HETEROCYCLIZATION REACTIONS OF CHLOROSULFONYL ISOCYANATE WITH ETHYL 3-OXO-2-(ARYLHYDRAZONO)BUTANOATES

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Abstract- Reaction of chlorosulfonyl isocyanate with ethyl 3-oxo-2-(arylhydrazono)butanoates (**1a-i**) gave thiadiazolotriazinediones (**3a-i**) and thiatriazinothioxapyridazines (**6a-i**). Here a 1:2 reaction of the butanoate and CSI followed by cyclization is postulated.

Chlorosulfonyl isocyanate (CSI, O=C=N-SO_2-Cl) is reported[1] to effect a number of heterocyclizations with various bifunctional compounds to produce useful and sometimes novel heterocycles. Many amino compounds having an ester or carbonyl function, on reaction with CSI, give the corresponding heterocycles.[1-3] In these reactions the CSI is reported to react first at the active hydrogen centre (NH), followed by a cyclocondensation.

Ethyl 3-oxo-2-(arylhydrazono)butanoates (**1a-i**)[4] are reported to serve as useful starting materials for the synthesis of many heterocyclic compounds. The reactions of **1a-i** with various electrophilic reagents (for example, phenyl isocyanate, dimethyl acetylenedicarboxylate, etc) provide an intermediary adduct, which then cyclizes due to the presence of the ester/carbonyl functionality. Cyclization *via* the ester functionality produces a heterocycle carrying a free acetyl group. The latter can be functionalized further to the heterocyclic analogues of chalcones,[5] which have attracted considerable attention due to their interesting biological

activities.[5] We extended the reaction of ethyl 3-oxo-2-(arylhydrazono)-butanoates with chlorosulfonyl isocyanate to obtain the heterocycles, namely, acetyl substituted triazinones or thiatriazinones. It is interesting to note that the heterocycles obtained in these reactions do not carry any free acetyl group. Further investigation revealed that the initially formed heterocycle with a free acetyl group reacted further with the highly reactive heterocumulene chlorosulfonyl isocyanate, leading to the formation of another heterocycle.

RESULTS AND DISCUSSION

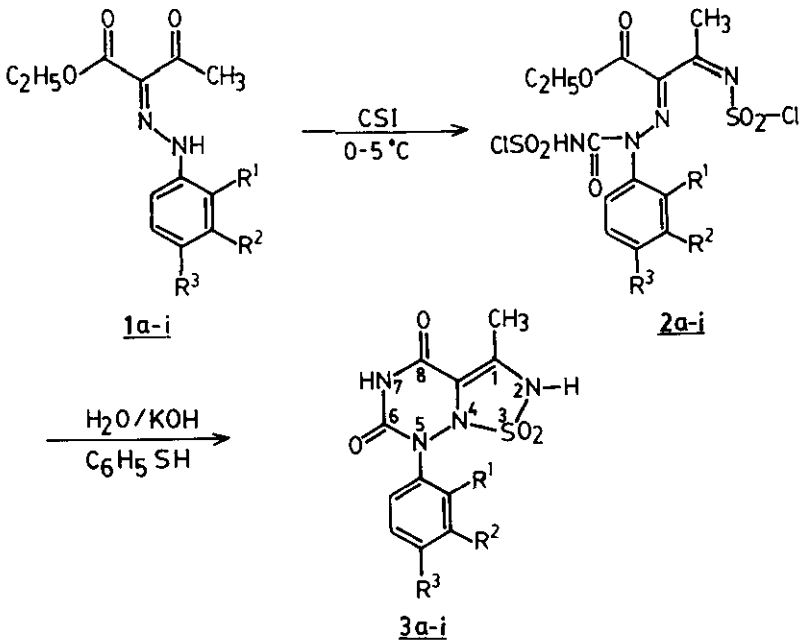
Reaction of CSI with ethyl 3-oxo-2-(p-chlorophenylhydrazono)butanoate (**1a**) at 0-5°C followed by hydrolysis gave **3a** in 37.5% yield.[6] The mass spectral parent ion (m/z: 330 (M^++2), 328 (M^+)) and fragmentation pattern (m/z: 43 (CONH), 64 (SO_2), 125 (ClC_6H_4N), 127 ($ClC_6H_4NH_2$), 152 ($M^+-SO_2+ClC_6H_5$), 153 (ClC_6H_4NCO), 193 ($M^+-SO_2+CONHCO$), 218 ($M^+-SO_2+ClC_6H_3$) 264 (M^+-SO_2), 267 (M^+-CONH_2OH), 292 (M^+-HCl) of **3a** indicate that it is formed by the introduction of -CONH- and $-SO_2-$ moieties. The above conclusion was confirmed by the characteristic ir absorption bands of **3a** corresponding to -CONHCO- (1730, 1710 cm^{-1}) and $-SO_2-$(1380, 1190 cm^{-1}) moieties. The involvement of ester as well as carbonyl functionalities of **1a** in the cyclocondensation reaction with CSI to form **3a** was confirmed by the absence of ethoxy and acetyl proton signals in its ^{1}H-nmr spectrum. However, it shows two deuterium exchangeable (NH) proton signals at δ 4.16-4.60 and three methyl protons (as a singlet) at δ 1.50, which is in agreement with the assigned structure viz., 5-(p-chlorophenyl)-2,3,5,6,7,8-hexahydro-1-methyl-2,3,4-thiadiazolo[4,3-a]triazine-6,8-dione-3,3-dioxide.

