Reaction of trithiazyl trichloride with active methylene compounds

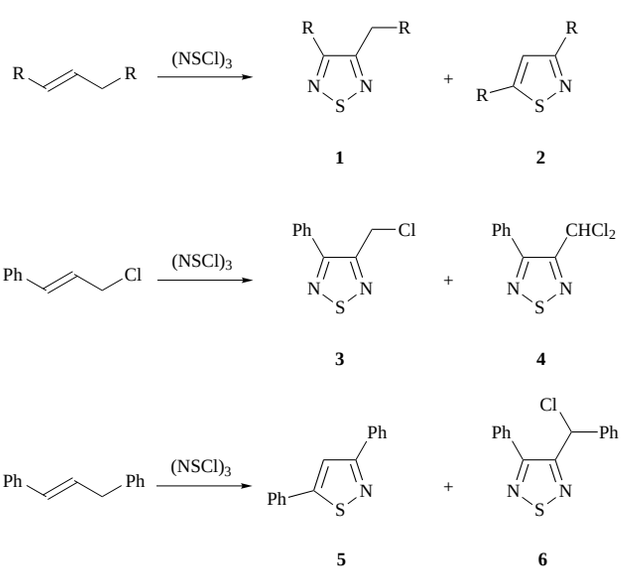
Xiao-Guang Duan, Xiao-Lan Duan and Charles W. Rees

Department of Chemistry, Imperial College of Science, Technology and Medicine, London, UK SW7 2AY

Activated allylic compounds react with trithiazyl trichloride, $(NSCl)_3$, to give 1,2,5-thiadiazoles 1 and isothiazoles 2. An allylic 2-substituent normally prevents formation of an aromatic 1,2,5-thiadiazole, and isothiazole formation becomes the major pathway. Simple allylic compounds are not very reactive towards $(NSCl)_3$ but a terminal electron withdrawing group (CO_2Et) enhances the reactivity. With unsymmetrical allylic compounds, isothiazole formation is regiospecific placing the more electron withdrawing group adjacent to the ring sulfur. 1,3-Diketones give 3-acyl-1,2,5-thiadiazoles; unsymmetrical 1,3-diketones give these thiadiazoles regiospecifically, explicable by cyclisation of an intermediate onto the more reactive carbonyl group. 1,4-Diketones give 3,4-diacyl-1,2,5-thiadiazoles; thus 1,2-dibenzoyl-ethane, -ethene and -ethyne all give 3,4-dibenzoylthiadiazole (40–44%). Many of these trithiazyl trichloride reactions provide attractive one-step routes to 1,2,5-thiadiazoles and isothiazoles.

Activated allylic compounds with $(NSCl)_3$

Simple allylic compounds could react with trithiazyl trichloride (the 'trimer'), $(NSCl)_3$,[1] as a two-carbon unit to give 1,2,5-thiadiazoles **1**[2] or as a three-carbon unit to give isothiazoles **2**.

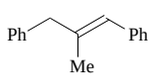
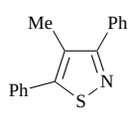
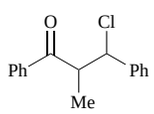
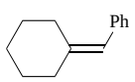
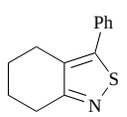
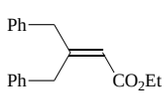
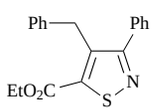
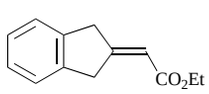
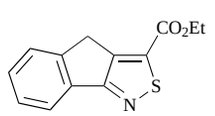
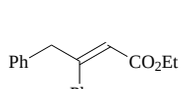
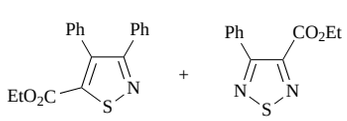
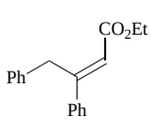


When cinnamyl chloride was treated with trimer (1 mol) in boiling benzene the thiadiazole **3** was formed in relatively good yield (56%)); no isothiazole was isolated. With two moles of trimer in boiling tetrachloromethane the reaction was more complex: **3** was isolated in low yield (17%), together with the more chlorinated thiadiazole **4** (12%). 1,3-Diphenylpropene[3] reacted with the trimer in the opposite mode however, to give an isothiazole. With two moles of the reagent in boiling tetrachloromethane a substantial amount of 3,5-diphenylisothiazole **5** (53%), but no 1,2,5-thiadiazole was obtained; with one mole, the isothiazole **5** was formed in lower yield (29%), together with a small amount of chlorinated thiadiazole **6** (14%).

The introduction of a substituent on the central carbon of the allylic system should prevent formation of an aromatic 1,2,5-thiadiazole, and isothiazole formation could then become the major pathway. This proved to be very largely, though not exclusively, so (Table 1).

Compound **7** (as an *E*/*Z* mixture)[4] and compound **8**[5] were prepared by literature methods, and the remaining compounds **9**, **10**, **11a** and **11b** were readily prepared by Wadsworth–Emmons reaction of triethyl phosphonoacetate and the respective ketone, at room temperature overnight. Compound **11**,

Table 1 Reaction of 2-substituted allylic compounds with $(NSCl)_3$ in boiling tetrachloromethane

Allylic compound	Product (%)		
		+	
7	**12** (19%)		**13** (26%)
			
8	**14** (7%)		
			
9	**15** (32%)[a]		
			
10	**16** (25%)[a]		
			
(*Z*)-**11a**	**17** (6%)[a]		**18** (23%)[a]
			
(*E*)-**11b**	**17** (66%)[a]		

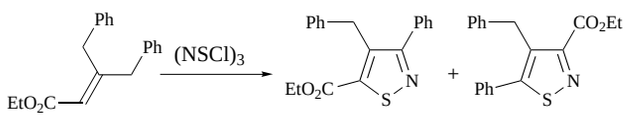
[a] With 4 Å molecular sieves.

previously reported as a mixture of isomers,[6] was separated into the *Z* (**11a**) and the *E* isomer (**11b**) whose structures were confirmed by their NOE ^{1}H NMR spectra.

