Covalent Adduct Formation in 1,2,4-Thiadiazolo Activated Pyrimidinones

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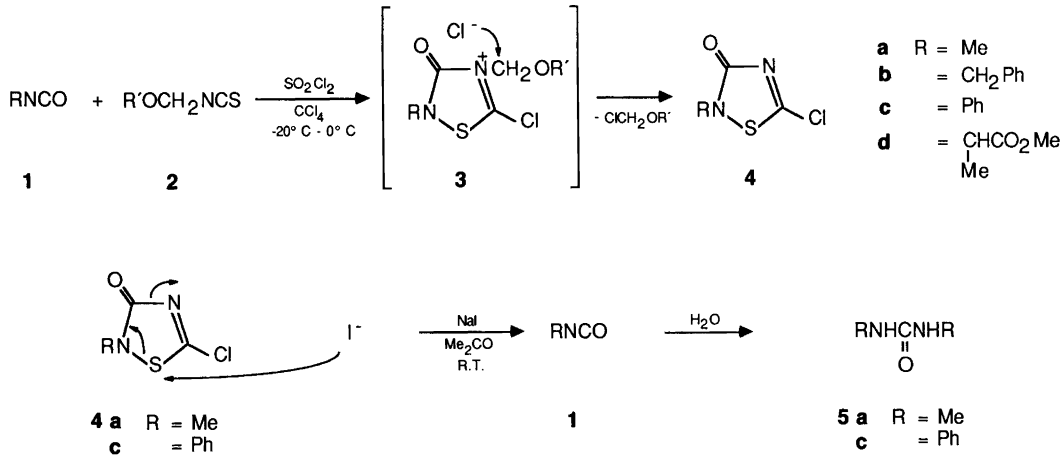
Preparation of 1-(1,2,4-thiadiazol-5-yl)-2(1*H*)-pyrimidinones is described. The polarization from the thiadiazole ring enhances the π-electron deficiency of the pyrimidine ring. The latter forms covalently bound adducts with hydroxylic solvent molecules in a regiospecific manner. The adducts are stable, isolable molecules, but on heating in a hydroxylic solvent exchange of the solvent molecule in the adduct may take place.

Aromatic stabilization in azoles and azines decreases with increase in the number of heteroatoms which cause an increase in the π-electron deficiency. In studies of 2-pyrimidinones we have also noticed that small changes in the electronic properties of the N-1 substituent are transmitted through the nitrogen into the π-electron system of the pyrimidine ring. This is seen for instance in the ease of removal of solvent molecules from the adducts of the heterocycles which have been in contact with hydroxylic solvents, and by ^{1}H NMR spectroscopy which reveals equilibria in solution between the fully conjugated ring and the corresponding solvent adduct.[1] We now describe studies on pyrimidine derivatives substituted with a strongly polarizing group at N-1. An acyl group at N-1 would satisfy the electronic requirement for polarization, but these derivatives are generally unstable and reactive. A polarizing effect similar to that of the acyl function, but this time with chemical stability, can be achieved by the use of another π-electron deficient heterocycle. The latter must be substituted in such a manner that it is chemically stable and is not itself in-

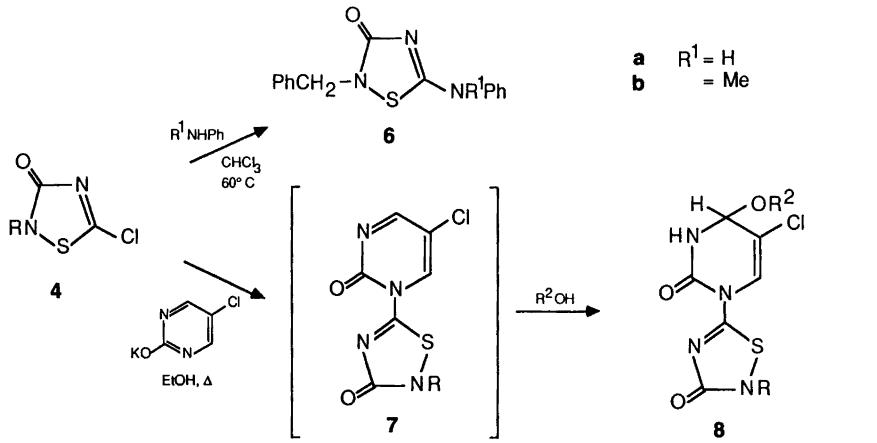


Scheme 1.

