REGIOSELECTIVE CYCLOCONDENSATIONS OF CHLOROCARBONYLSULFENYL CHLORIDE WITH HYDRAZONES: EFFECTIVE SYNTHESIS OF A CLASS OF SULFUR AND NITROGEN CONTAINING HETEROCYCLES WITH -COS- LINKAGE

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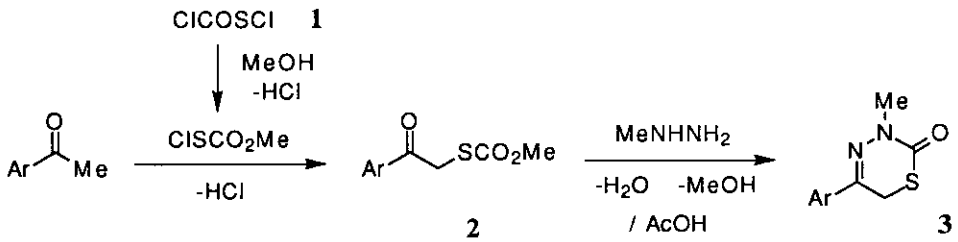
Abstract - Regioselective cyclocondensations of several hydrazones with chlorocarbonylsulfenyl chloride afforded 1,3,4-(3*H*,6*H*)-thiadiazin-2-one derivatives and 3(2*H*)-(dimethylamino)thiazolones. The -COS- linkage was effectively incorporated into the *S*, *N*-containing heterocycles.

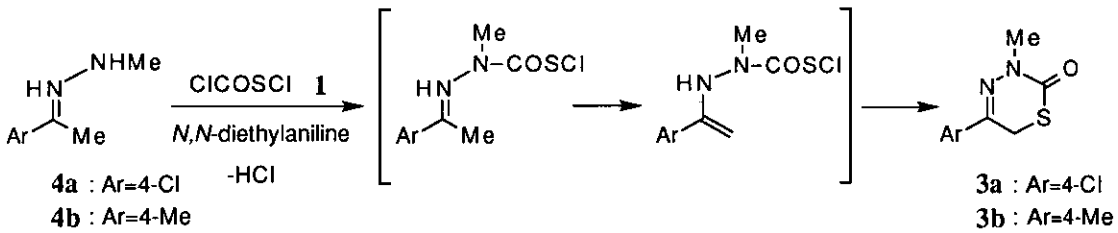
The electrophilic bifunctional reagents such as chlorosulfonyl isocyanate ($ClSO_2NCO$)[1] and chlorocarbonylsulfenyl chloride (ClCOSCl; abbreviated CCSC; **1**)[2] used for cyclocondensation reactions are recognized as important synthetic building blocks for preparing heterocyclic sulfur- and/or nitrogen-containing compounds. During our continuing synthetic studies in search of *S*, *N*-containing heterocycles,[3] we have reported the effective and practical syntheses of 2(3*H*)-benzothiazolone derivatives employing CCSC (**1**).[4,5] Since some of these 2(3*H*)-benzothiazolones and 2(3*H*)-thiazolones comprise useful pesticides, medicines, and dyestuffs,[4,6] their synthesis is considered of practical importance. Recently, we have reported the regioselective preparation of α-methoxycarbonylsulfenyl ketones and aldehydes (**2**), which serve as a favorite synthon for 2(3*H*)-thiazolones, 5-aryl-3-methyl-1,3,4-(3*H*,6*H*)-thiadiazine-2-ones (**3**) as an isoster of 2(3*H*)-thiazolones, and 3-thiolindoles.[7]

Sulfenyl compounds (**2**) are obtained by the coupling reaction between the corresponding ketones or