These allylic compounds were treated with $(NSCl)_3$ (1 equiv.) in boiling tetrachloromethane overnight. In all cases isothiazoles were formed and, in one case only, a 1,2,5-thiadiazole was also formed (Table 1). The simplest compounds were not very reactive towards the trimer owing to the low reactivity of the allylic hydrogens; compound **8** gave the isothiazole **14** in only 7%. Compound **7**, with a benzylic methylene group, gave the isothiazole **12** in slightly better yield (19%), together with the chlorinated and oxidised product **13**. To enhance the allylic reactivity further, and hopefully to suppress side reactions, we introduced an electron withdrawing group, by preparing the esters **9** and **10**. These gave the corresponding isothiazoles **15** and **16** in better yield than **12** and **14**.

The *Z* and *E* isomers of compound **11** showed quite different behaviour towards $(NSCl)_3$; the *E* isomer **11b** gave isothiazole **17** in unusually high yield (66%) whilst the *Z* isomer gave the same isothiazole as a minor product together with the unexpected 1,2,5-thiadiazole **18** in which *C*-debenzylation had occurred on aromatisation (Scheme 1).

We note that in the reactions of $(NSCl)_3$ with unsymmetrical allylic compounds, such as **8**, **9**, **10** and **11**, two isothiazoles



9 **15** **15a**

could be formed, but in each case we have isolated only one (**14**, **15**, **16** and **17** respectively). Thus in the reaction of ester **9**, isothiazoles **15** and **15a** could have been formed but only **15** was isolated. In the ^{1}H NMR spectrum of this product, one sharp singlet was seen at 3.68 ppm for the benzylic protons indicating that it was not a mixture of isomers; its mass spectrum showed a peak at *m*/*z* 103 for the fragment $PhCN^+$, indicating structure **15** rather than **15a**. The structures of the other isothiazoles were assigned similarly. We cannot rule out that the undetected isomers were formed in very minor amounts, but the reactions are regioselective (at least) in favour of the isothiazole with the electron withdrawing ester group in the 5-position (see Scheme 2 below).

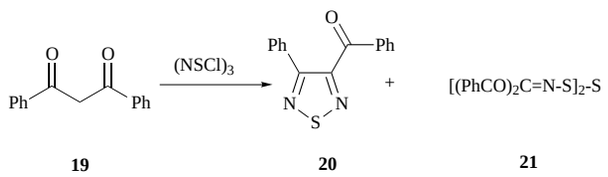
Active methylene compounds with $(NSCl)_3$

Since these reactions of active allylic compounds with $(NSCl)_3$ involve the methylene group, some other active methylene compounds, such as keto alkenes and diketones, were treated similarly with the trimer. It has already been shown that 1,3-diketones are converted into 3-acyl-1,2,5-thiadiazoles (7–50%) by treatment with tetrasulfur tetranitride, S_4N_4, in boiling toluene,[7] and some of these diketones have now been treated with the more reactive reagent $(NSCl)_3$ for comparison. Heating dibenzoylmethane **19** with 1 equiv. of the reagent in tetrachloromethane gave a complex reaction mixture from which only colourless 3-benzoyl-4-phenyl-1,2,5-thiadiazole **20** (20%) and bright yellow bis(dibenzoylmethylideneamino) trisulfide **21** (5%) could be obtained. The formula of **21** was based on elemental analysis; no molecular ion could be seen in the mass spectrum where the base peak, *m*/*z* 105, was that of the benzoyl fragment, and a peak for $(M^+ - S)/2$ at *m*/*z* 268 was observed. The ^{1}H NMR spectrum showed only phenyl protons and the IR spectrum showed a strong carbonyl absorption at 1657 cm^{-1}. Thiadiazole **20** was made alternatively, and in better yield (60%), by treating benzylideneacetophenone **22** with 2 equiv. of $(NSCl)_3$ in boiling tetrachloromethane. Conversion of dibenzoylmethane **19** into thiadiazole **20** requires the elimination of water (see Scheme 3 below) which will decrease the

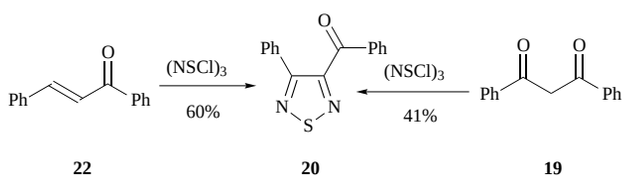
Table 2 Reaction of 1,3-diketones with $(NSCl)_3$ in boiling tetrachloromethane in the presence of molecular sieves

R	R^1	Diketone	Thiadiazole	Yield (%)
Ph	Ph	**19**	**20**	41[a]
4-$MeOC_6H_4$	Ph	**23**	**26**	33
Ph	Me	**24**	**27**	25
o-Phenylene		**25**	**28**	16[b]

[a] With bis(dibenzoylmethylideneamino) trisulfide **21** (11%). [b] With recovered **25** (61%).



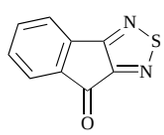
19 **20** **21**



22 **20** **19**

yield of **20** and contribute to the complexity of the reaction mixture. To minimise this problem the reaction was repeated in the presence of 4 Å molecular sieves, with 1.5 equiv. of $(NSCl)_3$. After heating under reflux for 12 h the reaction mixture was cleaner than without molecular sieves, and the yields of the thiadiazole **20** (41%) and the trisulfide **21** (11%) were doubled.

We also treated the following 1,3-dicarbonyl compounds with trimer (1.5 equiv.) and molecular sieves in boiling tetrachloromethane for 12 h: 1-(4-methoxyphenyl)-3-phenylpropane-1,3-dione **23**, benzoylacetone **24**, indane-1,3-dione **25**, pentane-2,4-dione and the diester, di-*tert*-butyl malonate. In spite of the presence of the molecular sieves the reactions were sometimes rather complex and the yields of 1,2,5-thiadiazoles were not high (Table 2). The ester did not react with trimer under the standard conditions and the reaction of pentane-2,4-dione was complex and 3-acetyl-4-methyl-1,2,5-thiadiazole was not isolated. The reaction of indane-1,3-dione **25** was slow, though excess of $(NSCl)_3$ (3 equiv.) was used and the reaction time extended to 24 h; much unreacted **25** (61%) remained and 8*H*-indeno[1,2-*c*][1,2,5]thiadiazol-8-one **28** (16%) was isolated.