volved in adduct formation. Our choice was a 1,2,4-thiadiazole which was stabilized by an 3-oxo function and variously substituted at N-2. The thiadiazole **4**, used in the alkylation reactions, has a halogen in the 5-position which is the most reactive position for nucleophilic substitution in this ring system.

The thiadiazoles **4** were prepared as described for **4c** except for minor adaptations of the experimental procedures. Chlorination of an isothiocyanate in the presence of an isocyanate leads to an *N,N'*-disubstituted thiadiazolium salt.[2] If the isothiocyanate substituent is part of an alkoxy group, the corresponding substituent in the cyclic product **3** is cleaved as a chloromethyl ether yielding the N-2 substituted 1,2,4-thiadiazole **4**.[3] The reagent of choice was ethoxymethyl isothiocyanate[4] rather than methoxymethyl isothiocyanate, in order to avoid the formation of the carcinogenic chloromethyl ether. The benzyl isocyanate is available from benzylamine and silver isocyanate,[5] and methyl α-isocyanatopropionate by the reaction of the amino acid ester and diphosgene.[6] The cyclization reaction leading to **4** is run in the cold to avoid polymerization of the isothiocyanate.[7] The reaction with phenyl isocyanate was complete after 2–3 h, whereas the product from the benzyl isocyanate reaction or the methyl α-isocyanatopropionate reaction was collected after one week in the cold. The product **4d** from *S*-alanine methyl ester is optically active. For analysis of enantiomeric composition using ^{1}H NMR (200 MHz), tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium (III) was added in portion of from 0.1 to 0.5 molar equiv. to a solution of **4d** in deuteriochloroform. The signal from the methine proton of the side-chain was shifted from 5.2 to 6.6 ppm and appeared as a singlet. Unfortunately, the singlet for the methyl group was partly hidden by absorption from the shift reagent. Measurements on the racemate **4d** gave two well resolved peaks of equal intensity at 6.6 and 6.8 ppm. The enantiomeric composition in the product from *S*-alanine methyl ester was then estimated by gradual addition of a solution of the racemic product to a solution of the former in an NMR tube. The end point for the addition was the first detection of a signal for the methyl group in the *R*-form. This corresponds to 12 % of *R*-isomer.

The reactivity of **4** towards nucleophiles was initially studied attempting a halogen interchange reaction in the 2-phenyl-1,2,4-thiadiazole **4c**. When the latter was treated with sodium iodide in acetone solution at room temperature, the product was identified as *N,N'*-diphenylurea. The course of this reaction is rationalized by initial attack by the iodide ion on the sulfur with



Scheme 2.

cleavage of the *N-S* bond and regeneration of phenyl isocyanate. Presumably the latter, during the aqueous work-up of the reaction, is partly decarboxylated via its carbamic acid and partly reacts with the aniline generated to form the urea **5c**.[8] The methyl derivative **4a** was much less reactive, but GC monitoring showed that also in this case *N,N'*-dimethylurea was the major product. From the literature it is also known that the *N-S* bond of isothiazoles and hetero-substituted isothiazoles can be cleaved by nucleophiles.[9] In aminolysis of **4**, however, the chlorine atom is displaced. The product **6a** from the reaction between **4b** and aniline was poorly soluble in organic solvents. The poor solubility is ascribed to intermolecular hydrogen bonding from the NH function to the oxygen of the oxo group. Hydrogen bonding was prevented by using *N*-methylaniline as the nucleophile, and the product **6b** was readily soluble in organic solvents.

