Reactions of Tetrasulfur Tetranitride with Bromomethyl Ketones. One Pot Synthesis of 3,5-Diaroyl- and 3,5-Diacyl-1,2,4-thiadiazoles

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Reactions of tetrasulfur tetranitride (S_4N_4) with aryl and alkyl bromomethyl ketones **1** in chlorobenzene at reflux temperature gave 3,5-diaroyl- and 3,5-diacyl-1,2,4-thiadiazoles **2** in 17-60% yields. No 1,2,5-thiadiazoles were detected. By heating of the two reactants at 115° without the solvent were also obtained **2** in 5-13% yields. Hydrolysis of **2** with sodium hydroxide in a mixture of ethanol, ethyl acetate, and water (v:v, 4:2:1) at 75° to 85° afforded the heretofore inaccessible 3-aroyl- and 3-acyl-1,2,4-thiadiazoles **3** in 17-79% yields.

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Reactions of tetrasulfur tetranitride with organic compounds have received considerable attention during recent years partly because of their utility in the one step synthesis of sulfur and nitrogen containing heterocyclic compounds [1-7]. Of the reactions, the reactions with various ketones are of particularly interest. That is, the reactions with aryl and alkyl ketones [8-11], cyclic ketones [8-11], and 1,3-diketones [12] in refluxing solvent gave 3,4-disubstituted-1,2,5-thiadiazoles as the main products. Heating of aryl methyl ketones with tetrasulfur tetranitride without the solvent also led to 3-aryl-1,2,5-thiadiazoles [4]. It has been suggested that the formation of the 1,2,5-thiadiazoles is achieved by the intramolecular cyclization of either $-\overset{O}{\overset{\|}{C}}-\underset{|}{CH}-N=S=N$ or $-\overset{O}{\overset{\|}{C}}-\underset{|}{C}=N-S-N=$ moiety which is formed somehow by the reactions of ketones with tetrasulfur tetranitride.

On the other hand, when dibenzyl ketone was reacted with tetrasulfur tetranitride in toluene at reflux temperature, 3-benzyl-4-phenyl-1,2,5-thiadiazole was isolated as the main product (32%) as usual and 3,5-diphenyl-1,2,4-thiadiazole in less than 1% yield [8], which was the first isolation of 1,2,4-thiadiazole from the reactions of ketones with tetrasulfur tetranitride. All of the ketones studied so far are characterized as simple ketones without having a good leaving group at α position of the carbonyl group. In order to understand the leaving group effects, the reactions of alkyl and aryl halomethyl ketones with tetrasulfur tetranitride were studied.

Results and Discussion.

A mixture of a halomethyl ketone **1** (2 mmoles) and tetrasulfur tetranitride (4 mmoles) in chlorobenzene (15 ml) was refluxed for 16-48 hours until tetrasulfur tetranitride had disappeared completely. After the solvent was removed *in vacuo*, the residue was chromatographed on a silica gel column. From the reaction mixture were isolated 3,5-diaroyl- or 3,5-diacyl-1,2,4-thiadiazole **2** as a main product along with sulfur, unreacted **1**, and unidentified complex mixture. No 1,2,5-thiadiazole derivatives were detected. The results are summarized in Table 1.

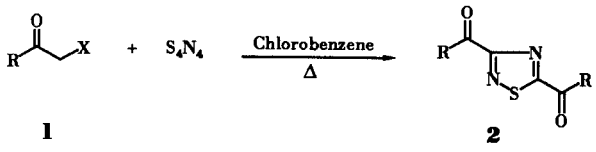
Table 1

Synthesis of 3,5-Diaroyl- (**2a-2g**) and 3,5-Diacyl-1,2,4-thiadiazoles (**2h**)

1	R	X	Time hours	Yield [a] **2**, %	mp °C
a	C_6H_5	Cl	48	60 (9)	65-66 (*n*-hexane-carbon tetrachloride) (lit [3] 68-69)
	C_6H_5	Br	48	58 (5)	
	C_6H_5	I	24	17 (6)	
b	*p*-MeC_6H_4	Br	48	39 (6)	57-58 (carbon tetrachloride)
c	*p*-ClC_6H_4	Br	24	37 (10)	200-202 (carbon tetrachloride)
d	*p*-BrC_6H_4	Br	24	36 (7)	120-121 (carbon tetrachloride)
e	*m*-$MeOC_6H_4$	Br	24	17 (6)	100-101 (carbon tetrachloride)
f	*p*-PhC_6H_4	Br	24	24 (13)	146-147 (carbon tetrachloride)
g	2-Thienyl	Br	16	35 [b] (5)	29-31 (*n*-hexane-carbon tetrachloride)
h	1-Adamantyl	Br	24	26 (5)	93-94 (carbon tetrachloride)

[a] Isolated yields based on **1** reacted. [b] The reactions were performed at 120° in order to avoid the violent reaction. Numbers in the parenthesis represented yield based on tetrasulfure tetranitride in the reactions in which a mixture of a large excess of **1** and tetrasulfur tetranitride was heated at 115° in the absence of the solvent.

