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A facile catalyst and solvent-free synthesis of spiro thia heterocycles on grinding

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Abstract: An efficient and mild method for the synthesis of spiro 1,3-oxathiolan/oxathianes in the solid state reaction at room temperature has been described. This method is a good option to obtain the title compounds in quantitative yields in a simple and inexpensive way. Applying this methodology, different thia heterocycles were synthesized.

Keywords: spiro 1,3-oxathiolane/oxathianes; solid-state synthesis; room temperature.

INTRODUCTION

Development of organic solid state reaction has emerged as a frontier area of research in synthetic organic chemistry.[1] These reactions are especially appealing because they have certain advantages such as high efficiency, selectivity,[2] easy separation, purification, mild reaction conditions[3] and environmental acceptability.[4] This approach has been widely used in a variety of organic reactions.[5]

Experience has shown that compounds with biological activity are often derived from heterocyclic structures. Indeed, one of the richest sources of diversity for the medicinal chemist are small heterocyclic rings, which, in addition to often exhibiting biological activity, may serve as rigid scaffolds for further display of functionalities. 1,3-Oxathiolane/1,3-oxathianes are one such class of heterocycles which have attracted much attention as they have been reported to possess a wide range of biological activities, including antiviral,[6] anticonvulsant,[7] antiulcer[8] and antifungal activity.[9] In addition, they also showed anti-HIV and anti-HBV activity,[10] and oxathiolanes act both as agonists[11–13] and antagonists on muscarinic receptors.[12] Cevimeline (*cis*-2-methylspiro[1,3-oxathiolane-5,3'-quinuclidine] hydrochloride) is a selective M_1 receptor agonist. It induces atropine-sensitive contractions of isolated guinea pig ilea and trachea preparations (EC_{50} values are

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3.5 and 3 μM, respectively) and reverses AF64A-induced cognitive impairments *in vivo*.[14]

A literature survey showed that many different protocols have been developed for the synthesis of various 1,3-oxathiolane derivatives. However, the general applicability of the reported methods are limited as the reactions require prolonged heating using dry toluene and the catalysts p-toluenesulfonic acid (*p*-TSA),[15] the dimethyltin diiodide–HMPTA complex,[16] LiBr,[17] *etc*. Furthermore, purification of the product requires tedious workup with further use of large amount of volatile organic solvents. In order to circumvent these difficulties and to develop a facile green chemical approach, our attention was focused on the development of an alternative method for the synthesis of spiro 1,3-oxathiolane/oxathianes.

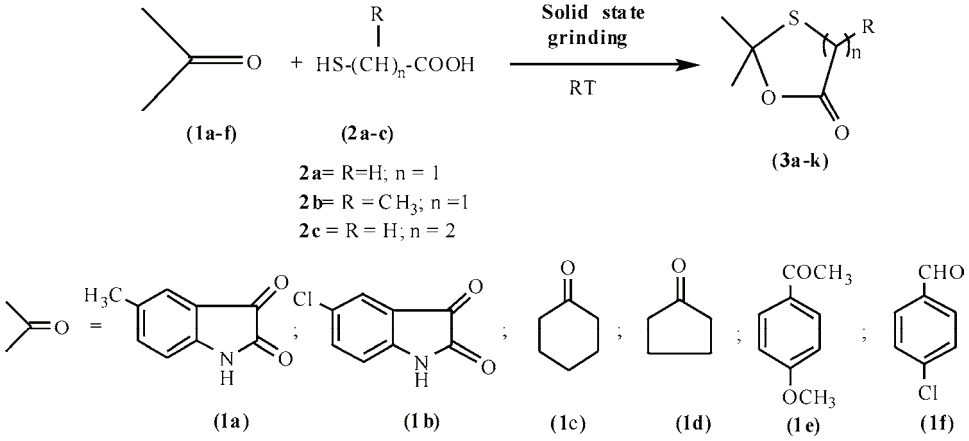
On the other hand, spiro-oxindole derivatives occupy a special place in organic and medicinal chemistry because these compounds are well-known as microtubule assembly inhibitors (spirotryprostatin A and B),[18] muscarinic M1, serotonin receptor modulators (pteropodine and isopteropodine)[19] and nonpeptidyl growth-hormone secretagogues (MK-0677).[20] Horsfiline and elacomine are more straightforward derivatives of the naturally occurring oxindole alkaloids with cell cycle inhibition activity.[21]