5-Chloro-2(1*H*)-pyrimidinone was converted into its potassium salt to improve its nucleophilic properties before reaction with **4**. The anion of the pyrimidine is ampholytic but the *N*-heteroarylated product **7** was formed exclusively. However, since the reaction was run in hydroxylic solvents, the solvent adducts **8** were isolated. There was no sign of adduct formation involving the five-membered ring. The solvent molecule in the adduct **8** could not be removed by drying at reduced pressure and elevated temperature. Interchange of the hydroxylic molecule, however, can be effected. Thus the ethanol adduct is converted to the corresponding methanol adduct when the former is heated in methanol.

TLC is consistent with the exclusive formation of one regioisomeric adduct. The diagnostic NMR data are very similar, which leads us to conclude that it is the same regioisomer which is formed in all cases. For steric reasons formation of the 3,4-dihydro isomer **8** is suggested. ^{1}H NMR spectra recorded at 300 MHz show a doublet at 10.10 ppm, a singlet at 7.60 and a doublet at 5.40. The signal at 10.10 ppm disappeared on the addition of deuterium oxide to a solution in the NMR tube and is therefore ascribed to the NH proton. At the same time the doublet at 5.40 was changed into a singlet. The corresponding proton is therefore situated on the carbon adjacent to the NH proton. The downfield signal at 7.60 ppm is assigned to the proton on the sp^2 hybridized carbon atom. The assignment is supported by a NOE experiment. Irradiation of the methylene protons of the ethoxy group had a strong influence on the signal at 5.40 ppm. The proton responsible for this signal is therefore located on the same carbon as the ethoxy group. Hence, the ^{1}H NMR data are consistent with the 3,4-dihydro adduct **8c**.

The thiadiazolopyrimidinones **7** belong to the group of 1-substituted 2(1*H*)-pyrimidinones which are potential inhibitors of the cell cycle during mitosis.[10] The activity is associated with adduct formation between the pyrimidine ring and a hetero-nucleophilic function at the receptor site. Since the activity is dependent on the presence of the fully conjugated pyrimidine ring, it was no surprise that the derivatives **7**, which are blocked as adduct **8** and tested as such (R^2 = Me, Et) were inactive as inhibitors in the mitotic phase.[11]

Experimental

The mass spectra under electron impact conditions were recorded at 70 eV ionizing energy. Isobutane was used for chemical ionizing (CI), the spectra are presented as *m/z* (% rel. int.). The ^{1}H NMR spectra were recorded at 60 MHz and the ^{13}C data at 15 MHz on a JMN-FX Fourier Transform spectrometer. The enentiomeric analysis of **4d** was performed at 200 MHz. The NOE experiment was carried out at 300 MHz.

*5-Chloro-2-methyl-1,2,4-thiadiazol-3(2*H*)-one* (**4a**). Sulfuryl chloride (18,.2 g, 135 mmol) was added dropwise with stirring at 0 °C to a solution of methyl isocyanate (7.70 g, 135 mmol) and ethoxymethyl isothiocyanate (15.90 g, 135 mmol) in dry tetrachloromethane (100 ml). The mixture was stirred at 0 °C for 3 d before the precipitate was collected by filtration and recrystallized from tetrachloromethane; yield 5.40 g (27 %), m.p. 108–110 °C (lit.[3], m.p. 98–100 °C).

*2-Benzyl-5-chloro-1,2,4-thiadiazol-3(2*H*)-one* (**4b**) was prepared as above from sulfuryl chloride (3.37 g, 25 mmol), benzyl isocyanate (3.33 g, 25 mmol) and ethoxymethyl isothiocyanate (2.94 g, 25 mmol). The reaction was run at −20 °C, and the product was collected by filtration after 7 d and recrystallized from tetrachloromethane, yield 1.38 g (24 %), m.p. 95–97 °C. Anal.