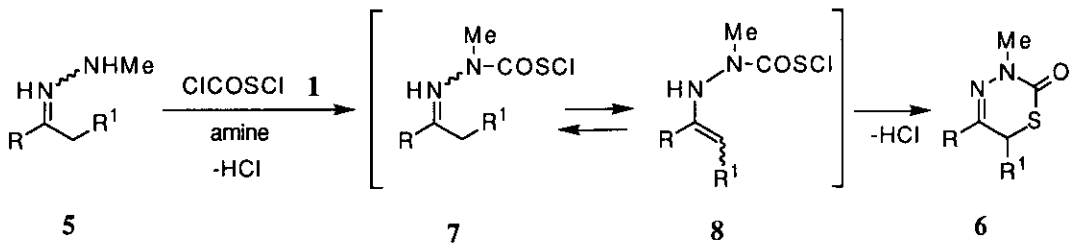


aldehydes and methoxycarbonylsulfenyl chloride which is prepared from CCSC (**1**) and methanol. However, this method for preparing **3** has the folowing drawbacks: (1) incorporation of key -COS- linkage requires stepwise condensation reactions; (2) substituent of 5-position and 6-position is only limited to aryl groups and hydrogen, respectively; and (3) somewhat harsh conditions (80 °C in AcOH solvent) are required to conduct this cyclocondensation.

To solve these problems, a more direct [2+4] cyclocondensation using CCSC (**1**) was examined. We now describe an alternative and more straightforward synthetic route for preparing 1,3,4-(3*H*,6*H*)-thiadiazin-2-ones; the one-pot cyclocondensation of methyl hydrazones (**4**) with CCSC (**1**) afforded 5-aryl-3-methyl-1,3,4-(3*H*,6*H*)-thiadiazin-2-ones (**3**) in better yields than the aforementioned method.



In addition, the present method is applicable to preparing 5,6-dialkyl-3-methyl-1,3,4-(3*H*,6*H*)-thiadiazin-2-ones (**6**) from methyl hydrazones (**5**) possessing an aliphatic substituent (R and R^1). Moreover, a new class of 3-aryl derivatives (**10**) could be obtained from aryl hydrazones (**9**) upon treatment with CCSC (**1**). These results are listed in Table 1.



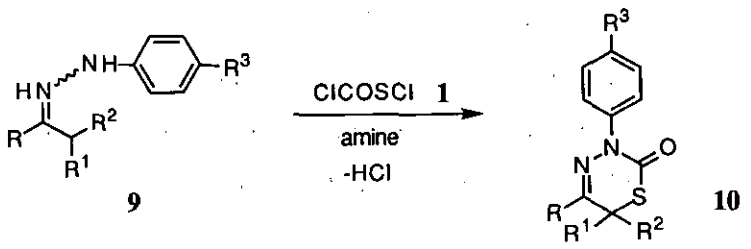


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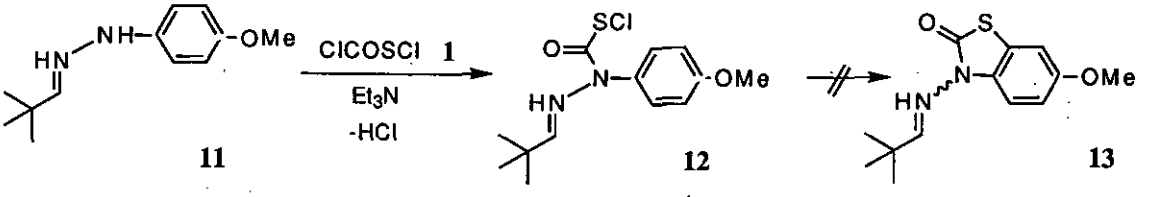
Table 1. Cyclocondensations of CCSC (1) with Methyl Hydrazones (5) and Aryl Hydrazones (9).[a]

Entry		Hydrazone				Amine	Product	Yield / %
		R	R^1	R^2	R^3			
1	**5a**	H	$PhCH_2$	--	--	Tributylamine	**6a**	42
2	**5b**	Me	*n*-C_5H_{11}	--	--	*N,N*-Diethylaniline	**6b**[b]	31
3	**5c**	Pr	Et	--	--	*N,N*-Diethylaniline	**6c**	42
4	**9a**	*i*-Pr	Me	Me	MeO	*N,N*-Diethylaniline	**10a**	41
5	**9b**	*t*-Bu	H	H	MeO	*N,N*-Diethylaniline	**10b**	52