The formation of the bicyclic compound (**3a**) is shown in Scheme 1. Thus a bimolecular addition of CSI to the active hydrogen (NH) and ketocarbonyl centres of **1a** resulted in the formation of **2a**. Hydrolysis of this

intermediate in presence of benzenethiol effected cyclocondensation to form **3a**. It was not possible to isolate the initially formed iminosulfonyl derivative (**2a**) due to its inherent instability.[7] The reduction of N-chlorosulfonylimino group in presence of thiophenol and aqueous potassium hydroxide solution is documented in literature.[8]

Temperature is reported to influence the course and the nature of the products formed in the reaction of CSI with phenols.[1,9] A similar generalization, but to a limited extent, is valid in the reaction of CSI with amines. In the present study the influence of elevated temperature, 110°C (refluxing toluene) was studied in respect of the reaction of **1a** with CSI.

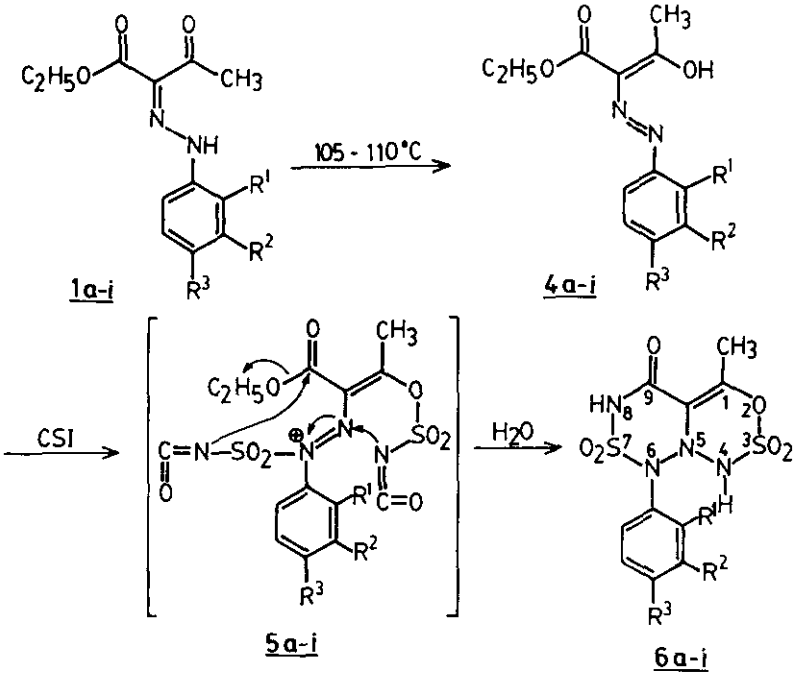
Scheme 1



1a-i 2a-i 3a-i

On the basis of mass spectroscopic data, the isolated product (**6a**) (38%) was found to be a 1:2 cycloadduct. The formation of **6a** by the addition of the sulfur of the sulfonyl moiety of CSI to **1a** is confirmed by the molecular ion (m/z: 380) and its fragmentation pattern (m/z: 346, 344 (M^+-HCl), 337 (M^+-CONH), 332 (M^+-SO), 319 (M^+-SON), 316 (M^+-SO_2), 301 (M^+-SO_2NH), 300 (M^+-SO_3), 285 (M^+-SO_3NH), 191 ($ClC_6H_4SO_2NH_2$), 125 (ClC_6H_4N), 64 (SO_2), 43 (CONH)). The prominent fragment ions of **6a** at m/z: 300 (M^+-SO_3) and 285 (M^+-SO_3NH) confirmed the presence of -SO_2- moeties attached to oxygen and nitrogen atoms of the described heterocycle.