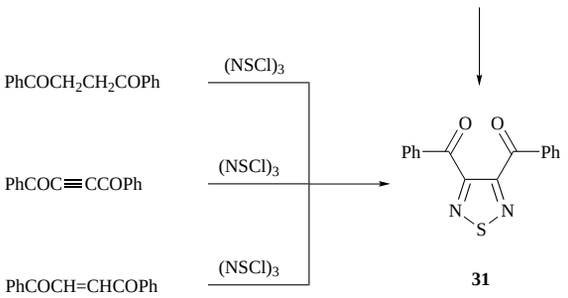
28

This product is identical with that from the reaction of indan-2-one with S_4N_4 in boiling toluene (4%).[8]

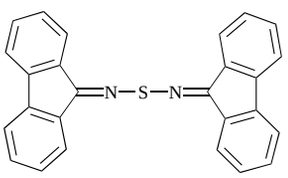
When the unsymmetrical 1,3-diketones **23** and **24** reacted with $(NSCl)_3$ only one of the two possible 1,2,5-thiadiazoles was isolated. This is explained by cyclisation of a key intermediate at the more reactive carbonyl group (see Scheme 3 below).

Somewhat surprisingly the butenone **29**, with 2 equiv. of trimer in boiling tetrachloromethane, gave 3,4-dibenzoyl-1,2,5-

29 **30**



31



32

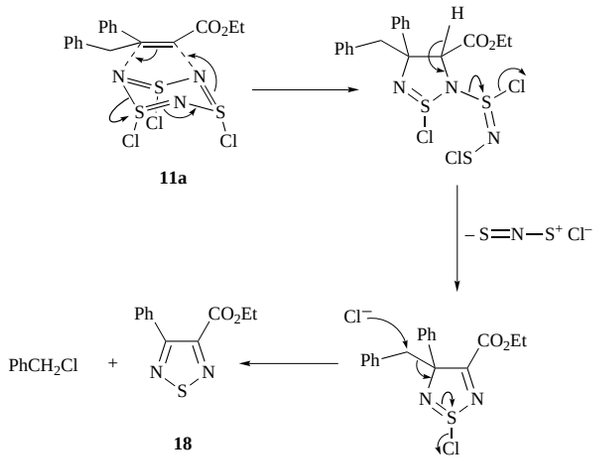
thiadiazole **31** (26%), identical with that formed, as expected, from (*E*)-1,2-dibenzoylethene.[2] Dibenzoylethyne and even 1,2-dibenzoylethane reacted smoothly with trimer (1.5 equiv.) in boiling tetrachloromethane (see mechanisms shown below) to give the same thiadiazole **31** in very similar yields (40–44%). Finally, when fluorene was similarly treated with trimer a moderate yield (40%) of a bright yellow compound, bis-(fluoren-9-ylideneamino) sulfide **32** was formed, identical with that from the reaction of fluorenone oxime with S_4N_4 in boiling toluene (22%).[9]

Reaction mechanisms

We have proposed mechanisms for the conversion of alkenes and alkynes into 1,2,5-thiadiazoles by trithiazyl trichloride $(NSCl)_3$ based upon its electrophilic attack on, or cycloaddition to, the carbon–carbon double or triple bond.[2] Since an N–S–N unit was transferred we assumed that the reacting species was the intact trimer, $(NSCl)_3$. When an S–N unit is transferred, *e.g.* to an allylic compound to form an isothiazole, it seems likely that the reacting species could be the highly reactive monomer, N≡S–Cl, which is freely available in solution at the reaction temperatures. We now suggest extensions of the trimer mechanisms for the formation of the 1,2,5-thiadiazoles reported (Schemes 1, 3 and 4) together with a mechanism for the formation of isothiazoles (Scheme 2).

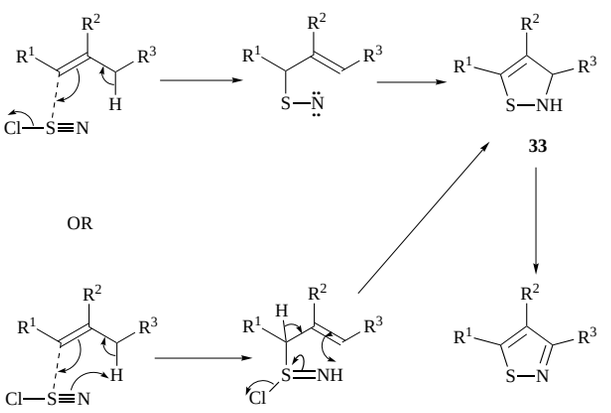
Conversion of the 2-substituted allylic compound **11a** into thiadiazole **18** presents the added complexity of debenzylation, which could occur as shown in Scheme 1. The more usual conversion of 2-substituted allylic compounds (**7**, **8**, **9**, **10** and **11**) into isothiazoles (**12**, **14**, **15**, **16** and **17** respectively) could result from their reaction with the monomer as shown in Scheme 2, which would also explain the observed regiochemistry. The dihydroisothiazole **33** is aromatised by dehydrogenation, possibly *via* chlorination of **33** by more of the reagent.