The unique structural array and the highly pronounced pharmacological activity displayed by the class of spirooxindole compounds have made them attractive synthetic targets.[19b,22] In continuation of earlier interest on the synthesis of spiro thia heterocycles,[23] herein an easy, practical and efficient procedure for the synthesis of spiro 1,3-oxathiolanes containing different alicyclic/heterocyclic moieties, *e.g*., indole, cyclohexane, cyclopentane, by the solid state reaction at room temperature in 2–3 min after grinding the two reactants in an agate mortar is reported for the first time (Scheme 1). The method can also be extended to reaction of aromatic aldehydes/ketones giving 2-(substituted aryl)-4-methyl-1,3--oxathiolane derivatives.

RESULTS AND DISCUSSION

As an initial endeavor, 5-methylisatin **1a** and mercapto acid **2a** were heated under reflux in dry toluene. After 4 h, only 60 % of the expected product **3a** was obtained after workup and recrystallization from ethanol. In an attempt to improve the yields of the reaction and acknowledging the benefits of grinding,[24] the same reaction was performed under solvent-free conditions at room temperature by grinding both reaction components in a mortar at room temperature (Scheme 1). It was observed that the mixture, which was initially in a partial liquid state, solidified during the grinding process to a light colored solid mass and thin layer chromatography, at this moment, indicated complete conversion to the desired product and TLC studies showed 100 % conversion of the reactants to the pro-

duct in quantitative yield in 2–3 min at room temperature. The pure product spiro derivative **3a** (monitored by TLC) was obtained after thorough washing with water and recrystallization with ethanol**.**



Compound	=O	R (n)	Compound	=O	R (n)
3a	**1a**	H (n = 1)	**3g**	**1c**	H (n = 2)
3b	**1a**	CH_3 (n = 1)	**3h**	**1d**	H (n = 1)
3c	**1a**	H (n = 2)	**3i**	**1d**	H (n = 2)
3d	**1b**	H (n = 1)	**3j**	**1e**	CH_3 (n = 1)
3e	**1b**	H (n = 2)	**3k**	**1f**	CH_3 (n = 1)
3f	**1c**	H (n = 1)			

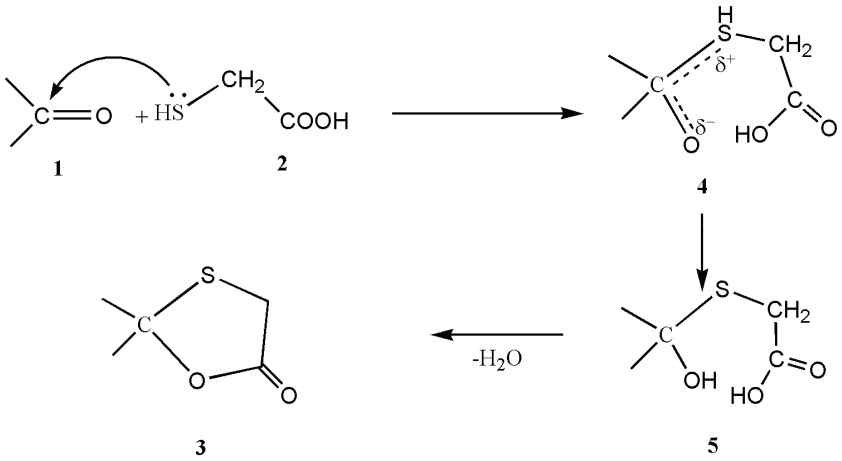
Scheme 1. The synthesis of the title compounds.

This cyclocondensation reaction is two-step reaction. The first step involves nucleophilic attack of thiol group on carbon oxygen double bond of carbonyl group giving the intermediates **4** and **5** (hydroxyalkylthio acid) which on elimination of water molecule gives product **3** (Scheme 2).

