# Cycloaddition Reaction: Synthesis of 5-Substituted 1,3,4-Thiadiazolo[3,2-*a*]pyrimidin-6-one†

*J. Chem. Research (S)*, 1999, 36–37†

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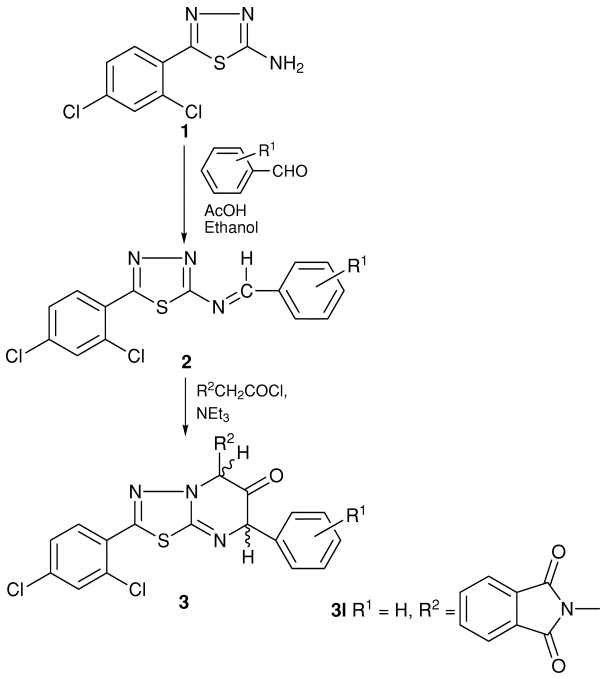
1,3,4-Thiadiazolo[3,2-*a*]pyrimidin-6-ones are synthesised by a (4 + 2) cycloaddition reaction of arylidineamino-1,3,4-thiadiazole and aryl ketenes formed *in situ*.

The diverse and interesting biological activity reported[1–5] to be shown by the thiadiazolo pyrimidine nucleus led us to synthesise the title compounds 1,3,4-thiadiazolo[3,2-*a*]-pyrimidin-6-ones. The synthesis involves a cycloaddition reaction involving a heterodiene system which is of great potential in the synthesis of heterocyclic compounds.[6,7] Dienes containing two nitrogen atoms are also of great importance in natural product synthesis.[8]

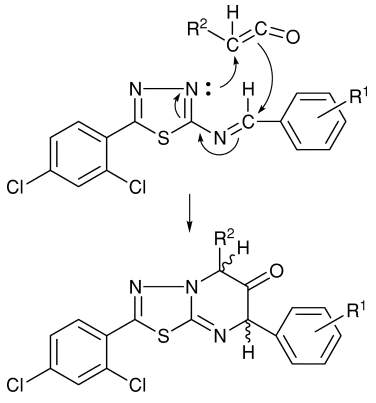
In this paper a (4 + 2) cycloaddition reaction of arylidineamino-1,3,4-thiadiazole with ketenes is reported. Literature reports show that the cycloaddition of arylidine amines with phenylacetyl chloride in presence of triethylamine generally gives an azetidinone[9] (*β*-lactam) ring system. However, the reaction of Schiff base **2** with ketenes, in our case, gives substituted 1,3,4-thiadiazolopyrimidin-6-ones in good yield (Table 1). The ketene which takes part in the cycloaddition reaction is formed *in situ* during the reaction of phenylacetyl chloride with triethylamine. In this system a part of the heterocyclic moiety (1,3,4-thiadiazole) incorporated with the Schiff base comprises a heterodiene system and is the 4$\pi$ component in the Diels–Alder reaction. 5-(2,4-dichlorophenyl)-1,3,4-thiadiazolo[3,2-*a*]pyrimidine-6-ones **3** were synthesised (Scheme 1) by the dropwise addition of chloroacetyl chloride, phenylacetyl chloride or *p*-methoxyphenylacetyl chloride in dioxane to a solution of an arylidineamino-1,3,4-thiadiazole in dioxane at 0–10 °C.