Scheme 2



The above conclusion was further confirmed by the presence of characteristic ir absorption bands of **6a** corresponding to -CONH- (1710 cm^{-1}) and SO_2/SO_3(1385, 1310, 1110, 1060 cm^{-1}) moieties respectively. The involvement of both carbonyl and ester functionalities of **1a** in the cyclization process with CSI to produce **6a** was confirmed by the absence of ethoxy and acetyl proton signals in its ^{1}H-nmr spectrum. However, it showed two deuterium exchangeable proton (NH) signals as a broad singlet at δ 4.30 and three methyl protons as a singlet at δ 1.40. Based on the above spectral data the compound (**6a**) was assigned as 6-(p-chlorophenyl)-2,3,4,6,7,8,9-heptahydro-1-methyl-5,6,7,8,9-thiatriazinone-7,7-dioxo[5,4-a]-2,3,4,5-thioxapyridazine-3,3-dioxide.

A mechanism which accounts for the formation of **6a** is shown in Scheme 2. Thus at elevated temperature a bimolecular addition of the sulfur (of the sulfonyl group of CSI) to the two nucleophilic centers of **4a** takes place to produce the reactive diisocyanate intermediate (**5a**), which undergoes cyclocondensation to form **6a**. The isomerization of **1a** to **4a** at elevated temperature is reported in literature.[4] The enhanced reactivity of the acetyl group of **1a** towards CSI is responsible for the formation of 1:2 rather than 1:1 cycloadduct.

The butanoates (**1b-i**) undergo reaction with CSI at 0-25°C and 105-110°C in an analogous manner as described earlier to produce the corresponding thiadiazolotriazinediones (**3b-i**) and thiatriazinothioxapyridazines (**6b-i**). Analytical and spectral data of all these compounds are given in Table-1.

Table-1: Analytical and spectral data of compounds (**3a-i**) and (**6a-i**)

Compound No.	Analytical data Found (Calcd) C	H	N	Spectral data ir cm^{-1}	pmr δ	mass m/z(rel. int.)
		$C_{11}H_9N_4O_4SCl$		3400-3300, 1730,	1.50(s, 3H), 4.16-	330(M^++2,6),
3a	40.11	2.63	16.87	1710, 1640, 1380,	4.60(b,NH,2H),	329(M^++1,2),
	(40.19)	(2.75)	(17.09)	1190, 830	7.50(m,4H)	328(M^+,14),
						125(100)
		$C_{11}H_{10}N_4O_4S$		3450-3300, 1725,	1.60(s,3H), 4.40	
3b	44.75	3.21	18.91	1640, 1370, 1180,	(b,NH,2H),	294(M^+,16),
	(44.89)	(3.40)	(19.04)	760, 710	7.40(m,5H)	77(100)
		$C_{12}H_{12}N_4O_4S$		3350, 1730, 1705,	1.45(s,3H),	
3c	46.59	3.71	18.01	1640, 1370, 1170,	2.50(s,3H),	308(M^+,10),
	(46.75)	(3.92)	(18.17)	830	4.30(b, NH,2H),	105(100)
					7.50(m,4H)	
		$C_{11}H_9N_5O_6S$		3450, 1735, 1650,	1.50(s,3H), 4.20-	
3d	38.72	2.48	20.43	1600, 1520, 1350,	4.40(b,NH,2H),	293(M^+-46,
	(38.94)	(2.67)	(20.64)	1190, 740	7.50-8.00(m,4H)	40), 76(100)
		$C_{11}H_9N_4O_4SBr$		3400, 1730, 1630,	1.55(s,3H), 4.10-	
3e	35.16	2.24	14.85	1600, 1390, 1200,	4.40(b,NH,2H),	375(M^++2,15),
	(35.40)	(2.43)	(15.01)	780	7.50-8.15(m,4H)	373(M^+,10),
						156(100)
		$C_{12}H_{12}N_4O_5S$		3350, 1740, 1710,	1.51(s,3H),	
3f	44.31	3.52	17.15	1620, 1380, 1260,	3.95(s,3H),4.40-	324(M^+,4),
	(44.44)	(3.72)	(17.27)	1190, 830	4.65(b,NH,2H),	106(100)
					7.50-8.00(m,4H)	
		$C_{11}H_9N_4O_4SCl$		3350, 1780, 1705,	1.50(s,3H), 4.20-	
3g	40.10	2.61	16.85	1640, 1360, 1180,	4.60(b,NH,2H),	330(M^++2,6),
	(40.19)	(2.75)	(17.04)	740	7.50(m,4H)	328(M^+,10),
						125(100)
		$C_{11}H_9N_4O_4SCl$		3350, 1735, 1705,	1.50(s,3H),	
3h	40.13	2.61	16.86	1640, 1390, 1180,	4.55(b,NH,2H),	330(M^++2,10),
	(40.19)	(2.75)	(17.04)	760	7.50-8.00(m,4H)	328(M^+,10),
						125(100)

contd.....

