ZrCl4/TMSCl as an Efficient Catalyst for Synthesis of 4,6-Substituted 2-Alkylthio-6*H*-1,3-thiazines

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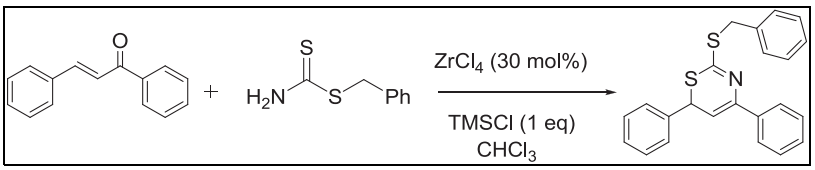

4,6-Substituted-2-alkylthio-6*H*-1,3-thiazines were synthesized by the reaction of *S*-alkyl dithiocarbamates and α, β-unsaturated ketones in the presence of $ZrCl_4$/TMSCl. The procedure is simple and efficient and gives good to high yields of products.

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INTRODUCTION

1,3-Thiazines are a class of heterocyclic compounds with several biological activities such as antibacterial, antitumor, insecticidal, and fungicidal [1]. Cephalosporins, which possess a 1,3-thiazine nucleus, are presently in clinical use as antibiotics [2]. Also, 1,3-thiazines are important synthetic intermediates in organic synthesis [3].

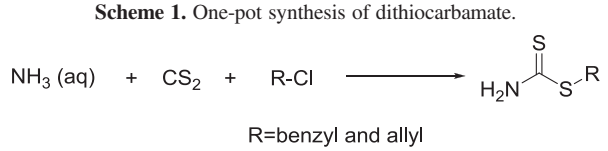
Usually, 1,3-thiazines are synthesized by condensation of dithiocarbamic acids or its salts, thioamides, and thioureas with α,β-unsaturated ketones and esters [4]. In addition, 1,3-thiazines are prepared with condensation reaction of thioamides with the appropriate halocarbonyl derivatives [5]. Recently, Koketsu *et al.* have reported an efficient method for synthesis of 2-alkylthio-4-hydroxy-4*H*-5,6-dihydro-1, 3-thiazine and their dehydration products by using BF_3 as Lewis acid [6].

RESULTS AND DISCUSSION

Dithiocarbamates were synthesized by the one-pot three-component reaction of aqueous ammonia, carbon disulfide, and alkyl halide (Scheme 1) [7]. Previously, syntheses of the dithiocarbamate, such as *S*-methyl dithiocarbamate and *S*-phenyl dithiocarbamate, were reported by the reaction of a dithiophosphoric acid with a thiocyanate [8,9] or by the reaction of thioacetic acid with thiocyanates in the presence of a Lewis acid [6].

Reaction of chalcone and benzyl dithiocarbamate has been chosen as a model reaction to investigate the catalyst and solvent effect. For this purpose, different catalysts such as ZnI_2, $CeCl_3{\cdot}7H_2O$, $ZrCl_4$, $ZrOCl_2$, HPW, $MgClO_4$, La_2O_3, SbF_3, and CsI were applied for this transformation, and we have found that the best yields were obtained when 30 mol% of $ZrCl_4$ was used in the presence of TMSCl (1 equiv). Also, investigation of the solvent effect on the reaction shows that the best yield was obtained in $CHCl_3$ (Table 1). The reaction gives 2-alkylthio-6*H*-1,3-thiazine as the only product (Scheme 2).

Scheme 1. One-pot synthesis of dithiocarbamate.