To optimize the method, the cyclocondensation reaction was examined using different quantities of mercapto acid and it was found that the yield of isolated product increased as the molar ratio of mercapto acid increased and the optimum molar ratio of carbonyl compound to mercapto acid for complete formation of the spiro product was determined to be 1:1.5.

The structures of the products **3a**–**k** were established by spectral and elemental analyses. The IR spectra of compounds **3a**–**e** showed a characteristic absorption band at 1715–1690 cm^{-1} due to the two carbonyl groups and the remaining compounds showed only one C=O absorption band at 1710–1702 cm^{-1}. The *spiro* compound **3b** where R=CH_3 contains two chiral centers and hence exists in two diastereomeric forms, which was confirmed by the appearance of two sets of signals in its ^{1}H-NMR spectrum giving two sets of doublet (J = 4.44 Hz) due to

CH–CH_3 at δ 1.67/1.98 ppm and a quartet (J = 4.44 Hz) due to CH–CH_3 at δ 4.39/4.79 ppm and a broad singlet at δ 8.24/8.58 ppm (NH) in a 3:1 molar ratio, corresponding to the two diastereomeric forms **3b** and **3b'**. However, the complex multiplets of the aromatic protons of the two diastereomers could not be resolved.



Scheme 2. The suggested mechanism for the formation of the title compounds.

The structural elucidations of the products were based on their spectral (IR, ^{1}H- and ^{13}C-NMR and mass) data as given below.

*5-Methylspiro[indoline-3,2'-[1,3]oxathiolane]-2,5'-dione (**3a**)*. M.p. 190 °C; Anal. Calcd. for $C_{11}H_9NO_3S$: C, 56.16; N, 5.95; S, 13.63 %. Found: C, 56.35; N, 5.97; S, 13.67 %. IR (KBr, cm^{-1}) 3280–3340 (NH str.), 1714 (C=O), 1690 (C=O), 1570, 1495, 1180. ^{1}H-NMR (300 MHz, $CDCl_3$, δ / ppm): 2.35 (3H, *s*, CH_3), 3.85–4.48 (2H, *dd*, J = 13.8 Hz, CH_2), 6.98–7.52 (3H, *m*, Ar–H), 9.08 (1H, *bs*, NH exchanges with D_2O). ^{13}C-NMR (74.46 MHz, $CDCl_3$, δ / ppm): 21.2 (CH_3), 34.8 (CH_2), 85.2 (spiro carbon) 120.8, 127.7, 128.3, 130.7, 133.8, 139.1 (aromatic carbons), 168.3 (C=O), 171.2 (C=O). MS (*m*/*z*): 236 $(M+H)^+$.

*4',5-Dimethylspiro[indoline-3,2'-[1,3]oxathiolane]-2,5'-dione (**3b**)*. M.p. 100 °C; Anal. Calcd. for $C_{12}H_{11}NO_3S$: C, 57.82; N, 5.62; S, 12.86 %. Found: C, 58.01; N, 5.64; S, 12.90 %. IR (KBr, cm^{-1}) 3285–3330 (NH str.), 1715 (C=O), 1695 (C=O), 1580, 1490, 1175. ^{1}H-NMR (300 MHz, $CDCl_3$, δ / ppm): 2.38 (3H, *s*, CH_3), diastereomeric ratio (3:1) 1.67/1.98 (3H, *d*, J = 4.44 Hz, CH–C**H**$_3$) 4.39/ /4.79 (1H, *q*, J = 4.44 Hz, C**H**–CH_3), 6.98–7.54 (3H, *m*, Ar–H), 8.24/8.58 (1H, *bs*, NH exchanges with D_2O). ^{13}C-NMR (74.46 MHz, $CDCl_3$, δ / ppm): 16.52 (CH–CH_3), 22.6 (CH_3), 44.19 (**C**H–CH_3), 82.24 (spiro carbon) 121.2, 124.6, 128.3, 130.2, 134.4, 138.2 (aromatic carbons), 168.22 (C=O), 172.90 (C=O). MS (*m*/*z*): 250 $(M+H)^+$.