Scheme 1



1 **2**

R = aryl, alkyl
X = Cl, Br

It is interesting to know that there is no general synthetic method for **2** although numerous synthetic methods of 3,5-disubstituted-1,2,4-thiadiazoles using the compounds other than tetrasulfur tetranitride have been reported [13]. In fact, all the compounds prepared are new one except for **2a** which is the only known 3,5-diaroyl-1,2,4-thiadiazole [3]. However, compound **2a** was obtained by a rather laborious method. That is, reaction of phenylacetylene with tetrasulfur tetranitride gave 4-(4-phenyl-1,2,5-thiadiazol-3-ylimino)-5-phenyl-1,3,2-dithiazole in 5% yield, which was oxidized to 4-(1-oxo-4-phenyl-1,2,5-thiadiazol-3-ylimino)-5-phenyl-1,3,2-dithiazole in 90% yield by treatment with nitrogen dioxide in dichloromethane at −20°. Either hydrolysis of the monoxide with dilute hydrochloric acid in tetrahydrofuran or oxidation of the monoxide with nitrosyl tetrafluoroborate in acetonitrile gave **2a** in 79% and 75% yields, respectively. No other phenylacetylene derivatives gave 1,2,4-thiadiazole derivatives. Accordingly, a one step synthesis of **2a** in 60% yield using the readily available **1a** (X = Cl) or **1a** (X = Br) appears to be superior to the reported method. Furthermore, this method can be applied to other phenacyl bromides **1b-1f** with either an electron donating or withdrawing group at phenyl group, aryl halomethyl ketone (**1g**), and alkyl halomethyl ketone **1h** with no α-hydrogen in the alkyl group to obtain **2**.

Reaction of **1a** (X = I) under the same conditions afforded **2a** in 17% yield but the reaction occurred very vigorously. Since the melting point of tetrasulfur tetranitride obtained by the standard method is known to be about 178° [14] and tetrasulfur tetranitride is stable in chlorobenzene at reflux temperature, it is conceivable that decomposition of **1a** (X = I) to give a complex mixture overwhelms the formation of **2a**.

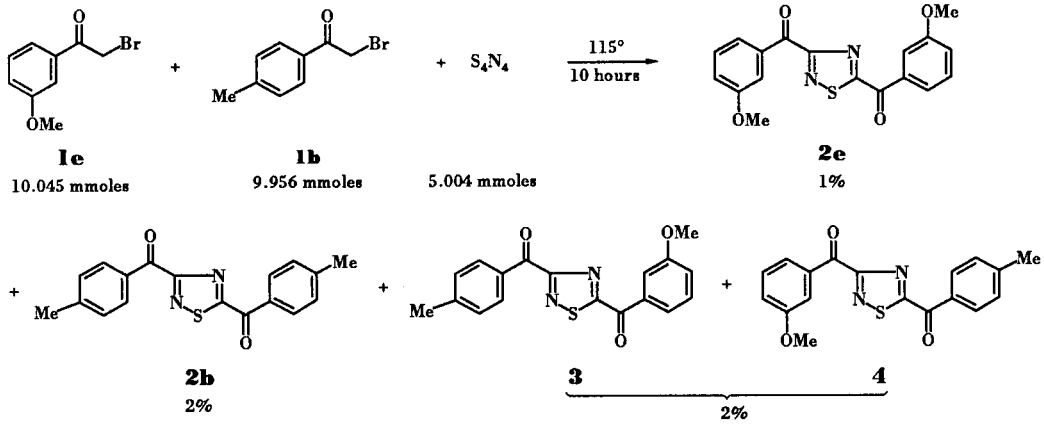
It is noteworthy that the *ortho* protons of the benzoyl group at C-5 of 1,2,4-thiadiazole appear further downfield than those at C-3. This result is consistent with the ^{1}H nmr assignments in 1,2,4-thiadiazoles where the C-5 protons are farther downfield than the C-3 protons [13,14]. In addition, the ^{13}C nmr data of some of the compounds **2** shows clearly that compound **2** are indeed 1,2,4-thiadiazoles instead of 1,2,5-thiadiazoles (*vide infra*).

