178.03 (C═S); IR (υ cm^{-1}, $CHCl_3$): 1717 (C═O of lactam), 1678 (C═O of lactone), 1153 (C═S); MS: *m/z*: 267 $[M]^+$, 269 $[M+2]^+$. *Anal*. Calcd for $C_{11}H_6ClNO_3S$: C, 49.36; H, 2.26; N, 5.23; S, 11.98. Found: C, 49.43; H, 2.19; N, 5.31; S, 11.93.

2,3-Dihydro-3-(4-methylphenyl)-2-thioxo-1,3-oxazepine-4,7-dione (Table 4, entry 3). ^{1}H-NMR (DMSO-d_6, 400 MHz, ppm): $\delta = 2.35$ (s, 3H), 6.27 (d, 1H, $J = 7.44$ Hz), 6.48 (d, 1H, $J = 7.44$ Hz), 6.88 (d, 2H, $J = 8.88$ Hz), 7.57 (d, 2H, $J = 8.88$ Hz); ^{13}C-NMR (DMSO-d_6, 125 MHz, ppm): $\delta = 127.33$, 129.51, 132.58, 132.46, 136.55, 144.62, 167.43, 171.04, (C═O), 177.86 (C═S); IR (υ cm^{-1}, $CHCl_3$): 1715 (C═O of lactam), 1677 (C═O of lactone), 1157 (C═S); MS: *m/z*: 247 $[M]^+$. *Anal*. Calcd for $C_{12}H_9NO_3S$: C, 58.29; H, 3.67; N, 5.66; S, 12.97. Found: C, 58.41; H, 3.78; N, 5.58; S, 13.06.

2,3-Dihydro-3-(4-methoxyphenyl)-2-thioxo-1,3-oxazepine-4,7-dione (Table 4, entry 4). ^{1}H-NMR (DMSO-d_6, 400 MHz, ppm): $\delta = 3.43$ (s, 3H), 6.30 (d, 1H, $J = 7.48$ Hz), 6.56 (d, 1H, $J = 7.48$ Hz), 6.90 (d, 2H, $J = 8.84$ Hz), 7.59 (d, 2H, $J = 8.84$ Hz);^{13}C-NMR (DMSO-d_6, 125 MHz, ppm): $\delta = 55.13$, 117.88, 129.23, 131.15, 132.18, 135.46, 144.62, 167.98, 171.15, (C═O), 178.80 (C═S); IR (υ cm^{-1}, $CHCl_3$): 1715 (C═O of lactam), 1677 (C═O of lactone), 1159 (C═S); MS: *m/z*: 263 $[M]^+$. *Anal*. Calcd for $C_{12}H_9NO_4S$: C, 54.75; H, 3.45; N, 5.32; S, 12.18. Found: C, 55.04; H, 3.37; N, 5.36; S, 12.11.

2,3-Dihydro-3-(4-nitrophenyl)-2-thioxo-1,3-oxazepine-4,7-dione (Table 4, entry 5). ^{1}H-NMR (DMSO-d_6, 400 MHz, ppm): $\delta = 6.33$ (d, 1H, $J = 7.52$ Hz), 6.40 (d, 1H, $J = 7.52$ Hz), 7.15 (d, 2H, $J = 8.76$ Hz), 7.54 (d, 2H, $J = 8.76$ Hz); ^{13}C-NMR (DMSO-d_6, 125 MHz, ppm): $\delta = 117.51$, 128.77, 130.75, 132.41, 136.61, 145.07, 168.26, 171.28, (C═O), 177.91 (C═S); IR (υ cm^{-1}, $CHCl_3$): 1714 (C═O of lactam), 1677 (C═O of lactone), 1157 (C═S); MS: *m/z*: 278 $[M]^+$. *Anal*. Calcd for $C_{11}H_6N_2O_5S$: C, 47.48; H, 2.17; N, 10.07; S, 11.52. Found: C, 47.81; H, 2.11; N, 9.97; S, 11.56.

3-Benzyl-2,3-dihydro-2-thioxo-1,3-oxazepine-4,7-dione (Table 4, entry 6). ^{1}H-NMR (DMSO-d_6, 400 MHz, ppm): $\delta = 4.31$ (s, 2H); 6.32 (d, 1H, $J = 7.72$ Hz), 6.42 (d, 1H, $J = 7.72$ Hz), 7.03–7.16 (m, 5H);^{13}C-NMR (DMSO-d_6, 125 MHz, ppm): $\delta = 44.60$, 127.82, 128.55, 129.28, 131.88, 133.71, 135.08, 166.93, 170.85, (C═O), 178.35 (C═S); IR (υ cm^{-1}, $CHCl_3$): 1717 (C═O of lactam), 1680 (C═O of lactone), 1153 (C═S); MS: *m/z*: 247 $[M]^+$. *Anal*. Calcd for $C_{12}H_9NO_3S$: C, 58.29; H, 3.67; N, 5.66; S, 12.97. Found: C, 58.41; H, 3.72; N, 5.75; S, 13.02.

3-Cyclohexyl-2,3-dihydro-2-thioxo-1,3-oxazepine-4,7-dione (Table 4, entry 7). ^{1}H-NMR (DMSO-d_6, 400 MHz, ppm): $\delta = 0.79$–1.08 (m, 5H), 1.50–1.68 (m, 5H), 3.51 (m, 1H), 6.32 (d, 1H, $J = 7.16$ Hz), 6.49 (d, 1H, $J = 7.16$ Hz);^{13}C-NMR (DMSO-d_6, 125 MHz, ppm): $\delta = 22.90$, 27.06, 33.81, 51.22, 127.35, 130.68, 166.27, 169.33, (C═O), 178.33 (C═S); IR (υ cm^{-1}, $CHCl_3$): 1706 (C═O of lactam), 1672 (C═O of lactone), 1160 (C═S); MS: *m/z*: 239 $[M]^+$. *Anal*. Calcd for $C_{11}H_{13}NO_3S$: C, 55.21; H, 5.48; N, 5.85; S, 13.40. Found: C, 55.07; H, 5.40; N, 5.90; S, 13.48.

3-(Phenylamino)-2,3-dihydro-2-thioxo-1,3-oxazepine-4,7-dione (Table 4, entry 8). ^{1}H-NMR (DMSO-d_6, 400 MHz, ppm): $\delta = 4.02$ (brs, 1H, NH), 6.30 (d, 1H, $J = 7.24$ Hz), 6.57 (d, 1H, $J = 7.24$ Hz), 6.93–7.11 (m, 5H); ^{13}C-NMR (DMSO-d_6, 125 MHz, ppm): $\delta = 112.74$, 117.28, 126.11, 128.27, 132.85, 148.17, 166.08, 170.61, (C═O), 178.39. (C═S). IR (υ cm^{-1}, $CHCl_3$): 1710 (C═O of lactam), 1678 (C═O of lactone), 1158 (C═S); MS: *m/z*: 248 $[M]^+$. *Anal*. Calcd for $C_{11}H_8N_2O_3S$: C, 53.22; H, 3.25; N, 11.28; S, 12.92. Found: C, 52.99; H, 3.22; N, 11.35; S, 13.01.

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