$C_9H_7ClN_2OS$: C, H. ^1H NMR ($CDCl_3$): δ 4.88 (CH_2Ph), 7.40 (Ph, s). ^{13}C NMR: δ 48.4 (CH_2Ph, t), 128.6–135.0 (Ph), 162.9 (C-5, s), 168.8 (C-3, s). IR (KBr): 1690 (CO) cm^{-1}. MS: 228/226 (0.7/2, *M*), 191 (11), 150 (4), 106 (3), 91 (100).

5-Chloro-2-phenyl-1,2,4-thiadiazol-3(2H)-one (**4c**) was prepared as described in the literature.[3] ^{13}C NMR ($CDCl_3$): δ 124.7–134.4 (Ph), 160.4 (C-5), 166.5 (C-3).

S-*5-Chloro-2-(1-methoxycarbonylethyl)-1,2,4-thiadiazol-3(2H)-one* (**4d**). Sulfuryl chloride (4.05 g, 30 mmol) was added dropwise with stirring at 0 °C to a solution of methyl *S*-isocyanatopropionate (3.50 g, 27 mmol) and ethoxymethyl isothiocyanate (3.53 g, 40 mmol) in tetrachloromethane. The mixture was stirred at 0 °C for 1 week before the solvent was distilled off. The residue was dissolved in chloroform and chromatographed on a silica gel column using chloroform as eluent. The product was a non-crystalline yellow material; yield 3.70 g (62 %). Anal. $C_6H_7ClN_2O_3S$: C, H. ^1H NMR ($CDCl_3$): δ 1.54 (*Me*CH, d, J = 8 Hz), 3.80 (OMe), 5.10 (MeC*H*, q, J = 8 Hz). ^{13}C NMR ($CDCl_3$): δ 18.3 (*Me*CH, q), 52.8 (OMe, q), 53.2 (Me*CH*, d), 162.7 (C-5, s), 169.0 (C-3, s), 171.0 (CO_2Me, s). IR (film): 1700 and 1750 cm^{-1} (CO). MS: 224/222 (5/13, *M*), 165 (35), 162 (100), 86 (27), 79 (13), 74 (26).

N,N′-*Dimethylurea* (**5a**). 5-Chloro-2-methyl-1,2,4-thiadiazol-3(2*H*)-one (3.01 g, 20 mmol) and sodium iodide (6.0 g, 40 mmol) were dissolved in acetone, and the solution stirred for 3 d at ambient temperature. The black mixture was treated with aqueous sodium thiosulfate and extracted with ether, and the crude product was recrystallized from benzene; yield 1.39 g (7 %), m.p. 100–102 °C (lit.[12] m.p. 108 °C).

N,N′-*Diphenylurea* (**5b**) was prepared from **4b** as described for **5a**. The crude product was recrystallized from acetone/water; yield 2.60 g (61 %), m.p. 244–246 °C (lit[12] m.p. 235 °C).

5-Anilino-2-benzyl-1,2,4-thiadiazol-3(2H)-one (**6a**). Aniline (0.25 g, 2.6 mmol) was added dropwise with stirring to a solution of 2-benzyl-5-chloro-1,2,4-thiadiazol-3(2*H*)-one (0.30 g, 1.3 mmol) in chloroform (25 ml) at 60 °C. TLC monitoring showed the reaction to be complete when all the aniline had been added. The solvent was then distilled off, and the residue was triturated with water and recrystallized from ethanol; yield 0.30 g (81 %), m.p. 222–224 °C. Anal. $C_{15}H_{13}N_3OS$: C, H. ^1H NMR (DMSO-d_6): δ 4.82 (CH_2Ph), 7.2–7.7 (2 Ph). IR (KBr) 1630 (CO) cm^{-1}. MS: 283 (19, *M*), 150 (2), 145 (22), 118 (6), 106 (5), 91 (100).

