[4+2] Diels–Alder cycloaddition reaction of 2-benylidineamino-4-phenyl-1,3-thiazoles with sulfene and their antifungal activities

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2-Benzylidineamino-4-phenyl-1,3-thiazole undergoes [4+2] Diels–Alder cycloaddition reaction with sulfene resulting in good yield of a mixture of isomeric 2,6-diphenyl-2*H*,4*H*-[1,3]thiazolo[3,2-*c*][1,3,5]thiadiazine 3,3-dioxides and 3,7-diphenyl[1,3]thiazolo[3,2-*b*] [1,2,4]thiadiazine 5,5-dioxides derivatives are reported.

Keywords: Diels–Alder reaction, sulfene, thiadiazine-dioxides, isomers

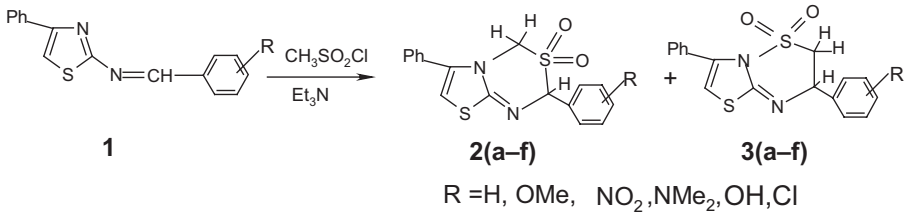
The 1,2,4 and 1,3,5-thiadiazine and its derivatives are an important class of compounds which possess widespread pharmacological properties such as insecticidal and accaricidal[1] activity. They are also reported to have antifungal[2] and antiatherosclerotic activity.[3] Recently Evain *et al.* has reported[4] the first example of thiazolo thiadiazine family. 2-Aminothiazoles is the versatile intermediate for highly functionalised heterocycles of widespread pharmaceutical use.[5] Our interest in synthesis and biological activities of thiadiazine dioxide molecules led us to synthesis of several isomeric 1,3-thiazolo thiadiazine dioxide derivatives from 2-amino-4-phenyl-1,3-thiazole.

Among all the strategies described in the literature for the construction of heterocycles, the [4+2] Diels–Alder cycloaddition reaction between a diene and a dienophile is one of the most versatile routes.[6,7,8] It has been observed that [4+2] Diels–Alder cycloaddition reaction involving sulfene is very rare. Sulfenes have received little attention as dienophiles.[9,10] The suitable use of diene and dienophiles determines the wide range of cycloadducts. Literature reports[7] shows that [4+2] cycloaddition reaction involving 1,3-diazabutadienes with heterodienophile sulfene gives only one cycloadduct.

In this paper, we have reported the synthesis of several previously unknown isomeric 2,6-diphenyl-2*H*,4*H*-[1,3] thiazolo[3,2-*c*][1,3,5]thiadiazine 3,3-dioxides (**2a–2e**) and 3,7-diphenyl[1,3]thiazolo[3,2-*b*][1,2,4]thiadiazine 5,5-dioxides (**3a–3e**) in high yield by [4+2] cycloaddition reaction from 2-benzylidineamino-4-phenyl-1,3-thiazole and methanesulfonyl chloride in presence of triethylamine and subsequent separation of the isomers by column chromatography. The column chromatography (silicagel, 9:1 petroleum ether: ethyl acetate) of the crude product afforded two fractions **2** and **3**. The first fraction **2** (major product, 70% **2a**, TLC, $R_f = 0.61$) and the second fraction **3** (minor product, 20%, **3a**, $R_f = 0.12$). (Scheme 1 and Table 1).

The structure of the compounds has been assigned **2** and **3** on the basis of analytical and spectroscopic (IR,^{1}H NMR, MS) data. The IR spectra of **2a** showed characteristic SO_2 stretching frequency around 1167 and 1370 and for **3a** around 1178 and 1330 cm^{-1} respectively.