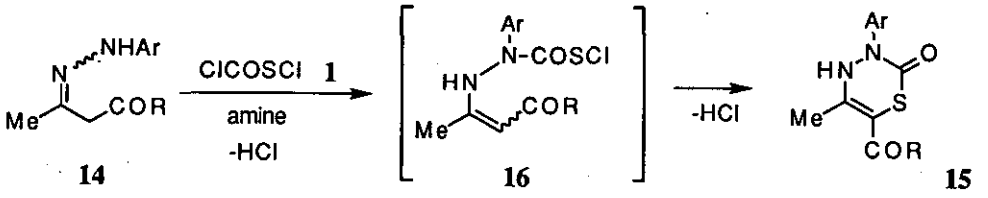
[a] The reactions were carried out at 0 °C-room temperature for 10 h. Molar ratio of **5** (or **9**): **1** : amine = 1 1.1 : 1.1. [b] A regioisomer (R=*n*-C_6H_{13}; R^1=R^2=H) was contained in < 10%.

All three reactions using hydrazones (**4**, **5**, and **9**) proceeded smoothly under milder reaction conditions (using 1.1 equiv. of amine at 0 °C-room temperature in toluene or THF solvent) compared with those using **2**. The amine as the HCl scavenger is considered to work in the acylation step, whose plausible mechanism is similar to the case of the previous synthesis of 2(3*H*)-benzothiazolones.[4] It is noted that this S-C bond formation proceeded with moderate regioselectivity (Table 1, Entry 2), i.e., in thermodynamically controlled manner, which is consistent with the tendency of α-methoxycarbonylsulfenylation[7] and α-thiocyanation of ketones.[8] Although hydrazones (**5**) are a mixture of the *E*- and *Z*- forms, it is postulated that the initial acylated hydrazone intermediate (**7**) can change by tautomerization to the reactive hydrazines intermediate (**8**), which in turn is able to undergo the desired cyclization.

Hydrazone (**11**) is apparently an unsuitable substrate for the present cyclocondensation. Nevertheless, we tested a similar reaction using **11** expecting the preparation of the corresponding 2(3*H*)-benzothiazolone (**13**).[4] This trial resulted only in the isolation of considerably stable sulfenyl chloride (**12**) in 80% yield, which did not cyclize to give **13** even with the aid of $AlCl_3$ or H_2SO_4.



We also found that aryl hydrazones (**14**), derived from active methylene compounds such as methyl acetoacetate and 2,4-pentanedione, more smoothly underwent this cyclocondensation to give 1,3,4-(3*H*,4*H*)-thiadiazin-2-ones (**15**) in better yields, the result of which could be accounted for easier formation of reactive intermediate (**16**). Being encouraged by these results, the use of the *N*,*N*-dimethylhydrazones of methyl acetoacetate (**17a**) and 2,4-pentanedione (**17b**) was next tried. Consequently, an alternative [2+3] cyclocondensation proceeded to afford 3(2*H*)-dimethylaminothiazol-2-ones (**18a** and **18b**) in good yields (~ 80%).

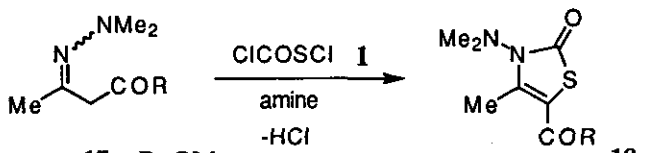


In conclusion, several types of cyclocondensation utilizing the characteristics of CCSC (**1**) are described. These cyclocondensation proceeded regioselectively and realized the preparation of a class of *S*, *N*-containing heterocycles with -COS- linkage.

Table 2. Cyclocondensations of CCSC (1) with Hydrazones of Methyl Acetoacetate and 2,4-Pentanedione (14).[a]

Entry	Hydrazones			Product	Yield / %
		Ar	R		
1	**14a**	Ph	OMe	**15a**	71
2	**14b**	Ph	Me	**15b**	66
3	**14c**	4-Cl-Ph	OMe	**15c**	58
4	**14d**	4-Me-Ph	OMe	**15d**	46

[a] The reactions were carried out using triethylamine as a base at 0 °C-room temperature for 10 h. Molar ratio of **14** : **1** : amine = 1: 1.1: 1.1.