*2-Benzyl-5-(*N*-methylanilino)-1,2,4-thiadiazol-3(2H)-one* (**6b**) was prepared as above from 2-benzyl-5-chloro-1,2,4-thiadiazol-3(2*H*)-one (0.20 g, 0.88 mmol) and *N*-methylaniline in 57 % yield (0.15 g), m.p. 139–140 °C. Anal. $C_{16}H_{15}N_3OS$: C, H. ^1H NMR ($CDCl_3$): δ 3.58 (NMe), 4.78 (CH_2Ph), 7.3–7.5 (2 Ph). ^{13}C NMR ($CDCl_3$): δ (NMe, q), 47.8 (N-CH_2, t), 128–142 (2 Ph), 166.3 (C-3, s), 172.6 (C-5, s). IR (KBr): 1660 cm^{-1}. MS: 297 (7, *M*), 193 (5), 192 (20), 132 (6), 106 (5), 91 (100).

5-Chloro-4-methoxy-1-[2-methyl-3(2H)-oxo-1,2,4-thiadiazol-5-yl]-3,4-dihydro-2(1H)-pyrimidinone (**8a**). A solution of the potassium salt of 5-chloro-2(1*H*)-pyrimidinone[13] (1.68 g, 10 mmol) in methanol (50 ml) was added dropwise with stirring to a solution of 5-chloro-2-methyl-1,2,4-thiadiazol-3(2*H*)-one (1.50 g, 10 mmol) in boiling ethyl acetate (50 ml) and the mixture heated for 0.5 h. The product which separated from the cold mixture was filtered off and recrystallized from ethyl acetate; yield 1.76 g (72 %), m.p. 174–176 °C (decomp.). Anal. $C_8H_9ClN_4O_3S$: C, H. ^1H NMR (DMSO-d_6): δ 3.10 and 3.20 (NMe and OMe), 5.30 (H-4, broad), 7.54 (H-6, s), 9.90 (NH, broad). ^{13}C NMR ($CDCl_3$): δ 28.7 (NMe, q), 5.19 (OMe, q), 81.1 (C-4, d, J = 174 Hz), 112.4 (C-5, s), 122.7 (C-6, J not resolved), 150.1 (C-2, s), 161.9 (C-3′, s), 163.6 (C-5′,s). IR (KBr): 1670 and 1700 cm^{-1} (CO). MS(CI): 279/277 (1/3, *M*+H), 247 (43), 245 (100). MS: 276 (0, *M*), 246 (15), 244 (41), 209 (30), 202 (23), 159 (22), 142 (100), 134 (40).

1-[2-Benzyl-3(2H)-oxox-1,2,4-thiadiazol-5-yl]-5-chloro-4-ethoxy-3,4-dihydro-2(1H)-pyrimidinone (**8b**). A solution of the potassium salt of 5-chloro-2(1*H*)-pyrimidinone (0.84 g, 5 mmol) in ethanol (50 ml) was added dropwise with stirring to a boiling solution of 2-benzyl-5-chloro-1,2,4-thiadiazol-3(2*H*)-one in ethanol (50 ml) and the mixture heated under reflux for 0.5 h. The prod-

uct which precipitated from the cold mixture was recrystallized from ethanol; yield 0.36 g (45%), m.p. 188–190°C (decomp.). ^{1}H NMR (DMSO-d_6): δ 1.16 and 3.60 (OEt), 4.86 (CH_2Ph, s) 5.44 (H-4, broad), 7.42 (Ph, s), 7.72 (H-6, s). IR (KBr): 3075 (NH), 1670 and 1700 cm^{-1} (CO). MS(CI): 323/321 [43/100, (*M*+H) − EtOH]. MS: 322/320 (2/5, *M*-EtOH), 285 (5), 180 (12), 132 (8), 92 (8), 91 (100).