The ^{1}H NMR spectra (in $CDCl_3$, δ ppm) of **2** showed methine proton absorption at δ 3.55–4.00 and for methylene proton (–CH_2–) at around δ 3.19–3.40, for aromatic proton δ 6.46–7.24 (m, Ar–H) and for C-2 proton singlet at δ 8.10 ppm appeared.The ^{1}H NMR spectra for 3 showed methylene proton absorption at δ 3.64 as doublet, methine proton as multiplet at δ 4.90 ppm, aromatic proton appeared at δ 6.40–7.35 ppm and C-2 proton appeared as singlet at δ 8.20 ppm. It has been found that the product **3** is *cis* as *J* of C-6 and C-7 is 5 Hz. Mass spectra of **2a** showed molecular



Scheme 1

Table 1 Physical data of compound **2** and **3**

Product	R	Yield/%	m.p./°C	R_f [a]	*m/z*
2a	H	70	135	0.61	342(100%)
3a	H	20	128	0.12	342(33%)
2b	4-OMe	63	112	0.74	372(100%)
3b	4-OMe	17	127	0.22	372(25%)
2c	4-NO_2	65	98	0.59	387(100%)
3c	4-NO_2	19	84	0.19	387(15%)
2d	4-NMe_2	63	108	0.63	385(100%)
3d	4-NMe_2	19	122	0.11	385(12%)
2e	4-OH	53	103	0.53	358(100%)
3e	4-OH	29	98	0.35	358(20%)
2f	4-Cl	68	92	0.68	376(100%)
3f	4-Cl	18	105	0.21	376(33%)

[a]Solvent system for TLC: Petroleum ether, ethyl acetate (7:3).

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Table 2 Analytical and spectroscopic data for compounds **2** and **3**

Compd	Molecular formula	Found (Required)/%			IR(KBr,υ cm^{-1})	^1H NMR ($CDCl_3$,δ = 0 ppm)
		C	H	N		
2a	$C_{17}H_{14}N_2O_2S_2$	59.52	4.16	8.24	1167,1370	3.20(s,2H,–CH_2); 3.65(s,1H,C_7–H);
		(59.63	4.12	8.18)		6.46–7.20(m,11H,Ar–H andC_2–H)
3a		59.24	3.94	7.95	1178,1330	3.64(d,2H,–CH_2); 4.90(dd,1H,C_7–H);
		(59.63	4.12	8.18)		6.40–7.32(m,11H,Ar–H andC_2–H)
2b	$C_{18}H_{16}N_2O_3S_2$	58.14	4.06	7.42	1165,1372	3.40(s,2H,–CH_2); 3.78(s,3H,OMe);
		(58.04	4.33	7.52)		3.84(s,1H,C_7–H); 6.20–7.60(m,10H, Ar–H andC_2–H)
3b		57.80	4.54	7.28	1174,1334	3.70(d,2H,–CH_2); 3.82(s,3H,OMe);
		(58.04	4.33	7.52)		4.92(dd,1H,C_7–H); 6.35–7.74(m,10H, Ar–H andC_2–H)
2c	$C_{17}H_{13}N_3O_4S_2$	52.86	3.21	10.58	1165,1371	3.40(s,2H,–CH_2); 4.00(s,1H,C_7–H);
		(52.70	3.38	10.85)		6.69–7.95(m,10H,Ar–H andC_2–H)
3c		52.48	3.54	11.18	1170,1335	3.72(d,2H,–CH_2); 4.92(dd,1H,C_7–H);
		(52.70	3.38	10.85)		6.62–7.96(m,10H,Ar–H andC_2–H)
2d	$C_{19}H_{19}N_3O_2S_2$	59.12	4.98	10.72	1168,1374	2.85(s,6H,NMe_2); 3.22(s,2H,–CH_2);
		(59.20	4.97	10.90)		3.55(s,1H,–CH–); 6.50–7.40(m,10H, Ar–H and C_2–H)
3d		58.96	5.04	11.26	1178,1331	2.90(s,6H,NMe_2); 3.92(d,2H,–CH_2);
		(59.20	4.97	10.90)		4.90(dd,1H,C_7–H); 6.62–7.76(m,10H, Ar–H,C_2–H)
2e	$C_{17}H_{14}N_2O_3S_2$	56.68	3.76	7.94	1167,1375	3.19(s,2H,–CH_2); 3.70(s,1H,C_7–H);
		(56.97	3.94	7.82)		5.62(s,1H,–OH); 6.30–7.30(m,10H, Ar–H andC_2–H)
3e		57.24	4.26	8.04	1174,1332	3.82(d,2H,–CH_2); 4.92(dd,1H,C_7–H); 5.74(s,1H,–OH);
		(56.97	3.94	7.82)		6.25–7.42(m,10H,Ar–H,C_2–H)
2f	$C_{17}H_{13}N_2O_2S_2Cl$	54.00	3.56	7.29	1165,1372	3.32(s,2H,–CH_2); 3.72(s,1H,C_7–H);
		(54.17	3.48	7.43)		6.52–7.48(m,10H,Ar–H andC_2–H)
3f		54.34	3.62	7.70	1178,1330	3.84(d,2H,–CH_2); 4.92(dd,1H,C_7–H);
		(54.17	3.48	7.43)		6.62–7.60(m,10H,Ar–H and C_2–H)