The reactions of **1** with tetrasulfur tetranitride were also carried out without the solvent. Heating of a mixture of excess amounts of **1** and tetrasulfur tetranitride at 115° with stirring makes tetrasulfur tetranitride soluble in the molten **1** concomitant with the color change from an orangish color to a darker one. However, the reaction with **1f** was performed at 130° since the melting point of **1f** was 124° to 125° whereas the reaction with **1g** at 95° with tetrasulfur tetranitride turned to a black tar at 100°. From these reactions were isolated the same compounds as in the reactions performed in the presence of the solvent. No 1,2,5-thiadiazole were detected. The yields are listed in the parenthesis in Table 1.

In the meantime, the reaction of a mixture of equal molar amounts of two different bromomethyl ketones, *i.e.* **1b** and **1e**, with tetrasulfur tetranitride in the absence of the solvent gave unreacted **1b** and **1e**, and sulfur along with four different 3,5-diaroyl-1,2,4-thiadiazoles, *i.e.* **2b**, **2e**, 5-(*m*-methoxybenzoyl)-3-(*p*-methylbenzoyl)-1,2,4-thiadiazole (**3**), 3-(*m*-methoxybenzoyl)-5-(*p*-methylbenzoyl)-1,2,4-thiadiazole (**4**). A mixture of **3** and **4** was inseparable by chromatography and was analyzed by ^{1}H nmr spectroscopy.

The results indicate that the formation of the 1,2,4-thiadiazole rings can be achieved intermolecularly without

Scheme 2



regard to whether they are identical molecules or not. The yields of the four products depend on the reactivity of the intermediates whose which identities are still unknown.

The structure of **2a** was established based on the comparison of the spectroscopic data and physical properties with those of the reported values [3]. The ^{1}H nmr spectrum of **2a** showed a multiplet at δ 7.34 to 7.90, due to six protons of the *meta* and *para* protons of the two benzoyl groups, a two doublet with J = 8.0 Hz and 2.0 Hz, assigned to be two *ortho* protons of the benzoyl group at C-3, a double doublet with J = 8.0 Hz and 2.0 Hz, assigned to the two *ortho* protons of the benzoyl group at C-5. Other 3,5-diaroyl-1,2,4-thiadiazoles **2b-2d, 2f** showed essentially the same ^{1}H nmr patterns as that of **2a**. Aside from that, the ^{1}H nmr spectrum of **2e** exhibited a multiplet at δ 7.00-8.51 due to the presence of methoxy groups at the *meta* positions. Compound **2g** exhibited a double doublet with J = 4.0 Hz and 0.8 Hz at δ 8.47 and a double doublet with the same coupling constants at δ 8.74. The former was assigned to be a proton at C-3 of thiophene ring bonded to C-3 of the 1,2,4-thiadiazole, coupled with a proton at C-4 and C-5, respectively and the latter a proton at C-3 of the thiophene ring bonded to C-5 of the 1,2,4-thiadiazole coupled in the same fashion as in the thiophene bonded to C-3 of the 1,2,4-thiadiazole. Compound **2h** exhibited a singlet at δ 1.75 due to twelve methylene protons delta to the carbonyl groups and a broad peak at δ 1.85 to 2.45 due to eighteen protons consisting of twelve methylene protons beta to the carbonyl groups and six methine protons.

Compound **2a** was treated with concentrated hydrochloric acid in a mixture of ethanol and ethyl acetate for 2 hours at either room temperature or at 75° to 85° but **2a** was quantitatively recovered. Hydrolysis of **2a** with sodium hydroxide in a mixture of ethanol, ethyl acetate, and water (v:v, 4:2:1) at 75° to 85° gave 3-benzoyl-1,2,4-thiadiazole (**5a**) the yield of which was variable depending on the concentration of the base and the reaction time as shown in Table 2.

Other 3,5-diaroyl- and 3,5-diacyl-1,2,4-thiadiazoles were hydrolyzed under the most satisfactory conditions (Entry 3) shown in Table 2. All of the compounds **5** are not previously synthesized. The results are summarized in Scheme 3.