Table-1 continued

		$C_{12}H_{12}N_4O_5S$		3340, 1745, 1720,	1.55(s,3H),	
3i	44.28	3.54	17.07	1610, 1385, 1250,	3.90(s,3H),	324(M^+,5),
	(44.44)	(3.72)	(17.27)	1185, 830, 740	4.60(s,NH,2H),	106(100)
					7.50-8.20(m,4H)	
		$C_{10}H_9N_4O_6S_2Cl$		3450, 1720, 1620,	1.40(s,3H),	
6a	31.38	2.21	14.62	1530, 1230, 1200,	4.30(b,NH,2H),	379(M^+-1,18),
	(31.57)	(2.36)	(14.51)	1040, 830	7.20-7.90(m,4H)	75(100)
		$C_{10}H_{10}N_4O_6S_2$		3450, 1430, 1630,	1.38(s,3H),	
6b	34.51	2.71	15.95	1540, 1230, 1070,	4.45(b,NH,2H),	348(M^++2,10),
	(34.68)	(2.91)	(16.17)	750, 710	7.50(m,5H)	346(M^+,8),
						77(100)
		$C_{11}H_{12}N_4O_6S_2$		3450, 1740, 1620,	1.45(s,3H),	
6c	36.42	3.18	15.43	1240, 1080, 830,	2.60(s,3H),	360(M^+,5),
	(36.66)	(3.35)	(15.59)		4.40(b,NH,2H),	90(100)
					7.40-7.80(m,4H)	
		$C_{10}H_9N_5O_8S_2$		3450, 1730, 1600,	1.50(s,3H),	
6d	30.52	2.18	17.73	1530, 1380, 1260,	4.50(b,2H,NH),	391(M^+,3),
	(30.69)	(2.31)	(17.89)	1090, 760, 710	7.50-8.20(m,4H)	75(100)
		$C_{10}H_9N_4O_6S_2Br$		3400, 1730, 1610,	1.50(s,3H),	
6e	28.03	2.04	13.06	1360, 1250, 1090,	4.62(b,2H,NH),	345(M^+-Br,16),
	(28.24)	(2.13)	(13.17)	740	7.40-8.20(m,4H)	75(100)
		$C_{11}H_{12}N_4O_7S_2$		3450, 1740, 1620,	1.45(s,3H),	
6f	34.91	3.41	14.73	1390, 1240, 1170,	3.85(s,3H),	378(M^++2,6),
	(35.10)	(3.21)	(14.88)	1100, 830	4.51(b,2H,NH),	376(M^+,4),
					7.55(m,4H)	92(100)
		$C_{10}H_9N_4O_6S_2Cl$		3450, 1720, 1610,	1.45(s,3H),	
6g	31.38	2.23	14.62	1530, 1230, 1190,	4.50(b,2H,NH),	380(M^+,2),
	(31.54)	(2.38)	(14.71)	1060, 750, 705	7.50(m,4H)	125(100)
		$C_{10}H_9N_4O_6S_2Cl$		3450, 1720, 1610,	1.40(s,3H),	
6h	31.36	2.42	14.61	1520, 1240, 1200,	4.41(b,2H,NH),	382(M^++2,3),
	(31.54)	(2.38)	(14.71)	1080, 780	7.40-7.90(m,4H)	380(M^+,2),
						125(100)
		$C_{11}H_{12}N_4O_7S_2$		3400, 1720, 1630,	1.50(s,3H),	
6i	34.82	3.45	14.78	1380, 1250, 1180,	3.90(s,3H),	376(M^+,2),
	(35.10)	(3.21)	(14.88)	1090, 740	4.65(b,2H,NH),	92(100)
					7.50-8.00(m,4H)	

TABLE-2. Yields and melting points of the products obtained in the reaction of CSI and ethyl 3-oxo-2-(arylhydrazono)butanoates (**1a-i**)