ion peak at *m/z* 342 (M^+, 100%) and **3a** showed molecular ion peak at *m/z* 342 (M^+, 33%).

Experimental

M.p.s were determined on a Buchi apparatus. Mass spectra were recoded with a LC-MS, Bruker (Model Esquire-3000) mass spectrometer. IR spectra were recorded on a Perkin-Elmer system 2000 FTIR spectrometer and ^1H NMR spectra were recorded on a varian T-60/90 MHz spectrometer.

Preparation of 2,6-diphenyl-2H,4H-[1,3]thiazolo[3,2-c][1,3,5] thiadiazine 3,3-dioxide (**2a**) *and 3,7-diphenyl[1,3]thiazolo[3,2-b] [1,2,4]thiadiazine 5,5-dioxide* (**3a**): In a typical experiment, to a solution of 2-benzylidineamino-4-phenyl-1,3-thiazole (0.528 g, 0.002 mol), in dry 1,4-dioxane (20 ml) was added triethylamine (0.56 ml, 0.004 mol) and to this solution was added methanesulfonyl chloride (0.23 ml, 0.003 mol) in 1,4-dioxane (15 ml) drop by drop 0–5°C under stirring during 30 min. The stirring was continued for a period of 3–4 hr. at the same temperature. The reaction mixture was then poured into ice (100 gm) and extracted with chloroform (2 × 40 ml) and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave the crude product in 80–90% yield. The crude products were separated by column chromatography (silica gel, 9:1, petroleum ether: ethyl acetate) afforded **2a** and **3a,** the product, **2a**, yield 70%, m.p. 135°C and the product **3a,** yield 20%, m.p. 128°C. For **2a,** IR (KBr,υ cm^{-1}) 1370, 1167(SO_2); ^1H NMR (δ ppm, $CDCl_3$) 3.20(s,2H,-CH_2), 3.65(s,1H,-C_7-H), 6.46-7.20(m,11H,Ar-H and C_2-H); mass m/z 342(M^+, 100%). For **3a**, IR (KBr,υ cm^{-1}) 1330, 1178(SO_2); ^1H NMR (δ ppm, $CDCl_3$) 3.64(d,2H,-CH_2), 4.90(dd,1H,C_7-H), 6.40–7.32(m,11H,Ar–H and C_2–H); mass *m/z* 342(M^+, 33%).

Biological activity screening

Due to the diverse and interesting biological activities of 1,2,4 and 1,3,5-thiadiazine ring system, we screened these compounds for their antifungal activities against *Rhizoctonia solani* and *Drechslera oryzae*, two important fungal pathogens causing diseases on rice crop. Their antifungal activities were evaluated according to the inhibition zone technique.[12] It has been observed that the thiazolothiadiazine dioxide compounds have excellent antifungal activities. Comparatively significant activity was observed in compounds bearing substituent NMe_2 (compound no. **2d** and **3d**) at a concentration of 1 mg/ml. The control (without treatment) sets of experiments with both the fungal pathogens exhibited no inhibition of growth. However, the standard fungicide (carbendazim) showed 98.56 and 98.26% inhibition of *Rhizoctonia solani* and *Drechslera oryzae* respectively at the same concentration of 1 mg/ml.

In conclusion, we have synthesised an important class of isomeric thiazolo-1,2,4 and 1,3,5-thiadiazine derivatives from easily prepared 2-amino-4-phenyl-1,3-thiazole.

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