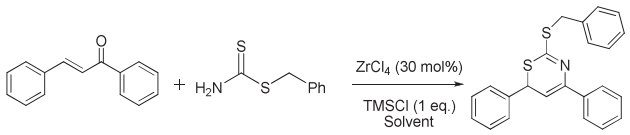
After optimization of the reaction conditions, the generality of these conditions was examined by using different chalcone derivatives. As shown in Table 2, all chalcones gave good to high yields of 2-alkylthio-6*H*-1,3-thiazines. Electron-donating and electron-withdrawing groups on the chalcone do not affected the yields. Reaction of cyclohexenone with benzyl dithiocarbamate gave 2-alkylthio-4-hydroxy-4*H*-5,6-dihydro-1, 3-thiazine in high yields. Structures of the products were confirmed by IR, ^{1}H-NMR, ^{13}C-NMR, CHN analysis, and mass spectroscopy. ^{1}H-NMR spectrum shows a peak as doublet ($J = 5.8$ Hz) around 5.88 ppm that is related to C-5. Also, the peak at 4.85 ppm as doublet ($J = 5.8$ Hz) was assigned to hydrogen at C-6. The hydrogens of benzyl group appeared at around 4.47 and 4.56 ppm as doublet with coupling constant of 13.6 Hz, whereas for allyl group, these hydrogens appeared as multiplet at 3.97 ppm. The ^{13}C-NMR spectra clearly confirm the structure of products and the chemical shifts of C-2 at 159.5 ppm, and the presence of two peaks at the aliphatic region for C-6 and $-SCH_2$ were in the ranges reported in the literature [4,6]. Also, mass spectrometry and CHN analysis confirm the molecular formulas.

CONCLUSIONS

In conclusion, we have developed an efficient method for the synthesis of 4,6-substituted-2-alkylthio-6*H*-1,3-thiazines with the reaction of alkyl dithiocarbamates and chalcones in the presence of $ZrCl_4$ and TMSCl. The procedure is simple and mild and gives good to high yield of products.

Table 1

Solvent effect in the reaction of benzyl dithiocarbamate and chalcone.



Entry	Solvent	Yield(%)[a,b]
1	Methanol	Trace
2	Ether	22
3	DMSO	N.R.
4	THF	Trace
5	Acetonitrile	44
6	CH_2Cl_2	53
7	**$CHCl_3$**	**63**
8	DMF	N.R.
9	$CHCl_3$ (without TMSCl)	13[c]

[a]Isolated yield.
[b]Reaction condition: chalcone (1 mmol), benzyl dithiocarbamate (1.1 mmol), $ZrCl_4$ (30 mol%), TMSCl (1 mmol), and solvent (2 mL) at 60°C.
[c]Without using TMSCl.

Scheme 2. Synthesis of 2-alkylthio-6*H*-1,3-thiazines.

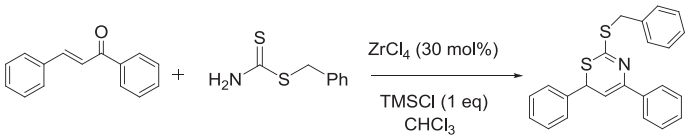
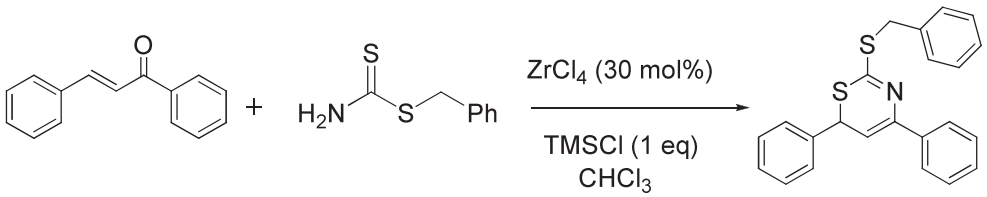
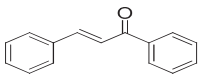
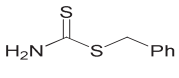
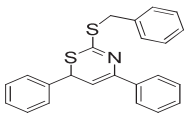
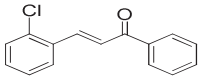
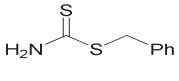
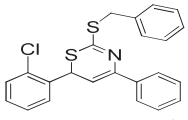
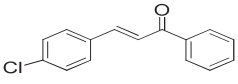
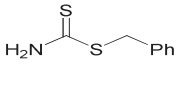
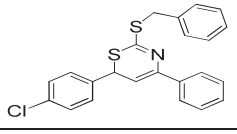