*5-Methylspiro[indoline-3,2'-[1,3]oxathiane]-2,6'-dione (**3c**)*. M.p. 110 °C; Anal. Calcd. for $C_{12}H_{11}NO_3S$: C, 57.82; N, 5.62; S, 12.86 %. Found: C, 57.63; N, 5.60; S, 12.82 %. IR (KBr, cm^{-1}) 3290–3328 (NH str.), 1712 (C=O), 1692 (C=O) 1585, 1498, 1170. ^{1}H-NMR (300 MHz, $CDCl_3$, δ / ppm): 2.36 (3H, *s*, CH_3), 2.66 (2H, *t*, CH_2), 2.85 (2H, *t*, CH_2), 6.92–7.58 (3H, *m*, Ar–H), 9.02 (1H, *bs*, NH exchanges with D_2O). ^{13}C-NMR (74.46 MHz, $CDCl_3$, δ / ppm): 20.8 (CH_3), 32.4 (CH_2), 38.2 (CH_2), 86.3 (spiro carbon), 121.2, 124.8, 128.3, 132.3, 136.4, 140.2 (aromatic carbons), 166.8 (C=O), 174.2 (C=O). MS (*m*/*z*): 250 $(M+H)^+$.

*5-Chlorospiro[indoline-3,2'-[1,3]oxathiolane]-2,5'-dione (**3d**)*. M.p. 135 °C; Anal. Calcd. for $C_{10}H_6ClNO_3S$: C, 46.98; N, 5.48; S, 12.54 %. Found: C, 47.14; N, 5.46; S, 12.58 %. IR (KBr, cm^{-1}) 3290–3320 (NH str.), 1708 (C=O), 1692 (C=O), 1580, 1490, 1180, 740. ^{1}H-NMR (300 MHz, $CDCl_3$, δ/ ppm): 3.82–4.46 (2H, *dd*, *J* = 13.9 Hz, CH_2), 6.98–7.50 (3H, *m*, Ar–H), 8.88 (1H, *bs*, NH exchanges with D_2O). ^{13}C-NMR (74.46 MHz, $CDCl_3$, δ / ppm): 35.2 (CH_2), 89.6 (spiro carbon), 120.1, 124.3, 128.4, 130.2, 136.2, 140.4 (aromatic carbons), 169.4 (C=O),174.3 (C=O). MS (*m*/*z*): 256 $(M+H)^+$.

*5-Chlorospiro[indoline-3,2'-[1,3]oxathiane]-2,6'-dione (**3e**)*. M.p. 180 °C; Anal. Calcd. for $C_{11}H_8ClNO_3S$: C, 48.99; N, 5.19; S, 11.89 %. Found: C, 48.83; N, 5.17; S, 11.85 %. IR (KBr, cm^{-1}) 3292–3318 (NH str.), 1715 (C=O), 1695 (C=O), 1575, 1480, 1178, 745. ^{1}H-NMR (300 MHz, $CDCl_3$, δ/ ppm): 2.62 (2H, *t*, CH_2), 2.83 (2H, *t*, CH_2), 6.98–7.52 (3H, *m*, Ar–H), 9.06 (1H, *bs*, NH exchanges with D_2O). ^{13}C-NMR (74.46 MHz, $CDCl_3$, δ/ ppm): 30.1 (CH_2), 37.5 (CH_2), 86.5 (spiro carbon), 122.8, 128.4, 129.3, 130.4, 136.8, 140.4 (aromatic carbons), 167.3 (C=O), 173.3 (C=O). MS (*m*/*z*): 270 $(M+H)^+$.