17a: R=OMe **18a**

17b: R=Me **18b**

EXPERIMENTAL

All melting points were determined on a hot stage microscope apparatus (Yanagimoto) and are uncorrected. ^{1}H Nmr spectra were recorded on a Hitachi R-24 B (60 MHz) or JEOL EX-90 (90 MHz) spectrometer using TMS as an internal standard in $CDCl_3$. ^{13}C Nmr spectra were recorded on a JEOL α (400 MHz) spectrometer using TMS as an internal standard in $CDCl_3$. Mass spectra were obtained on a Hitachi M-80 spectrometer. Ir spectra were recorded on a Hitachi 270-30 spectrophotometer. Silica gel column chromatography was performed on a Merck Art. 7734. Methyl- and arylhydrazones were prepared by the known procedure.[9]

5-(4-Chlorophenyl)-3-methyl-1,3,4-(3*H*,6*H*)-thiadiazin-2-one (3a).

To a stirred solution of 4-chloroacetophenone methylhydrazone (183 mg, 1.0 mmol) and *N*,*N*-diethylaniline (164 mg, 1.1 mmol) in toluene (2.0 ml) was added CCSC (**1**, 144 mg, 1.1 mmol) at 0-5 °C.

The reaction mixture was allowed to warm to room temperature followed by being stirred for 10 h. 1M-HCl aqueous solution (20 ml) was added to the mixture, which was extracted with EtOAc (20 ml). The organic phase was washed with 1M-HCl aqueous solution, sat. aqueous $NaHCO_3$ solution, brine, dried (Na_2SO_4), concentrated. The crude residue was purified by silica gel column chromatography (chloroform and/or hexane/ethyl acetate = 5:1) to give the desired compound (125 mg, 52 %). Colorless crystals; mp 156-157 °C (lit.,[5] 157-159 °C).

5-(*p*-Tolyl)-3-methyl-1,3,4-(3*H*,6*H*)-thiadiazin-2-one (3b).

With a similar procedure as that for preparing **3a**, the desired compound was obtained in 64 % yield. Colorless crystals; mp 94-96 °C (lit.,[5] 94-95 °C).

6-Benzyl-3-methyl-1,3,4-(3*H*,6*H*)-thiadiazin-2-one (6a).

With a similar procedure as that for preparing **3a**, except using tributylamine as acid scavenger in place of *N,N*-diethylaniline, the desired compound was obtained. Yellow oil; Anal. Calcd for $C_{11}H_{12}N_2OS$: C, 59.97; H, 5.49; N, 12.72. Found C, 59.69; H, 5.68; N, 12.44. ^{1}H Nmr δ=3.05 (1H, dd, *Jgem* = 12 Hz, *J* = 2 Hz), 3.60 (1H, dd, *Jgem* = 12 Hz, *J* = 2 Hz), 3.35 (3H, s), 3.80-4.05 (1H, m), 7.05 (1H, d, *J* = 3 Hz), 7.10-7.50 (5H, m); ir (film) ν_{max}: 1720 cm^{-1}.

6-Pentyl-3,5-dimethyl-1,3,4-(3*H*,6*H*)-thiadiazin-2-one (6b).

With a similar procedure as that for preparing **3a**, except using THF as solvent in place of toluene, the desired compound was obtained. Yellow oil; Anal. Calcd for $C_{10}H_{18}N_2OS$: C, 56.04; H, 8.46; N, 13.07. Found C, 55.88; H, 8.40; N, 12.91. ^{1}H Nmr δ=0.90 (3H, t, *J* = 7 Hz), 1.10-2.00 (6H, m), 2.15 (3H, s), 2.30-2.60 (2H, m), 3.25-3.40 (1H, m), 3.35 (3H, s); ir (film) ν_{max}: 1720 cm^{-1}. A regioisomer of **6b** i.e., 5-hexyl-3-methyl-1,3,4-(3*H*,6*H*)-thiadiazin-2-one: ^{1}H Nmr δ=0.90 (3H, t, *J* = 7 Hz), 1.10-2.00 (9H, m), 2.15 (3H, s), 2.30-2.60 (2H, m), 3.25-3.40 (1H, m), 3.35 (3H, s), 3.40 (2H, s); ir (film) ν_{max}: 1720 cm^{-1}.