Table 2

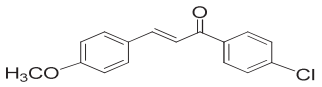
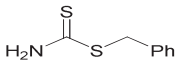
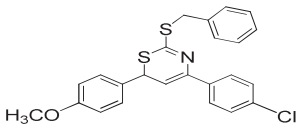
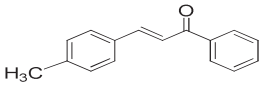
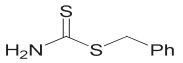
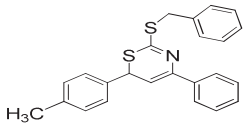
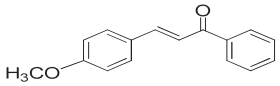
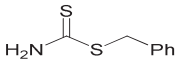
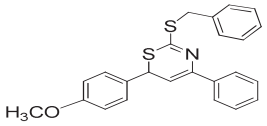
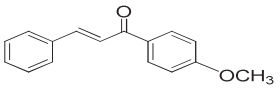
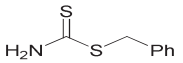
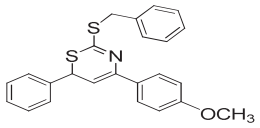
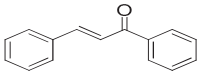
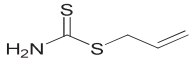
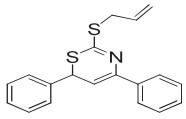
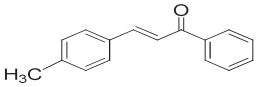
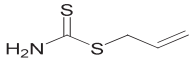
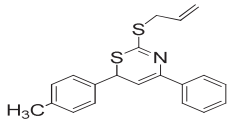
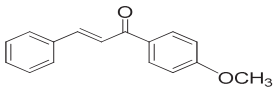
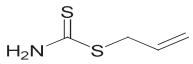
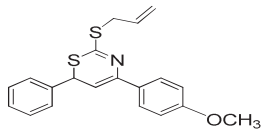
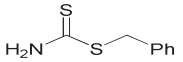
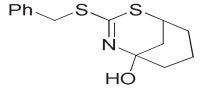
Synthesis of various 2-alkylthio-1,3-thiazines.



Entry	ketone	dithiocarbamate	product	yield(%)[a]
1				63
2				59
3				65

(*Continued*)

Table 2
(*Continued*)

4				53
5				58
6				65
7				61
8				69
9				69
10				58
11				75[6]

[a]Isolated yields. Reaction conditions: chalcone (1 equiv), dithiocarbamate (1.1 equiv), $ZrCl_4$ (30 mol%), and TMSCl (1 equiv), 60°C, 18 h.

EXPERIMENTAL

General. All reactions were carried out in an atmosphere of air. Chemicals and solvents were purchased from Merck (Darmstadt, Germany) and Fluka (Switzerland) and used as received. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Brucker 300 MHz spectrometer. Chemical shifts are reported in (ppm) relative to TMS or $CDCl_3$ as internal. Chalcones were prepared according to the literature procedures.

General procedure for synthesis of dithiocarbamate. In a 100-mL round-bottom flask containing aqueous ammonia (24%, 30 mmol) in pyridine (20 mL), carbon disulfide (40 mmol) was added. The reaction mixture was stirred for 2 h to give a red solution. Alkyl halide (20 mmol) was added, and the mixture was stirred overnight to give a yellow solution. The product was extracted with ethyl acetate and washed three times with water and 5% HCl solution. Evaporation of the solvent gave viscous oil that was precipitated when treated with petroleum ether. The precipitate was filtered and washed with petroleum ether to give pure dithiocarbamate (30% isolated yield).

General procedure for synthesis of 2-alkylthio-6*H*-1, 3-thiazines. In a test tube equipped with magnet, chalcone (3 mmol), dithiocarbamate (3.3 mmol), $CHCl_3$ (4 mL), $ZrCl_4$ (30 mol %), and TMSCl (3 mmol) were added respectively. After 18 h stirring at 60°C, the reaction mixture was filtered to remove the catalyst, and the filtrate was evaporated in a vacuum to give the crude product. Purifications have been done by column chromatography using silica gel and ethyl acetate : petroleum ether (1:9).