The structure of compounds **3** were assigned on the basis of elemental analysis and spectroscopic (IR, $^1$H NMR and mass) data. The IR spectra (KBr) of compounds **3** showed




**Scheme 1**

*ν*(C=O) at *ca.* 1710 cm$^{-1}$ which is at much lower wavenumber than that for an azetidinone carbonyl.[9,10] The azetidinone molecule which is a strained four membered ring shows IR absorptions[11,12] at high wavenumber (1775–1780 cm$^{-1}$). Tsuji[13] studied the mass fragmentation modes of 1,3,4-thiadiazolo[3,2-*a*]pyrimidinones to determine the position of CO in the -5-ones and isomeric-7-ones and observed intense ions corresponding to loss of CO from the molecular ion. In both these types of compounds a retro-Diels–Alder (RDA) process was observed. This type of intense ion peak attributed to the loss of CO and a RDA process were not observed in the compounds prepared here. It has also been observed that *β*-lactam (azetidinone) molecules are less stable and have lower melting points[14,15]




**Scheme 2**

**Table 1** Physical data of arylidineamino-5-(2,4-dichlorophenyl)-1,3,4-thiadiazoles (**2a**–**1**) and 5-(2,4-dichlorophenyl)-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-6-ones (**3a**–**1**)[a]

| Compound | $R^1$ | $R^2$ | Yield (%) | mp/°C |
|---|---|---|---|---|
| **2a** | H | | 95 | 222 |
| **2c** | *p*-OMe | | 90 | 218 |
| **2d** | *p*-$NMe_2$ | | 87 | 210 |
| **2e** | *o*-(OH, OMe) | | 82 | 220 |
| **2g** | *o*-OH | | 84 | 213 |
| **3a** | H | Ph | 82 | 238 |
| **3b** | H | Cl | 75 | 140 |
| **3c** | *p*-OMe | Cl | 78 | 171 |
| **3d** | *p*-$NMe_2$ | Cl | 77 | 173 |
| **3e** | *o*-(OH, OMe) | Cl | 76 | 188 |
| **3f** | H | *p*-$C_6H_4OMe$ | 79 | 207 |
| **3g** | *o*-OH | *p*-$C_6H_4OMe$ | 78 | 211 |
| **3h** | *p*-NMe | *p*-$C_6H_4OMe$ | 82 | 238 |
| **3i** | *o*-OH | Ph | 81 | 232 |
| **3j** | *p*-OMe | Ph | 82 | 210 |
| **3k** | *p*-NMe | Ph | 81 | 242 |
| **3l** | H | $N(CO)_2C_6H_4$ | 76 | 222 |

[a]The structure of the compounds were confirmed on the basis of spectroscopic analyses.

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†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1999, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

**Table 2** Analytical and spectroscopic data for compounds **2a–l** and **3a–l**

| Compound | Molecular formula | Found (Required) (%) C | H | N | $\nu_{max}/cm^{-1}$ (KBr) | $\delta$H ($CDCl_3$–DMSO-$d_6$) |
|---|---|---|---|---|---|---|
| **2a** | $C_{15}H_9Cl_2N_3S$ | 54.12 (54.05 | 2.62 2.70 | 12.50 12.61) | 1600 (C=N) | 5.46 (s, 1H, =NCH) |
| **2d** | $C_{17}H_{14}Cl_2N_4S$ | 54.38 (54.26 | 3.48 3.72 | 14.95 14.89) | 1600 (C=N) | 2.20 (s, 6H, NMe, 5.48 (s, 1H, =NCH) |
| **2g** | $C_{15}H_9Cl_2N_3OS$ | 51.49 (51.58 | 2.39 2.58 | 12.00 12.03) | 1600 (C=N) | 5.48 (s, 1H, N=CH), 5.50 (s, 1H, OH) |
| **3a** | $C_{23}H_{15}N_3Cl_2OS$ | 61.09 (61.20 | 3.10 3.32 | 9.00 9.31) | 1606 (C=N), 1710 (C=O) | 3.92 (s, 2H, H-5, H-7), 6.1–7.2 (m, Ar-H) |
| **3b** | $C_{17}H_{10}N_3Cl_3OS$ | 49.68 (49.87 | 2.30 2.44 | 11.26 10.26) | 1600 (C=N) 1710 (C=O) | 3.94 (s, 2H, H-5, H-7), 6.1–7.2 (m, Ar-H) |
| **3c** | $C_{18}H_{12}N_3Cl_3OS$ | 49.11 (49.20 | 2.60 2.73 | 9.40 9.56) | 1600 (C=N), 1710 (C=O) | 3.1 (s, 3H, OMe), 3.98 (s, 2H, H-5, H-7), 6.2–7.2 (m, Ar-H) |
| **3e** | $C_{18}H_{12}N_3Cl_3O_3S$ | 47.30 (47.47 | 2.60 2.63 | 9.15 9.23) | 1610 (C=N), 1715 (C=O), 3400 (br, OH) | 3.02 (s, 3H, OMe), 3.94 (s, 2H, H-5, H-7), 5.8 (s, 1H, OH), 6.1–7.2 (m, Ar-H) |
| **3g** | $C_{24}H_{17}N_3Cl_2O_2S$ | 57.75 (57.94 | 3.25 3.42 | 8.18 8.45) | 1600 (C=N) 1710 (C=O) 3410 (OH) | 3.2 (s, 3H, OMe), 3.92 (s, 2H, H-5, H-7), 5,6 (s, OH), 6.00–7.1 (m, Ar-H) |
| **3h** | $C_{26}H_{22}N_4Cl_2O_2S$ | 59.23 (59.54 | 4.00 4.19 | 10.54 10.68) | 1610 (C=N), 1710 (C=O) | 3.4 (s, 3H, OMe), 3.94 (s, 2H, H-5, H-7), 5.7 (s, OH), 6.00–7.2 (m, Ar-H) |
| **3j** | $C_{24}H_{17}N_3Cl_2O_2S$ | 59.60 (59.88 | 3.40 3.53 | 8.52 8.73) | 1600 (C=N) 1710 (C=O) | 3.02 (s, 3H, OMe), 3.92 (s, H-5, H-7), 6.00–7.2 (Ar-H) |
| **3k** | $C_{25}H_{20}N_4Cl_2O_2S$ | 60.52 (60.72 | 4.00 4.04 | 11.20 11.33) | 1600 (C=N), 1710 (C=O) | 2.02 (s, 6H, $NMe_2$), 3.92 (s, 2H, H-5, H-7) 6.1–7.2, (m, Ar-H) |
| **3l** | $C_{25}H_{14}N_4Cl_2O_3S$ | 57.42 (57.69 | 2.38 2.69 | 10.51 10.76) | 1610 (C=N), 1685, 1710 (C=O) | 3.94 (s, 2H, H-5, H-7), 6.00–7.4 (m, Ar-H) |