Starting Material No.	Substituents			Products Yield[6] % (mp, °C)	
1	R^1	R^2	R^3	**3**	**6**
a	H	H	Cl	37.5(62)	38.0 (110)
b	H	H	H	30.5(105)	28.0 (115)
c	H	H	CH_3	40.4(95)	45.0 (125)
d	NO_2	H	H	28.0(75)	30.0 (60)
e	H	Br	H	40.0(108)	48.0 (73)
f	H	H	OCH_3	37.8(83)	45.0 (98)
g	Cl	H	H	30.0(55)	30.0 (122)
h	H	Cl	H	35.0(45)	45.0 (90)
i	OCH_3	H	H	36.0(74)	41.0 (65)

EXPERIMENTAL

All melting points are uncorrected and were taken on a Fisher-Johns melting point apparatus. The ir spectra were recorded on a Perkin Elmer (1600) spectrophotometer. ^{1}H-Nmr spectra were recorded on a Bruker WP-80 (80 MHz) spectrometer. Mass spectra were recorded on a JOEL-JMS-300D mass spectrometer.

Reactions of CSI with ethyl 3-oxo-2-(arylhydrazono)butanoate: 5-*p*-Chlorophenyl-2,3,5,6,7,8-hexahydro-1-methyl-2,3,4-thiadiazolo[4,3-*a*]triazin-6,8-dione-3,3-dioxide (3a)- To a stirred solution of **1a** (0.804 g, 0.003 mol) in dry dichloromethane (20 ml) was added CSI (0.27 ml, 0.003 mol) in the same solvent (5 ml) for 30 min at 0-5°C. It was stirred for additional

12 h at room temperature (25°C). The yellow semi-solid, obtained after solvent removal, was taken in acetone-water (9:1, 20 ml) containing benzenethiol (0.30 ml) and neutralized with aqueous potassium hydroxide solution (5%). After stirring for 4 h at room temperature, water (10 ml) was added and the reaction mixture was extracted with dichloromethane (3x20 ml). The combined extract was dried (Na_2SO_4) and concentrated in vacuum. The residue on trituration with petroleum ether (40-60°C) furnished **3a** (0.37g, 37.5%), mp 62°C, as a dark green solid; ir (KBr): 3400-3300, 3110, 2990, 1730, 1710, 1640, 1400, 1380, 1230, 1190, 1110, 1060, 830 cm^{-1}; ^{1}H-nmr ($CDCl_3$, TMS): δ 1.50 (singlet, 3H), 4.15-4.60 (broad, NH, 2H), 7.50(multiplet, 4H); ms, m/z: 330 (M^++2), 328 (M^+), 292, 267, 264, 220, 218, 196, 193, 153, 152, 151, 139, 128, 127, 126, 125, 111, 101, 999, 80, 75, 64, 62, 58, 43. The mother-liquor furnished **1a** (0.495 g). Alternatively, the product could also be separated by column chromatorgraphy (silica gel, eluent; ether-ethyl acetate (4:1)). Reactions of **1b-i** with CSI were carried out in an analogous manner (as outlined above) and gave **3b-i.** The yields and melting points of these compounds are collected in Table-2.

6-(p-Chlorophenyl)-2,3,4,6,7,8,9-heptahydro-1-methyl-5,6,7,8,9-thiatriazinone-7,7-dioxo[5,4-a]-2,3,4,5-thioxopyridazine-3,3-dioxide (6a)- To a refluxing solution of **1a** (0.54 g, 0.002 mol) in dry toluene (20 ml) was added CSI (0.18 ml, 0.002 mol) in the same solvent (5 ml) for a period of 10 min. Toluene was removed from the reaction mixture under diminished pressure and water (20 ml) was added. The aqueous mixture was extracted with dichloromethane (3x20 ml). The combined extracts was dried (Na_2SO_4) and concentrated in vacuum. Addition of petroleum ether (40-60°C) to the residue gave **6a** (0.28 g, 38%), mp 110°C, as a brown solid; ir (KBr): 3450-3400, 3110, 2995, 2940, 1710, 1530, 1510, 1385, 1310, 1230, 1110, 1060, 1020, 830 cm^{-1} ; ^{1}H-nmr ($CDCl_3$, TMS): δ 1.40 (singlet, 3H), 4.30 (broad, NH, 2H), 7.50(multiplet, 4H); ms, m/z: 380 (M^+), 379 (M^+-H), 378

6, 344, 339, 337, 332, 319, 301, 300, 293, 292, 285, 283,

266, 239, 220, 219, 191, 161, 151, 148, 125, 111, 102, 98, 90, 75, 62, 64, 43, 42. Compounds (**6b-i**) were synthesized in a similar manner to the above. The yields and melting points of all the compounds are summarized in Table-2.

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