Spectroscopic data for selected compounds. **Table 2**, **entry 1**: IR (KBr) υ_{max} (cm^{-1}) 1602, 1527, 962, 754, 693; ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 4.49 (1H, d, J = 13.4 Hz), 4.57 (1H, d, J = 13.5 Hz), 4.89 (1H, dd, J = 5.6 and 1.3 Hz), 5.88 (1H, dd, J = 5.9 and 1.5 Hz), 7.26–7.39 (13H, m), 7.78 (2H, d, J = 7.9 Hz); ^{13}C-NMR (300 MHz, $CDCl_3$) δ (ppm) 35.7, 44.3, 103.9, 125.3, 125.7, 126.0, 127.3, 127.7, 128.3 (2C), 128.6, 128.9, 136.7, 138.0, 140.3, 145.9, 159.6. CHN Calcd for $C_{23}H_{19}NS_2$; C, 73.99; H, 5.09; N, 3.75. Found C, 73.71; H, 5.23; N, 3.66. **Table 2**, **entry 2**: IR (KBr) υ_{max} (cm^{-1}) 1536, 960, 760, 700; ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 4.47 (1H, d, J = 13.5 Hz), 4.55 (1H, d, J = 13.5 Hz), 5.32 (1H, d, J = 7.0 Hz), 5.86 (1H, d, J = 7.0 Hz), 7.22–7.42 (12H, m), 7.83 (2H, d, J = 7.9 Hz); ^{13}C-NMR (300 MHz, $CDCl_3$) δ (ppm) 35.6, 40.2,