6-Ethyl-3-methyl-5-propyl-1,3,4-(3*H*,6*H*)-thiadiazin-2-one (6c).

With a similar procedure as that for preparing **6b**, the desired compound was obtained. Yellow oil; Anal. Calcd for $C_9H_{16}N_2OS$: C, 53.97; H, 8.05; N, 13.99. Found C, 53.78; H, 7.99; N, 13.74. ^{1}H Nmr δ=0.85-1.20 (6H, m), 1.40-1.95 (4H, m), 2.30-2.55 (2H, m), 3.20 (1H, dd, *J* = 10 Hz, 6 Hz), 3.40 (3H, s); ir (film) ν_{max}: 1720 cm^{-1}.

5-Isopropyl-3-(4-methoxyphenyl)-6,6-dimethyl-1,3,4-(3*H*,6*H*)-thiadiazin-2-one(10a).

With a similar procedure as that for preparing **3a**, the desired compound was obtained. Colorless crystals,

mp 98-99 °C ; Anal. Calcd for $C_{15}H_{20}N_2O_2S$: C, 61.62; H, 6.89; N, 9.58. Found C, 61.62; H, 6.94; N, 9.64. ^{1}H Nmr δ=1.20 (6H, d, *J* = 7 Hz), 1.60 (6H, s), 2.65-3.00 (1H, m), 3.80 (3H, s), 6.90 (2H, d, *J* = 8 Hz), 7.40 (2H, d, *J* = 8 Hz); ^{13}C nmr δ=21.94, 25.94, 30.84, 45.15, 55.48, 113.86, 126.17, 134.62, 160.54; ms *m/z* 292 (M^+); ir (film) ν_{max}: 1720 cm^{-1}.

5-(*tert*-Butyl)-3-(4-methoxyphenyl)-1,3,4-(3*H*,6*H*)-thiadiazin-2-one (10b).

With a similar procedure as that for preparing **3a**, the desired compound was obtained. Colorless crystals, mp 115-117 °C ; Anal. Calcd for $C_{14}H_{18}N_2O_2S$: C, 60.41; H, 6.52; N, 10.06. Found C, 60.41; H, 6.52; N, 9.91. ^{1}H Nmr δ=1.20 (9H, s), 3.50 (2H, s), 3.80 (3H, s), 6.90 (2H, d, *J* = 8 Hz), 7.40 (2H, d, *J* = 8 Hz); ir (film) ν_{max}: 1720 cm^{-1}.

Trimethylacetaldehyde chlorosulfenylcarbonyl(4-methoxyphenyl)hydrazone (12).

With a similar procedure as that for preparing **3a**, **12** was obtained. Light brown crystals, mp 117-119 °C; Anal. Calcd for $C_{13}H_{17}N_2O_2ClS$: C, 51.91; H, 5.70; N, 9.31. Found C, 51.69; H, 5.71; N, 9.27. ^{1}H Nmr δ=1.10 (9H, s), 3.85 (3H, s), 6.75 (1H, s), 6.90-7.20 (4H, m); ms *m/z* 300 (M^+)

Methyl [3-phenyl-5-methyl-2-oxo-1,3,4-(3*H*,4*H*)thiadiazin-6-yl]carboxylate (15a).

With a similar procedure as that for preparing **3a**, the desired compound was obtained. Colorless crystals, mp 141-143 °C; Anal. Calcd for $C_{12}H_{12}N_2O_3S$: C, 54.53; H, 4.58; N, 10.60. Found C, 54.27; H, 4.51; N, 10.46. ^{1}H Nmr δ=2.55 (3H, s), 3.85 (3H, s), 6.55-7.35 (5H, m), 6.70-6.85 (1H, br s; -NH-); ^{13}C nmr δ=12.79, 52.19, 99.93, 113.23, 122.51, 129.52, 133.09, 145.29, 146.00, 170.05; ms *m/z* 264 (M^+)

6-Acetyl-3-phenyl-5-methyl-1,3,4-(3*H*,4*H*)thiadiazin-2-one (15b).