*1-Oxa-4-thiaspiro[4.5]decan-2-one (**3f**)*. M.p. 125 °C; Anal. Calcd. for $C_8H_{12}O_2S$: C, 55.78; S, 18.62 %. Found: C, 55.60; S, 18.68 %. IR (KBr, cm^{-1}) 2880–2930 (CH str.), 1705 (C=O). ^{1}H-NMR (300 MHz, $CDCl_3$, δ/ ppm): 1.27––1.35 (2H, *t*, CH_2),1.52–1.65 (2H, *m*, CH_2) 2.06–2.30 (2H, *t*, CH_2), 1.86–1.98 (4H, *m*, CH_2), 3.85–4.48 (2H, *dd*, CH_2). ^{13}C-NMR (74.46 MHz, $CDCl_3$, δ/ ppm): 17.8, 26.7, 36.5 (cyclohexane ring carbons), 36.7 (CH_2), 84.2 (spiro carbon), 172.2 (C=O). MS (*m*/*z*): 173 $(M+H)^+$.

*1-Oxa-5-thiaspiro[5.5]undecan-2-one (**3g**)*. M.p. 130 °C; Anal. Calcd. for $C_9H_{14}O_2S$: C, 58.03; S, 17.21 %. Found: C, 58.22; S, 17.26 %. IR (KBr, cm^{-1}) 2870–2945 (CH str.), 1708 (C=O). ^{1}H-NMR (300 MHz, $CDCl_3$, δ/ ppm): 1.29––1.38 (2H, *t*, CH_2), 1.50–1.66 (2H, *m*, CH_2), 2.04–2.31 (2H, *t*, CH_2), 1.85–1.96 (4H, *m*, CH_2), 2.65 (2H, *t*, CH_2), 2.88 (2H, *t*, CH_2); ^{13}C-NMR (74.46 MHz, $CDCl_3$, δ/ ppm): 17.5, 26.8, 36.4 (cyclohexane ring carbons), 28.7 (CH_2), 38.2 (CH_2), 84.8 (spiro carbon), 172.8 (C=O). MS (*m*/*z*): 173 $(M+H)^+$.

*1-oxa-4-thiaspiro[4.4]nonan-2-one (**3h**)*. M.p. 150 °C; Anal. Calcd. for $C_7H_{10}O_2S$: C, 53.14; S, 20.27. Found: C, 53.32; S, 20.21. IR (KBr, cm^{-1}): 2885–

–2940 (CH str.), 1702 (C=O). ^{1}H-NMR (300 MHz, $CDCl_3$, δ / ppm): 1.28–1.36 (*t*, 2H, CH_2), 1.55–1.62 (*m*, 4H, CH_2), 2.08–2.13 (*t*, 2H, CH_2), 3.85–4.43 (*dd*, 2H, CH_2). ^{13}C-NMR (74.46 MHz, $CDCl_3$, δ / ppm): 17.2, 37.3 (cyclopentane ring carbons), 38.2 (CH_2), 89.5 (spiro carbon), 171.3 (C=O). MS (*m*/*z*): 159 $(M+H)^+$.

6-Oxa-10-thiaspiro[4.5]decan-7-one (***3i***). M.p. 120 °C; Anal. Calcd. for $C_8H_{12}O_2S$: C, 55.78; S, 18.62 %. Found: C, 55.96; S, 18.56 %. IR (KBr, cm^{-1}) 2865–2930 (CH str.), 1710 (C=O). ^{1}H-NMR (300 MHz, $CDCl_3$, δ / ppm): 1.27––1.38 (2H, *t*, CH_2), 1.57–1.63 (4H, *m*, CH_2), 2.08–2.17 (2H, *t*, CH_2), 2.66 (2H, *t*, CH_2), 2.89 (2H, *t*, CH_2). ^{13}C-NMR (74.46 MHz, $CDCl_3$, δ / ppm): 17.5, 36.8 (cyclopentane ring carbons), 28.5 (CH_2), 38.8 (CH_2), 84.6 (spiro carbon), 172.8 (C=O). MS (*m*/*z*) 173 $(M+H)^+$.