Conversion of 1,3-diketones into 1,2,5-thiadiazoles (Scheme 3) could proceed by electrophilic attack on the enol by the trimer, followed by cyclisation, in **34**, onto the more reactive carbonyl group, and this too would explain the observed regiochemistry. Loss of water and $[ClSNSCl]^+Cl^-$ then gives the



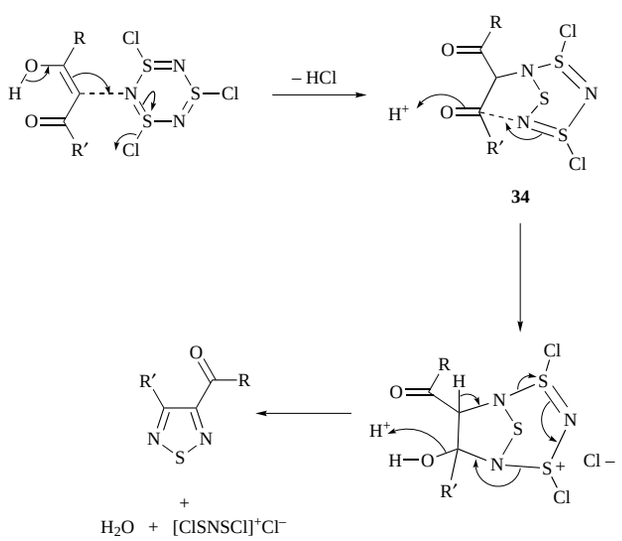
11a **18**

Scheme 1



33

Scheme 2



34

Scheme 3

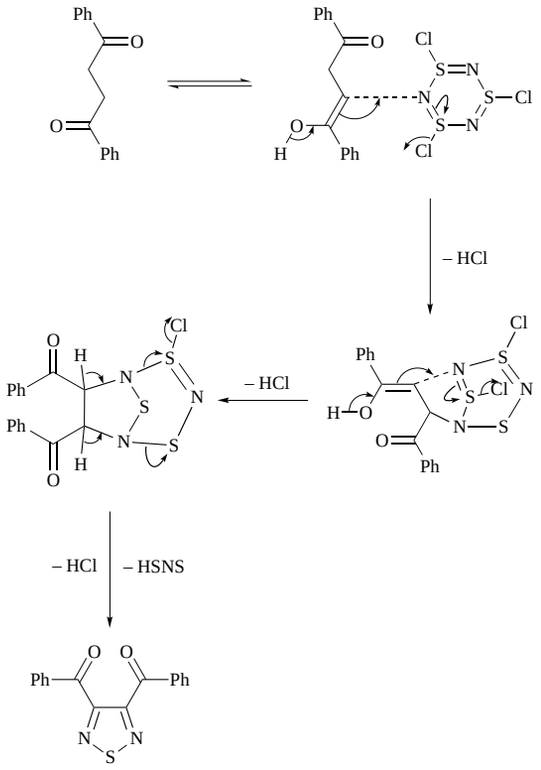
aromatic product. Formation of 3,4-dibenzoyl-1,2,5-thiadiazole **31** from 1,2-dibenzoylethane could result from similar attack on one enolic form followed by cyclisation *via* the second enol (Scheme 4).

Experimental

For general details see earlier parts of this series.[10]

1,3-Diphenyl-2-methylpropene 7

This was prepared by the literature method[4] and obtained as a colourless oil (30%), ν_{max}(neat)/cm^{-1} 3026, 2925, 1947, 1880, 1806, 1755, 1650, 1600, 1494, 1453, 1377, 1075, 1030, 917 and



Scheme 4

857; δ_H(270 MHz, $CDCl_3$) 1.79 (3H, s, CH_3), 3.47, 3.62 (2H, two singlets, ratio 2:1, $PhCH_2$), 6.38, 6.52 (1H, two singlets, ratio 2:1, alkene-H) and 7.14–7.37 (10H, m, ArH).

Phenylmethylidenecyclohexane 8

A solution of cyclohexyl bromide (0.01 mol, 1.87 ml) and triphenylphosphine (0.01 mol, 2.63 g) in sodium-dried benzene (50 ml) was stirred and heated under reflux. The initially clear solution rapidly became cloudy and the phosphonium salt precipitated as a pale yellow solid. The solid was collected and washed with ether to give the phosphonium salt.

Sodium hydroxide (80 mmol, 3 g) in benzene (15 ml) was added dropwise to a stirred suspension of the phosphonium salt (10 mmol, 4.26 g) and benzaldehyde (10 mmol, 1.0 ml) in water (15 ml) at room temperature over 20 min. Upon addition, the initially clear mixture became cloudy as triphenylphosphine oxide was formed. The stirring was continued for 3 h before the mixture was evaporated and the phenylmethylidenecyclohexane **8** (1.03 g, 60%) was isolated as a colourless oil, bp 104 °C/3 mmHg (lit.,[5] bp 83 °C/5 mmHg); ν_{max}(neat)/cm^{-1} 3027, 2927, 2854, 1654, 1598, 1494, 1447, 918, 736 and 699; δ_H(270 MHz, $CDCl_3$) 0.85–0.88 (2H, m, CH_2), 1.60–1.62 (4H, m, $2CH_2$), 2.25 (2H, t, CH_2), 2.36 (2H, t, CH_2), 6.22 (1H, s, alkene-H) and 7.15–7.29 (5H, m, ArH).

The following allylic compounds were synthesised by the Wadsworth–Emmons method with triethyl phosphonoacetate. To a dispersion of sodium hydride in mineral oil, triethyl phosphonoacetate was added dropwise. The mixture was stirred until it was colourless before the respective ketone was added. The solution was stirred at ambient temperature until the reaction was complete (TLC). The products were isolated by flash chromatography on silica gel.

Ethyl 3-benzyl-4-phenylbut-2-enoate 9. Colourless oil (Found: M^+, 280.1463. $C_{19}H_{20}O_2$ requires *M*, 280.1463); ν_{max}(neat)/cm^{-1} 3061, 3027, 1734, 1647, 1601, 1584, 1494, 1454, 1391, 1369, 1323, 1237, 1076, 1032, 800 and 752; δ_H(270 MHz, $CDCl_3$) 1.14 (3H, t, CH_3), 3.14 (2H, s, $PhCH_2$), 3.59 (2H, s, $PhCH_2$), 4.03 (2H, q, CH_2), 6.61 (1H, s, alkene-H) and 7.04–7.39 (10H, m, ArH); *m*/*z* 280 (M^+, 50%), 234 ($M^+ - CO_2$, 30), 206 ($M^+ - CO_2Et$, 30), 192 (35), 129 (10), 115 (25) and 91 ($PhCH_2^+$, 100).