With a similar procedure as that for preparing **3a**, the desired compound was obtained. Yellow oil, Anal. Calcd for $C_{12}H_{12}N_2O_2S$: C, 58.05; H, 4.87; N, 11.28. Found C, 57.88; H, 4.77; N, 11.05. ^{1}H Nmr δ=2.25 (3H, s), 2.30(3H, s), 7.25-7.50 (1H, br s; -NH-), 7.35-7.55 (5H, m); ms *m/z* 248 (M^+); ir (film) ν_{max}: 3250, 1725, 1650 cm^{-1}.

Methyl [3-(4-chlorophenyl)-5-methyl-2-oxo-1,3,4-(3*H*,4*H*)thiadiazin-6-yl]carboxylate (15c).

With a similar procedure as that for preparing **3a**, the desired compound was obtained. Colorless crystals, mp 142-144 °C; Anal. Calcd for $C_{12}H_{11}ClN_2O_3S$: C, 48.25; H, 3.71; N, 9.38. Found C, 48.01; H, 3.67; N, 9.56. ^{1}H Nmr δ=2.55 (3H, s), 3.85 (3H, s), 6.55 (2H, d, *J* = 12 Hz), 7.20 (2H, d, *J* = 12 Hz),

7.20-7.50 (1H, br s); ^{13}C nmr δ=13.50, 52.59, 100.64, 114.78, 127.74, 129.77, 144.26, 145.68, 162.04, 170.16; ir (KBr) ν_{max}: 3250, 1726, 1658 cm^{-1}.

Methyl [5-methyl-2-oxo-3-(*p*-tolyl)-1,3,4-(3*H*,4*H*)-thiadiazin-6-yl]carboxylate (15d).

With a similar procedure as that for preparing **3a**, the desired compound was obtained. Colorless crystals, mp 185-186 °C; Anal. Calcd for $C_{13}H_{14}N_2O_3S$: C, 56.10; H, 5.07; N, 10.06. Found C, 56.02; H, 4.98; N, 10.26. ^{1}H Nmr δ=2.25 (3H, s), 2.55 (3H, s), 3.85 (3H, s), 6.60 (2H, d, J = 10 Hz), 7.10 (2H, d, J = 10 Hz), 6.50-6.80 (1H, br s); ^{13}C nmr δ=12.74, 20.47, 52.10, 99.73, 113.25, 129.90, 131.74, 142.92, 145.86, 161.84, 169.79; ir (KBr) ν_{max}: 3427, 1722, 1664 cm^{-1}.

Methyl [3-dimethylamino-4-methyl-2-oxo-2(3*H*)-thiazol-3-yl]carboxylate (18a).

With a similar procedure as that for preparing **3a**, the desired compound was obtained in 82% yield. Colorless crystals, mp 87.5-88.5 °C; Anal. Calcd for $C_8H_{12}N_2O_3S$: C, 44.43; H, 5.59; N, 12.95. Found C, 44.21; H, 5.42; N, 12.98. ^{1}H Nmr δ=2.50 (3H, s), 2.95 (6H, s), 3.80 (3H, s); ms *m/z* 216 (M^+), 173 (M^++1-NMe_2).

5-Acetyl-3-dimethylamino-4-methyl-2(3*H*)-thiazolone (18b).

With a similar procedure as that for preparing **3a**, the desired compound was obtained in 77% yield. Colorless crystals, mp 78-80 °C; Anal. Calcd for $C_8H_{12}N_2O_2S$: C, 47.98; H, 6.04; N, 13.99. Found C, 47.77; H, 5.97; N, 14.07. ^{1}H Nmr δ=2.25 (3H, s), 2.30(3H, s), 2.95 (6H, s); ms *m/z* 200 (M^+), 157 (M^++1-NMe_2).

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