101.9, 125.7, 127.31, 127.35, 128.4, 128.59, 128.98, 129.2, 129.3, 129.9 (2C), 132.5, 136.7, 137.2, 137.9, 146.7, 159.5; CHN Calcd for $C_{23}H_{18}NS_2Cl$; C, 67.73; H, 4.41; N, 3.43. Found C, 67.69; H, 4.33; N, 3.47. **Table 2**, **entry 3**: IR (KBr) υ_{max} (cm^{-1}) 1625, 1595, 1527, 1488, 1090, 964, 763, 697; ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 4.49 (1H, d, J = 13.5 Hz), 4.61 (1H, d, J = 13.5 Hz), 4.85 (1H, d, J = 6.2 Hz), 5.88 (1H, d, J = 6.2 Hz), 7.25–7.41 (12H, m), 7.79 (2H, d, J = 8.2 Hz); ^{13}C-NMR (300 MHz, $CDCl_3$) δ (ppm) 35.7, 43.2, 103.1, 125.7, 127.8, 128.2, 128.4, 128.6, 128.8, 129.0, 129.2, 133.9, 136.6, 137.8, 138.9, 146.2, 159.0; *Anal*. Calcd for $C_{23}H_{18}NS_2Cl$; C, 67.73; H, 4.41; N, 3.43. Found C, 67.77; H, 4.65; N, 3.25. **Table 2**, **entry 4**: IR (KBr) υ_{max} (cm^{-1}) 1603, 1526, 1509, 1255, 1173, 961, 828; ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 3.80 (3H, s), 4.45 (1H, d, J = 13.5 Hz), 4.54 (1H, d, J = 13.5 Hz), 4.85 (1H, d, J = 5.9 Hz), 5.83 (1H, dd, J = 5.9 and 1.2 Hz), 6.88 (2H, d, J = 7.6 Hz), 7.21–7.37 (9H, m), 7.68 (2H, d, J = 8.6 Hz); ^{13}C-NMR (300 MHz, $CDCl_3$) δ (ppm) 35.7, 43.7, 55.3, 104.5, 114.3, 126.9, 127.7, 128.4(2C), 128.8 (2C), 129.0, 132.1, 134.0, 136.6, 144.8, 159.5, 160.0; *Anal*. Calcd for $C_{24}H_{20}NS_2OCl$; C, 65.83; H, 4.57; N, 3.20. Found C, 65.60; H, 4.58; N, 2.99.**Table 2**, **entry 5**: IR (KBr) υ_{max} (cm^{-1}) 1602, 1511, 1447, 1243, 1177, 964, 768, 697; ^{1}H-NMR ($CDCl_3$, 500 MHz) 2.40 (3H, s), 4.55(1H, d, J = 13.5 Hz), 4.62 (1H, d, J = 13.5 Hz), 4.91 (1H, d, J = 5.8 Hz), 5.92 (1H, d, J = 5.8 Hz), 7.19–7.45 (12H, m), 7.84 (2H, d, J = 7.2 Hz); ^{13}C-NMR ($CDCl_3$, 500 MHz); 21.6, 36.1, 44.6, 104.7, 126.2, 127.8, 128.1, 128.7, 128.8, 129.1, 129.5, 130.1, 137.3, 137.8, 138.5, 138.6, 146.3, 159.9; *Anal*. Calcd for $C_{24}H_{21}NS_2$; C, 74.41; H, 5.43; N, 3.62. Found C, 73.98; H, 5.68; N, 3.58. **Table 2**, **entry 6**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 3.80 (3H, s), 4.47 (1H, d, J = 13.3 Hz), 4.55 (1H, d, J = 13.5 Hz), 4.85 (1H, d, J = 5.9 Hz), 5.86 (1H, d, J = 5.9 Hz), 6.84 (2H, d, J = 8.7 Hz), 7.22–7.39 (10H, m), 7.77 (2H, d, J = 6.7 Hz); ^{13}C-NMR (300 MHz, $CDCl_3$) δ (ppm) 35.6, 43.7, 55.3, 104.2, 114.2, 125.4, 125.6, 127.3, 128.3, 128.4, 128.6, 128.8, 128.9, 132.3, 138.1, 145.8, 159.4, 159.8. MS (EI): m/z = 267, 135, 121, 105, 91(100), 84, 77, 65, 49, 35. **Table 2**, **entry 7**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 3.86 (3H, s), 4.48 (1H, d, J = 13.5 Hz), 4.57 (1H, d, J = 13.5 Hz), 4.89 (1H, d, J = 5.9 Hz), 5.78 (1H, d, J = 5.9 Hz), 6.91 (2H, d, J = 8.9 Hz), 7.27–7.42 (10H, m), 7.73 (2H, d, J = 8.9 Hz); ^{13}C-NMR (300 MHz, $CDCl_3$) δ (ppm) 36.9, 44.3, 55.3, 102.1, 113.8, 126.9, 127.3, 127.6, 127.9, 128.1, 128.6, 128.8, 130.7, 136.8, 140.5, 145.5, 159.1, 159.8. MS (EI): m/z = 280, 135, 121, 105, 91(100), 77, 65, 45, 32, 29, 27, 15. **Table 2**, **entry 8**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 3.88 (2H, m), 4.88 (1H, d, J = 5.9 Hz), 5.13–5.32 (2H, m), 5.87 (1H, d, J = 5.9 Hz), 5.98 (1H, m), 7.29–7.43 (8H, m), 7.79 (2H, dd, J = 7.9 and 1.2 Hz). MS (EI): m/z = 324, 121, 105, 77, 64, 57, 51, 45, 41, 39 (100), 32, 27. **Table 2**, **entry 9**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 2.36 (3H, s), 3.91–3.98 (2H, m), 4.86 (1H, d, J = 5.9 Hz), 5.14–5.34 (2H, m), 5.87–6.12 (2H, m), 7.14–7.81 (7H, m), 7.81 (2H, dd, J = 8.2 and 1.2 Hz); ^{13}C-NMR (300 MHz, $CDCl_3$) δ (ppm) 21.1, 34.2, 44.0, 104.0, 118.3, 125.6, 127.5, 128.2, 128.7, 129.3, 132.9, 137.4, 137.9, 138.0, 145.7, 159.0. MS (EI): m/z = 337, 264, 105, 91, 77, 51, 45, 41, 39 (100), 29. **Table 2**, **entry 10**: IR (KBr) υ(cm^{-1}) 1635, 1606, 1529, 1508, 1250, 1173, 1031, 964, 834, 699; ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 3.81–3.97 (5H, m), 4.87 (1H, d, J = 5.9 Hz), 5.13–5.33 (2H, m), 5.76 (1H, d, J = 5.9 Hz), 6.0 (1H, m), 6.92 (2H, d, J = 8.7 Hz), 7.25–7.40 (5H, m), 7.74 (2H, d, J = 8.8 Hz); ^{13}C-NMR (300 MHz, $CDCl_3$) δ (ppm) 34.2, 44.3, 55.3, 101.9, 113.9, 118.3, 128.0, 128.4, 128.8 (2C), 129.7, 132.9, 140.5, 145.4, 158.7, 159.8; *Anal*. Calcd for $C_{20}H_{19}NS_2O$; C, 67.98; H, 5.38; N, 3.97. Found C, 67.21; H, 5.93; N, 3.70.

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