Ethyl indan-2-ylideneacetate 10. Pale yellow oil (Found: M^+, 202.0992. $C_{13}H_{14}O_2$ requires *M*, 202.0994); ν_{max}(neat)/cm^{-1} 3057, 3020, 2982, 2937, 1735, 1614, 1462, 1393, 1369, 1332, 1301, 1251, 1176, 1097, 1032, 914, 796 and 755; δ_H(270 MHz, $CDCl_3$) 1.19–1.24 (3H, t, CH_3), 3.37 (2H, s, CH_2), 3.43 (2H, s, CH_2), 4.07–4.15 (2H, q, CH_2), 6.62 (1H, s, alkene-H) and 7.08–7.34 (4H, m, ArH); *m*/*z* 202 (M^+, 45%), 156 ($M^+ - CO_2$, 18), 126 ($M^+ - CO_2Et$, 14) and 76 (13).

(*Z*)-Ethyl 3,4-diphenylbut-2-enoate 11a.[6] Colourless oil; ν_{max}(neat)/cm^{-1} 3059, 2980, 2925, 1727 (C=O), 1642, 1604, 1548, 1453, 1376, 1265, 1223, 1162, 1075, 1034 and 877; δ_H(270 MHz, $CDCl_3$) 1.10 (3H, t, CH_3), 3.67 (2H, s, $PhCH_2$), 4.04 (2H, q, CH_2), 6.99 (1H, s, alkene-H) and 7.23–7.48 (10H, m, ArH); *m*/*z* 266 (M^+, 100%), 221 (10), 193 ($M^+ - CO_2Et$, 80), 178 (55), 165 (15), 152 (5), 115 (82), 91 ($PhCH_2^+$, 33) and 77 (Ph^+, 6).

(*E*)-Ethyl 3,4-diphenylbut-2-enoate 11b.[6] Colourless oil; ν_{max}(neat)/cm^{-1} 3059, 3027, 2980, 2930, 1727 (C=O), 1642, 1601, 1549, 1453, 1377, 1265, 1223, 1162, 1075, 1034, 877, 759 and 729; δ_H(270 MHz, $CDCl_3$) 1.16 (3H, t, CH_3), 4.10 (2H, q, CH_2), 4.41 (2H, s, $PhCH_2$), 6.14 (1H, s, alkene-H), 7.12–7.29 (10H, m, ArH); *m*/*z* 266 (M^+, 100%), 220 (M^+ − EtOH, 97), 192 (85), 178 (25), 165 (15), 152 (5), 131 (7), 115 (55), 91 ($PhCH_2^+$, 33) and 77 (Ph^+, 6).

Reactions of trithiazyl trichloride

With cinnamyl chloride. (*a*) Cinnamyl chloride (freshly distilled, 76 mg, 0.5 mmol) in benzene (1 ml) was added at room temperature to a stirred solution of trithiazyl trichloride (122 mg, 0.5 mmol) in benzene (4 ml) under nitrogen. The mixture was stirred and heated at reflux for 17 h under nitrogen. The solvent was evaporated and the residue was separated by chromatography on silica gel. Elution with dichloromethane (30%) in light petroleum gave 3-chloromethyl-4-phenyl-1,2,5-thiadiazole **3** as colourless needles (59 mg, 56%), mp 69–70 °C; ν_{max}(neat)/cm^{-1} 3066, 3027, 2925, 2854, 1578, 1497, 1468, 1455, 1442, 1402, 1304, 1274, 1222, 1178, 1158, 1076, 1015, 934, 919, 844 and 832; δ_H(270 MHz, $CDCl_3$) 4.80 (2H, s, CH_2Cl), 7.45–7.50 (3H, m, ArH) and 7.70–7.77 (2H, m, ArH); *m*/*z* 212 (M^+, isotope, 37%), 210 (M^+, 100), 175 (M^+ − Cl, 70), 135 ($PhCNS^+$, 62), 116 (18), 103 ($PhCN^+$, 17) and 77 (Ph, 18).

(*b*) To a stirred solution of trithiazyl trichloride (244 mg, 1 mmol) in tetrachloromethane (5 ml), cinnamyl chloride (76 mg, 0.5 mmol) in tetrachloromethane (1 ml) was added dropwise. The mixture was heated at reflux for 17 h under nitrogen. The solvent was evaporated and the residue was separated by chromatography on silica gel. Elution with dichloromethane (30%) in light petroleum gave 3-dichloromethyl-4-phenyl-1,2,5-thiadiazole **4** as a red oil (15 mg, 12%), δ_H(270 MHz, $CDCl_3$) 6.95 (1H, s, $CHCl_2$), 7.52–7.58 (3H, m, ArH) and 7.67–7.73 (2H, m, ArH); *m*/*z* 248 (M^+, isotope, 10.4%), 246 (M^+, isotope, 54), 244 (M^+, 75), 211 (M^+ − Cl, isotope, 28), 209 (M^+ − Cl, 76), 187 (26), 173 (M^+ − HCl − Cl, 100), 135 ($PhCNS^+$, 30) and 77 (Ph^+, 28). Elution with dichloromethane (40%) in light petroleum gave 3-chloromethyl-4-phenyl-1,2,5-thiadiazole **3** (21 mg, 17%), mp 69–70 °C, identical with that described in (*a*).