2-(4-Methoxyphenyl)-2,4-dimethyl-1,3-oxathiolan-5-one (***3j***). M.p. 140 °C; Anal. Calcd. for $C_{12}H_{14}O_3S$: C, 60.48; S, 13.46 %. Found: C, 60.68; S, 13.42 %. IR (KBr, cm^{-1}) 2875–2932 (CH str.), 1704 (C=O). ^{1}H-NMR (300 MHz, $CDCl_3$, δ / ppm): 1.39 (3H, *d*, CH_3), 1.86 (3H, *s*, CH_3), 3.72 (3H, *s*, CH_3), 3.88 (1H, *q*, CH), 6.98–7.52 (4H, *m*, CH). ^{13}C-NMR (74.46 MHz, $CDCl_3$, δ / ppm): 17.6 (CH_3), 20.2 (CH_3), 56.4 (CH_3), 90.2 (CH), 92.6 (spiro carbon), 122.8, 124.2, 128.4, 138.4, 142.2, 158.6 (aromatic carbons), 158.4 (C–O), 192.4 (C=O). MS (*m*/*z*): 239 $(M+H)^+$.

2-(4-Chlorophenyl)-4-methyl-1,3-oxathiolan-5-one (***3k***). M.p. 145 °C; Anal. Calcd. for $C_{10}H_9ClO_2S$: C, 52.52; S, 14.02 %. Found: C, 52.35; S, 14.06 %. IR (KBr, cm^{-1}) 2862–2938 (CH str.), 1708 (C=O). ^{1}H-NMR (300 MHz, $CDCl_3$, δ / ppm): 1.42 (3H, *d*, CH_3), 3.86 (1H, *q*, CH), 5.44 (1H, *s*, CH), 6.96–7.28 (4H, *m*, CH). ^{13}C-NMR (74.46 MHz, $CDCl_3$, δ / ppm): 17.4 (CH_3), 92.8 (CH), 88.4 (spiro carbon), 118.8, 122.4, 124.2, 128.4, 132.4, 138.8 (aromatic carbons), 194.6 (C=O). MS (*m*/*z*): 229 $(M+H)^+$.

EXPERIMENTAL

Melting points were determined in open glass capillaries and are uncorrected. The IR spectra (KBr) were recorded on a Shimadzu FT IR-8400S spectrophotometer and the ^{1}H- and ^{13}C-NMR spectra were recorded on Bruker DRX-300 in $CDCl_3$ at 300.15 and 75.47 MHz, respectively. TMS was used as the internal reference. The mass spectra of representative compounds were recorded on XEVO QTOF and Thermo LCQ Advantage Max Ion Trap spectrometers. Elemental microanalyses were performed on a Carlo-Erba 1108 CHN analyzer. The purity of all compounds was checked by TLC using silica Gel "G" coated glass plates and benzene: ethyl acetate (8:2) as the eluent.

General procedure for the synthesis of spiro compounds ***3a–k***

A mixture of the appropriate carbonyl compound **1** (1 mmol) and mercapto acids **2** (1.5 mmol) was thoroughly ground in an agate mortar. The grinding was continued until completion of the reaction (2–3 min), as monitored by TLC. On completion of the reaction, the mixture became a solid mass which was treated with water. The resultant product was filtered

and washed with water, recrystallized from methanol and dried under vacuum to yield the pure products.

CONCLUSIONS

An efficient, environmentally friendly, economically viable and cleaner methodology for the preparation of *spiro* [1,3-oxathiolane/oxathianes] under solid-state conditions at room temperature was developed. The reaction is fairly general, facile and is devoid of any side products. Due to the simplicity of the conditions, high yields and purity of the products, the above mentioned methodology should find utility in organic synthesis. In addition, this method is safer; it avoids the use of toxic or hazardous solvents. Furthermore, it was found that this solid state reaction is much faster and more efficient than the solution phase reaction, probably because the solid state reaction is a very high concentration reaction.

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И З В О Д

ЕФИКАСНА СИНТЕЗА СПИРО ТИЈА ХЕТЕРОЦИКЛА У ЧВРСТОЈ ФАЗИ

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Описана је синтеза спиро 1,3-оксатиолан/оксатиан у чврстој фази под благим реакционим условима, на собној температури. Поступак представља добар приступ за синтезу наведених једињења у квантитативном приносу на ефикасан начин по приступачној цени. Применом описаног поступка синтетисана су различита тија хетероциклична једињења.

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