compared to six membered pyrimidinones which have high melting points. In view of these observations compounds **3** were proposed to be 5-(2,4-dichlorophenyl)-1,3,4-thiadiazolopyrimidin-6-ones. A possible reaction pathway is shown in Scheme 2.

## Experimental

Melting points were taken in an oil heated Buchi apparatus and were uncorrected. The IR spectra were recorded on a Perkin Elmer 237 B spectrophotometer and the $^1$H NMR spectra were recorded on a JEOL FX-90 (90 MHz) NMR spectrometer with TMS as internal reference. The mass spectra of the compounds were taken on a Finigan Mat (INCOS 50, GC-MS) mass spectrometer. The purity of the compounds were checked by TLC.

*Preparation of Arylidineamino* 5-(2,4-*Dichlorophenyl*)-1,3,4-*thadiazole* (**2a**).—In a round bottomed flask, 2-amino-5-(2,4-dichlorophenyl)-1,3,4-thiadiazole (0.490 g, 0.002 mol) and benzaldehyde (0.212 g, 0.002 mol) were added to 100 ml of ethanol–chloroform (7:3) to which glacial acetic acid (1 ml) was added and the mixture refluxed for 6 h. The solvent was then removed under reduced pressure and the residue obtained was recrystallised from ethanol, mp. 222 °C, yield 95%, *m*/*z* 333 ($M^+$).

*Preparation of* 5-(2,4-*Dichlorophenyl*)-1,3,4-*thiadiazolo*[3,2-*a*]-*pyrimidin*-6-*one* (**3a**).—In a typical experiment, to a solution of benzylidineamino-5-(2,4-dichlorophenyl)-1,3,4-thiadiazole **2a** (0.333 g, 0.001 mol) in dioxane (25 ml) was added triethylamine (1 ml) and to this solution was added phenylacetyl chloride (0.154 g, 0.001 mol) in dioxane dropwise at 0 °C under stirring during 30 min. The reaction mixture was brought to room temperature and kept stirring for another 4 h at 60 °C. The reaction mixture after cooling to room temperature was poured into ice (100 g) and extracted with chloroform (2 × 40 ml), and dried over $Na_2SO_4$. Removal of the solvent under reduced pressure and recrystallisation of the residue gave a colorless solid: yield 0.336 g (75%), mp 238 °C. IR (KBr) $\nu$/$cm^{-1}$ 1710 (C=O), 1600 (C=N); *m*/*z* 451 ($M^+$), 118 (PhCH=C=O), 245 (2,4-dichlorophenyl-1,3,4-thiadiazole), 91 (PhCH/$PhCH_2$); $\delta_H$ 3.92 (s, 2H, C-5 and C-7), 6.1–7.2 (m, Ar-H).

*Received, 2nd March 1998; Accepted, 5th October 1998*
*Paper E/8/01720D*

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