With 1,3-diphenylpropene. (*a*) To a stirred solution of trithiazyl trichloride (244 mg, 1 mmol) in tetrachloromethane (3 ml), 1,3-diphenylpropene (97 mg, 0.5 mmol) in tetrachloromethane (1 ml) was added by a syringe slowly. No significant temperature or colour change was observed. The mixture was heated at reflux for 20 h under nitrogen; it turned green and then red. The solvent was evaporated and the residue was separated on silica gel. Elution with dichloromethane (50%) in light petroleum gave 3,5-diphenylisothiazole **5** (63 mg, 53%) as colourless needles, mp 85.5–86.5 °C (lit.,[11] 81 °C) (Found: C, 76.0; H, 4.3; N, 5.8. Calc. for $C_{15}H_{11}NS$: C, 76.0; H, 4.6; N, 5.9%); ν_{max}(Nujol)/cm^{-1} 3055, 1529, 1485, 1455, 1391, 1370,

1337, 1306, 1205, 1188, 1153, 1100, 1087, 1076, 1028, 1000, 984, 970, 920 and 910; δ_H(270 MHz, $CDCl_3$) 7.40–7.50 (6H, m, ArH), 7.61–7.68 (2H, m, ArH), 7.75 (1H, s, 4-H) and 7.97–8.01 (2H, m, ArH); *m*/*z* 237 (M^+, 100%), 204 (5), 135 ($PhCNS^+$, 17) 134 (24), 121 (5), 103 ($PhCN^+$, 7), 89 (6) and 77 (Ph^+, 16).

(*b*) 1,3-Diphenylpropene (194 mg, 1 mmol) in chloroform (0.5 ml) was added to a solution of trithiazyl trichloride (80 mg, 0.33 mmol) in chloroform (2.5 ml) at room temperature and then heated at reflux for 17 h. The solvent was evaporated and the residue was separated on silica gel. Elution with dichloromethane (50%) in light petroleum firstly gave a thin oil (230 mg) which appeared to be chlorinated starting material (based on the mass spectrum), and secondly gave 3-(α-*chlorobenzyl*)-4-*phenyl*-1,2,5-*thiadiazole* **6** as colourless needles (30 mg, 14%), mp 115–118 °C (Found: C, 62.8; H, 3.9; N, 9.9. $C_{15}H_{11}ClN_2S$ requires: C, 62.8; H, 3.8; N, 9.8%); ν_{max}(Nujol)/cm^{-1} 1398, 1247, 1223, 1198, 1170, 1079, 1015, 931, 886, 858, 841, 804, 783, 769, 741, 701, 663 and 655; δ_H(270 MHz, $CDCl_3$) 6.35 (1H, s, C*H*ClPh), 7.35–7.42 (3H, m, ArH), 7.52–7.58 (5H, m, ArH) and 7.60–7.65 (2H, m, ArH); *m*/*z* 286 (M^+, 12%), 251 (M^+ − Cl, 100), 173 (39), 148 (37), 135 ($PhCNS^+$, 5), 125 (11), 116 (14), 103 ($PhCN^+$, 9) and 91 (4).

Reactions of allylic compounds with trithiazyl trichloride

Either procedure A or B was used. In procedure A a mixture of the organic substrate (1 mmol) and the reagent (1 mmol) in tetrachloromethane (20 ml) was heated at reflux overnight. The solvent was then evaporated and the residue was separated by flash chromatography on silica, eluting with dichloromethane in light petroleum. In procedure B the same mixture in tetrachloromethane (25 ml) was heated at reflux overnight in the presence of 4 Å molecular sieves (2 g). The molecular sieves were then filtered off and washed with dichloromethane and the combined organic solution was evaporated and the residue was separated as in A.

With 1,3-diphenyl-2-methylpropene 7. Procedure A with compound **7** (208 mg) and trithiazyl trichloride (244 mg) gave 3,5-*diphenyl*-4-*methylisothiazole* **12** (48 mg, 19%), mp 145–147 °C (Found: C, 76.3; H, 5.3; N, 5.8%. $C_{16}H_{13}NS$ requires C, 76.5; H, 5.2; N, 5.6%); ν_{max}($CHCl_3$)/cm^{-1} 3084, 3001, 2380, 1881, 1490, 1456, 1238, 1220 and 804; δ_H(270 MHz, $CDCl_3$) 2.32 (3H, s, CH_3) and 7.39–7.67 (10H, m, ArH); *m*/*z* 251 (M^+, 75%), 250 (100), 217 (M^+ − S, 2), 147 (M^+ − PhCN, 10), 135 ($PhCNS^+$, 2), 121 ($PhCS^+$, 6), 115 (3), 104 (6), 103 ($PhCN^+$, 6) and 77 (Ph^+, 7) and 3-*chloro*-1,3-*diphenyl*-2-*methylpropan*-1-*one* **13** (62 mg, 26%), mp 97–99 °C; ν_{max}($CHCl_3$)/cm^{-1} 3020, 3010, 2440, 1881, 1710, 1480, 1456, 1240, 1220 and 899; δ_H(270 MHz, $CDCl_3$) 1.83 (3H, br, CH_3), 2.05 (1H, m, CHMe), 5.45 (1H, d, CHCl) and 7.27–7.40 (10H, m, ArH); *m*/*z* 260 (M^+ + 2, 0.6%), 258 (M^+, 1.9), 243 (M^+ − Me, 2.4), 223 (M^+ − Cl, 18), 222 (25), 205 (24), 179 (7), 145 (7), 118 (36), 115 (49), 105 ($PhCO^+$, 100) and 77 (Ph^+, 48).

With phenylmethylidenecyclohexane 8. Procedure A with compound **8** (172 mg) and trithiazyl trichloride (244 mg) gave 3-*phenyl*-4,5,6,7-*tetrahydro*-2,1-*benzisothiazole* **14** (15 mg, 7%) as a yellow oil (Found: M^+, 215.0768, $C_{13}H_{13}NS$ requires *M*, 215.0769); ν_{max}($CHCl_3$)/cm^{-1} 3027, 2936, 1667, 1599, 1492, 1446, 1409 and 913; δ_H(270 MHz, $CDCl_3$) 1.80–1.91 (4H, m, $2CH_2$), 2.79–2.89 (2H, t, CH_2), 2.91–2.94 (2H, t, CH_2) and 7.38–7.49 (5H, m, ArH); *m*/*z* 215 (M^+, 100%), 187 (15), 121 ($PhCS^+$, 10), 115 (15), 91 (25) and 77 (Ph^+, 14).