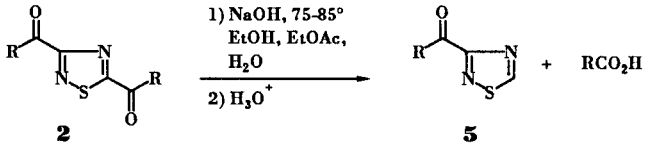
Table 2

Formation of 3-Benzoyl-1,2,4-thiadiazole (**5a**) by Hydrolysis of 3,5-Dibenzoyl-1,2,4-thiadiazole (**2a**) with Sodium Hydroxide in a Mixture of Ethanol, Ethyl Acetate, and Water (v:v, 4:2:1)

Entry	**2a**: Sodium hydroxide molar ratio	Time hours	Temperature	Yield **5a**, %
1	2:1	16	A	37
2	1:4	4	A	41
3	1:4	16	A	60
4	1:4	16	B	0

Isolated yield based on **2a**. A: 75-85°, B: Room temperature.

Scheme 3



2 **5**

	R	Yield, %		R	Yield, %
a,	C_6H_5	60	**e,**	*m*-$MeOC_6H_4$	40
b,	*p*-MeC_6H_4	79	**f,**	*p*-PhC_6H_4	71
c,	*p*-ClC_6H_4	79	**g,**	2-Thienyl	34
d,	*p*-BrC_6H_4	64	**h,**	1-Adamantyl	17

Surprisingly, the attempted hydrolysis of **2a** with sodium hydroxide in aqueous ethanol led to the complete decomposition of **2a**. The structure of **5** was identified based on the spectroscopic and mass spectra data, and elemental analyses. The ^{1}H nmr spectra of **5a-5d** and **5f** exhibited a multiplet due to two *ortho* protons adjacent to the carbonyl group between δ 8.0 and 8.4 and another multiplet due to the rest of the phenyl protons between δ 7.0 and 7.9. As expected, double doublets appeared in the most downfield part of the spectra of **2a-2d** and **2f** and disappeared in the spectra of **5a-5d** and **5f**. The C-5 protons of the 1,2,4-thiadiazole rings appear as a singlet between δ 9.85 and 10.03, which is consistent with the reported value [13].

EXPERIMENTAL

All melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Model 283 spectrophotometer. Nuclear magnetic resonance spectra were determined on a Varian EM 360 A and a Bruker 80 MHz spectrometers using tetramethylsilane as an internal standard. Mass spectra were obtained on a Varian MAT 711. Elemental analyses were determined by Korea Basic Science Center. Column chromatography was performed on silica gel (Merck, 70-230 mesh, ASTM). Tetrasulfur tetranitride [1], phenacyl iodide [17], and other bromomethyl ketones were synthesized by the literature method [18].

General procedure for the reaction of tetrasulfur tetranitride with halomethyl ketones (**1**) in the presence of the solvent.

To a solution of **1** (2 mmoles) in chlorobenzene (15 ml) was added tetrasulfur tetranitride (4 mmoles), which was refluxed for 16-48 hours until orangish tetrasulfur tetranitride disappeared completely to become a dark solution. After removal of the solvent *in vacuo*, the residue was dissolved in benzene (15 ml), which was filtered. The filtrate was evaporated to dryness and the residue was chromatographed on silica gel column (2 x 12 cm).

3,5-Dibenzoyl-1,2,4-thiadiazole (**2a**).

(i) Using Phenacyl Chloride (**1a**, X = Cl).

A mixture of phenacyl chloride **1a** (X = Cl) (618 mg, 3.997 mmoles) and tetrasulfur tetranitride (1,106 mg, 6.002 mmoles) in chlorobenzene (15 ml) was refluxed for 48 hours. After workup described in the general procedure, elution of the residue with *n*-hexane (100 ml) gave sulfur (616 mg, 2.402 mmoles). Elution next with a mixture *n*-hexane and benzene (v:v, 3:2, 200 ml) gave **1a** (X = Cl) (232 mg, 1.501 mmoles). Elution with benzene (60 ml) gave **2a** (219 mg, 0.744 mmoles, 60%); ^{1}H nmr (deuteriochloroform, 60 MHz): δ 7.34-7.90 (m, 6H), 8.42 (dd, 2H, J = 8.0, 2.0 Hz), 8.75 (dd, 2H, J = 8.0, 2.0 Hz); ^{13}C nmr (deuteriochloroform, 80 MHz): δ 128.65, 128.56, 128.39, 128.35, 130.65, 131.12, 134.05, 135.04, 171.05, 182.39, 184.28, 188.02; ir (sodium chloride): 1683 (C=O), 1653 (C=O), 1599, 1580, 1477, 1445, 1316, 1282, 1205, 1181, 1123, 1005, 996, 897, 860, 713, 688, 664 cm^{-1}; ms: (70 eV) m/z (%) 294 (5.8) (M$^+$), 105 (83.0), 77 (100).