*5-Chloro-4-ethoxy-1-[3(*2H*)-oxo-2-phenyl-1,2,4-thiadiazol-5-yl]-3,4-dihydro-2(*1H*-pyrimidinone* (**8c**) was prepared as **8b** above 5-chloro-2-phenyl-1,2,4-thiadiazol-3(2*H*)-one (1.06 g, 5 mmol) and the potassium salt of 5-chloro-2(1*H*)-pyrimidinone (0.84 g, 5 mmol) in ethanol; yield 1.30 g (75%), m.p. 186–188°C (decomp.; EtOH). Anal. $C_{14}H_{13}ClN_4O_3S$: C, H. ^{1}H NMR (DMSO-d_6): δ 1.10 and 3.50 (EtO), 5.40 (H-4, d, *J* = 4 Hz), 7.3–7.6 (Ph), 7.60 (H-6, s), 10.10 (NH, d, *J* = 2 Hz). ^{13}C NMR (DMSO-d_6): δ 14.9 and 61.0 (OEt), 80.2 (C-4, d, *J* = *168 Hz), 113.6 (C-5, s), 122.0 (C-6, J* not resolved), 126.4–135.6 (Ph), 150.2 (C-2, s), 159.3 (C-3′, s), 163.5 (C-5′, s). IR (KBr): 3080 (NH), 1710 and 1670 cm^{-1} (CO). MS(CI): 355/353 (0.8/2, *M*+H), 309/307 (50/100). MS: 308/306 (18/48, *M* − EtOH), 204 (100), 196 (20), 155 (14), 123 (32), 119 (12), 91 (15).

*5-Chloro-4-methoxy-1-[3(*2H*)-oxo-2-phenyl-1,2,4-thiadiazol-5-yl]-3,4-dihydro-2(*1H*)-pyrimidinone* (**8d**). *Method A:* The ethanol adduct **8c** from the reaction above (1.00 g, 2.8 mmol) was heated under reflux in methanol (100 ml) for 15 min before allowing the solution to cool. The product was precipitated in 85% (0.78 g) yield, m.p. 154–162°C (decomp.). Anal. $C_{13}H_{11}ClN_4O_3S$: C, H. ^{1}H NMR (DMSO-d_6): δ 3.28 (OMe), 5.38 (H-4, broad), 7.2–7.5 (Ph), 7.60 (H-6, s), 10.0 (NH, broad). ^{13}C NMR (DMSO-d_6): δ 48.4 (OMe), 81.0 (C-4, d, *J* = 175 Hz), 112.9 (C-5, s), 120.0 (C-6, *J* not resolved), 123.6–135.7 (Ph), 150.0 (C-2, s), 159.4 (C-3′, s), 163.3 (C-5′, s). IR (KBr): 3070 (NH), 1660 and 1690 cm^{-1} (CO). MS(CI): 341/339 (0.4/1, *M*+H), 309/307 (100). MS: 308/306 (23/64, *M* − MeOH), 204 (100), 196 (20), 155 (13), 123 (23), 119 (14), 91 (14).

Method B: When methanol instead of ethanol was used in the procedure for the preparation of **8c**, the methanol adduct **8d** was obtained.

*5-Chloro-4-ethoxy-1-[2-(1-methoxycarbonylethyl)-3(2*H*)-oxo-1,2,4-thiadiazol-5-yl]-3,4-dihydro-2(1*H*(**8e**)* was prepared as for **8b** above from *S*-5-chloro-2-(1-methoxycarbonylethyl)-1,2,4-thiadiazol-3(2*H*)-one (0.15 g, 0.67 mmol) and the potassium salt of 5-chloro-2(1*H*)-pyrimidinone (0.14 g, 0.67 mmol) in ethanol; yield 0.13 g (52%), m.p. 230°C (decomp.). ^{1}H NMR (DMSO-d_6): δ 1.20 and 3.60 (EtO), 1.60 (*Me*CH, d, *J* = 8 Hz), 3.70 (CO_2Me, s), 5.00 (Me*CH*, d, *J* = 8 Hz), 5.45 (H-4, broad), 7.70 (H-6, s), 10.10 (NH, broad), MS(CI): 319/317 (56/100, (*M*+H) − EtOH), 287 (2), 285 (5), 259 (20), 257 (38), 188 (12), 131 (18), 102 (46), 70 (17).

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