With ethyl 3-benzyl-4-phenylbut-2-enoate 9. Procedure B with compound **9** (283 mg) gave *ethyl* 4-*benzyl*-3-*phenylisothiazole*-5-*carboxylate* **15** (104 mg, 32%) as pale yellow oil (Found: M^+, 323.0981. $C_{19}H_{17}NO_2S$ requires *M*, 323.0980); ν_{max}($CHCl_3$)/cm^{-1} 3031, 3001, 1730 (C=O), 1491, 1447, 1408, 1372, 1335, 1265, 1219, 1190, 1030, 782, 777, 736 and 667; δ_H(270 MHz, $CDCl_3$) 1.09–1.28 (3H, t, CH_3), 3.71 (2H, s, $PhCH_2$), 4.00–4.08 (2H, q, CH_2) and 7.43–7.62 (10H, m, ArH); *m*/*z* 323 (M^+, 65%), 250 (M^+ − CO_2Et, 100), 217 (10), 147 (M^+ − CO_2Et − PhCN, 25), 115 (12), 103 ($PhCN^+$, 22) and 77 (Ph^+, 30).

With ethyl indan-2-ylideneacetate 10. Procedure B with compound **10** (203 mg) gave *ethyl* 4H-*indeno*[1,2-c]*isothiazole*-3-*carboxylate* **16** (45 mg, 25%) as orange–brown crystals, mp 131–132 °C (Found: M^+, 245.0511. $C_{13}H_{11}NO_2S$ requires *M*, 245.0511); ν_{max}($CHCl_3$)/cm^{-1} 3057, 3020, 2982, 2937, 1735 (C=O), 1614, 1462, 1393, 1369, 1332, 1301, 1251, 1176, 1097, 1032, 914 and 796; δ_H(270 MHz, $CDCl_3$) 1.44–1.49 (3H, t, CH_3), 3.97 (2H, s, CH_2), 4.43–4.51 (2H, q, CH_2), 7.36–7.39 (2H, m, ArH) and 7.55–7.64 (2H, m, ArH); *m*/*z* 245 (M^+, 60%), 200 (M^+ − CO_2, 13), 173 (M^+ − CO_2Et, 100), 146 (30), 140 (M^+ − CO_2Et − S, 50), 128 (M^+ − CO_2Et − CS, 7), 101 (5) and 86 (6).

With (*E*)-ethyl 3,4-diphenylbut-2-enoate 11b. Procedure B with compound **11b** (233 mg, 0.95 mmol) gave *ethyl* 3,4-*diphenylisothiazole*-5-*carboxylate* **17** (180 mg, 66%), mp 80–81 °C (Found: M^+, 309.0823. $C_{18}H_{15}NO_2S$ requires *M*, 309.0824); ν_{max}($CHCl_3$)/cm^{-1} 3031, 3001, 1740 (C=O), 1491, 1447, 1408, 1372, 1335, 1219, 1190, 1030, 782, 777, 736 and 667; δ_H(270 MHz, $CDCl_3$) 1.21–1.26 (3H, t, CH_3), 4.22–4.30 (2H, q, CH_2) and 7.19–7.38 (10H, m, ArH); *m*/*z* 309 (M^+, 100%), 280 (M^+ − Et, 30), 262 (M^+ − SN, 40), 236 (M^+ − CO_2Et, 22), 204 (M^+ − CO_2Et − S, 5), 190 (7), 133 (PhC_2S^+, 10) and 86 (6).

With (*Z*)-ethyl 4-phenyl-3-benzylbut-2-enoate 11a. Procedure B with compound **11a** (213 mg, 0.85 mmol) gave ethyl 3,4-diphenylisothiazole-5-carboxylate **17** (15 mg, 6%), mp 80–81 °C, identical with that described above and ethyl 4-phenyl-1,2,5-thiadiazole-3-carboxylate **18** (45 mg, 23%), identical with an authentic sample.

Reactions of 1,3-diketones with trithiazyl trichloride

Either procedure C or D was used. In procedure C a mixture of the organic substrate (2 mmol) and trithiazyl trichloride (2 mmol) in tetrachloromethane (30 ml) was heated at reflux under nitrogen for 12 h. The solvent was evaporated *in vacuo* and the residue was separated by column chromatography on silica, eluting with dichloromethane in light petroleum. In procedure D a mixture of the organic substrate (2 mmol), trithiazyl trichloride (3 mmol) and dry 4 Å molecular sieves (4 g) in tetrachloromethane (30 ml) was heated at reflux under nitrogen for 12 h. The mixture was then filtered and the molecular sieves were washed with dichloromethane and the combined organic solution was evaporated and worked up as above.

With dibenzoylmethane 19. (*a*) Procedure C and elution with dichloromethane (60%) in light petroleum gave 3-benzoyl-4-phenyl-1,2,5-thiadiazole **20** (110 mg, 20%) as colourless needles, mp 82–83 °C (lit.,[7] 81–83 °C); *m*/*z* 266 (M^+, 56%), 237 (12), 219 (3), 135 ($PhCNS^+$, 9) 105 ($PhCO^+$, 100), 77 (Ph^+, 63), 51 (25). Elution with dichloromethane gave *bis(dibenzoylmethylideneamino) trisulfide* **21** (56 mg, 5%) as yellow needles, mp 87–88 °C (Found: C, 63.3; H, 3.4; N, 4.9. $C_{30}H_{20}N_2O_4S_3$ requires C, 63.4; H, 3.5; N, 4.9%); ν_{max}($CHCl_3$)/cm^{-1} 3037, 3021, 1657 (C=O), 1598, 1450, 1319, 1288, 1245, 1182, 1003, 979 and 876; δ_H(270 MHz, $CDCl_3$) 7.4–7.5 (12H, m, PhH) and 7.52–7.63 (8H, m, PhH); *m*/*z* 268 (M^+ − S/2, 60%) and 105 ($PhCO^+$, 100).

(*b*) Procedure D gave 3-benzoyl-4-phenyl-1,2,5-thiadiazole **20** (220 mg, 41%) as colourless needles, mp 82–83 °C, identical with that described above and bis(dibenzoylmethylideneamino) trisulfide **21** (122 mg, 11%) as yellow needles, mp 87–88 °C, identical with that described above.

With 1,3-diphenylprop-2-en-1-one 22. Procedure C, but with trithiazyl trichloride (976 mg, 4 mmol) gave 3-benzoyl-4-phenyl-1,2,5-thiadiazole **20** (322 mg, 60%), mp 82–83 °C, identical with that described above.

With 1-(4-methoxyphenyl)-3-phenylpropane-1,3-dione 23. Procedure D, but with trithiazyl trichloride (366 mg, 3 mmol) gave 3-(4-*methoxybenzoyl*)-4-*phenyl*-1,2,5-*thiadiazole* **26** (198 mg, 33%) as colourless needles, mp 129–131 °C (Found: M^+, 296.0620. $C_{16}H_{12}N_2O_2S$ requires *M*, 296.0619); ν_{max}($CHCl_3$)/

cm^{-1} 3038, 3007, 1670 (C=O), 1601, 1518, 1461, 1423, 1395, 1268, 1195, 1163, 1044, 1030, 900 and 835; δ_H(270 MHz, $CDCl_3$) 3.90 (3H, s, OMe), 6.97–6.99 (2H, d, 4-$MeOC_6H_4$), 7.34–7.42 (3H, m, PhH), 7.66–7.72 (2H, m, PhH) and 7.93–7.95 (2H, d, 4-$MeOC_6H_4$); *m*/*z* 296 (M^+, 39%), 265 ($M^+ - S$, 2), 135 (4-$MeOC_6H_4CO^+$, 100), 103 ($PhCN^+$, 5), 92 (13) and 77 (Ph^+, 20).

With benzoylacetone 24. Procedure D, but with trithiazyl trichloride (732 mg, 3 mmol) gave 3-benzoyl-4-methyl-1,2,5-thiadiazole **27** (102 mg, 25%) as colourless crystals, mp 72–73 °C (lit.,[7] 72–73 °C); *m*/*z* 204 (M^+, 69%), 105 ($PhCO^+$, 100) and 77 (Ph^+, 88).

With indane-1,3-dione 25. Procedure D, but with trithiazyl trichloride (1.46 g, 6 mmol) and with refluxing for 24 h gave unreacted indane-1,3-dione **25** (178 mg, 61%) and 8*H*-indeno-[1,2-*c*][1,2,5]thiadiazol-8-one **28** (60 mg, 16%), mp 112–114 °C (lit.,[2] 113 °C).

With 1,2-dibenzoylethane. Procedure C, with trithiazyl trichloride (732 mg, 3 mmol) gave 3,4-dibenzoyl-1,2,5-thiadiazole **31** (235 mg, 40%) as colourless needles, mp 128–129 °C (lit.,[2,12] 124 °C); *m*/*z* 294 (M^+, 18%), 217 ($M^+ - Ph$, 4), 105 ($PhCO^+$, 100) and 77 (Ph^+, 50).

With 1,2-dibenzoylethyne. Procedure C with 1,2-dibenzoylethyne (234 mg, 1 mmol) and trithiazyl trichloride (366 mg, 1.4 mmol) gave 3,4-dibenzoyl-1,2,5-thiadiazole **31** (129 mg, 44%), mp 128–129 °C, identical with that described above.

With fluorene. Procedure C, but with refluxing for 24 h gave bis(fluoren-9-ylideneamino) sulfide **32** (155 mg, 40%) as yellow prisms, mp > 290 °C (lit.,[9] > 300 °C); *m*/*z* 388 (M^+, 81%), 342 ($M^+ - NS$, 16), 210 (99), 179 (100), 151 (16), 76 (12) and 64 (12).

With 1-phenyl-3-benzoylprop-1-ene 29. Procedure A with compound **29** (111 mg, 0.5 mol) gave 3,4-dibenzoyl-1,2,5-thiadiazole **31**, (38 mg, 26%), mp 128–129 °C, identical with that described above.

Acknowledgements

We thank Zeneca Specialties and MDL Information Systems (UK) Ltd for financial support and the Wolfson Foundation for establishing the Wolfson Centre for Organic Chemistry in Medical Science at Imperial College.

References

1 *Gmelin Handbook of Inorganic Chemistry*, 8th edn., *Sulfur-Nitrogen Compounds*, Part 2, Springer Verlag, Berlin, 1985, p. 92.
2 X.-G. Duan, X.-L. Duan, C. W. Rees and T.-Y. Yue, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2597.
3 L. M. Tolbert and M. E. Ogle, *J.Am. Chem. Soc.*, 1990, **112**, 9519.
4 C. L. Bumgardner and H. Iwerks, *J. Am. Chem. Soc.*, 1996, **88**, 5518.
5 *Dictionary of Organic Compounds*, Chapman and Hall, London, 6th edn., vol. 1, p. 705.
6 Y. Leroux and C. Jaquelin, *Synth. Commun.*, 1976, **6**, 597.
7 S. Mataka, A. Hosoki, K. Takahashi and M. Tashiro, *Synthesis*, 1982, 976.
8 S. Mataka, A. Hosoki, K. Takahashi and M. Tashiro, *J. Heterocycl. Chem.*, 1980, **17**, 1681.
9 S. Mataka, K. Takahashi, S. Ishi-i and M. Tashiro, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2905.
10 X.-L. Duan, R. Perrins and C. W. Rees, *J. Chem. Soc., Perkin Trans. 1*, 1997, 1617; C. W. Rees and T.-Y. Yuen, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2247.
11 R. A. Olofson, J. M. Landesburg, R. O. Berry, D. Leaver, W. A. H. Robertson and D. M. McKinnon, *Tetrahedron*, 1966, **22**, 2119.
12 S. Mataka, K. Takahashi, Y. Yamada and M. Tashiro, *J. Heterocycl. Chem.*, 1979, **16**, 1009.

Paper 7/03033I
Received 2*nd May* 1997
Accepted 6*th June* 1997