Anal. Calcd. for $C_{16}H_{10}N_2O_2S$: C, 65.29; H, 3.42; N, 9.51. Found: C, 65.01; H, 3.39; N, 9.38.

(ii) Using Phenacyl Bromide (**1a**, X = Br).

A mixture of **1a** (X = Br) (398 mg, 2.000 mmoles) and tetrasulfur tetranitride (737 mg, 4.000 mmoles) in chlorobenzene (15 ml) was refluxed for 48 hours. Workup as in the reaction with **1a** (X = Cl) gave sulfur (428 mg, 1.669 mmoles), **1a** (X = Br) (210 mg, 1.055 mmoles) and **2a** (80 mg, 0.272 mmole, 58%).

(iii) Using Phenacyl Iodide (**1a**, X = I).

A mixture of **1a** (X = I) (523 mg, 2.126 mmoles), tetrasulfur tetranitride (755 mg, 4.097 mmoles) in chlorobenzene (15 ml) was refluxed for 24 hours. Workup as in the reaction with **1a** (X = Cl) gave sulfur (122 mg, 0.476 mmole), unreacted **1a** (X = I) (114 mg, 0.463 mmole), and **2a** (42 mg, 0.143 mmole, 17%).

3,5-Di(*p*-methylbenzoyl)-1,2,4-thiadiazole (**2b**).

A mixture of **1b** (426 mg, 1.999 mmoles), tetrasulfur tetranitride (737 mg, 4.000 mmoles) in chlorobenzene (15 ml) was refluxed for 48 hours. Workup as in the reaction with **1a** (X = Cl) gave sulfur (193 mg, 0.752 mmole), unreacted **1b** (159 mg, 0.746 mmole), and **2b** (78 mg, 0.242 mmole, 39%); ^{1}H nmr (deuteriochloroform, 60 MHz): δ 7.45 (d, 4H, J = 8.8 Hz), 8.36 (d, 2H, J = 8.8 Hz), 8.71 (d, 2H, J = 8.8 Hz); ^{13}C nmr (deuteriochloroform, 80 MHz): δ 21.64, 21.72, 129.21, 129.31, 129.59, 131.01, 131.33, 132.74, 145.19, 146.43, 171.21, 181.66, 183.96, 188.31; ir (sodium chloride): 1668 (C=O), 1640 (C=O), 1602, 1316, 1283, 1216, 1204, 1176, 1120, 1001, 896, 862, 748, 613 cm^{-1}; ms: (70 eV) m/z (%) 322 (5.0) (M$^+$), 119 (100), 91 (52.4).

Anal. Calcd. for $C_{18}H_{14}N_2O_2S$: C, 67.06; H, 4.38; N, 8.69. Found: C, 67.19; H, 4.22; N, 8.65.

3,5-Di(*p*-chlorobenzoyl)-1,2,4-thiadiazole (**2c**).

A mixture of **1c** (469 mg, 2.009 mmoles), tetrasulfur tetranitride (737 mg, 4.000 mmoles) in chlorobenzene (15 ml) was refluxed for 24 hours. Workup as in the reaction with **1a** (X = Br) gave sulfur (99 mg, 0.386 mmole), unreacted **1c** (250 mg, 1.071 mmoles), and **2c** (57 mg, 0.174 mmole, 37%); ^{1}H nmr (deuteriochloroform, 60 MHz): δ 7.70 (d, 4H, J = 8.2 Hz), 8.47 (d, 2H, J = 8.2 Hz), 8.81 (d, 2H, J = 8.2 Hz); ^{13}C nmr (deuteriochloroform, 80 MHz): δ 128.91, 129.32, 131.66, 132.27, 132.56, 133.45, 140.89, 142.11, 170.72, 181.06, 182.67, 187.82; ir (sodium chloride): 1670 (C=O), 1647 (C=O), 1583, 1399, 1275, 1201, 1174, 1089, 999, 860, 843, 753 cm^{-1}; ms: (70 eV) m/z (%) 141 (42.4), 139 (100), 113 (12.7), 111 (32.7).

Anal. Calcd. for $C_{16}H_8Cl_2N_2O_2S$: C, 52.91; H, 2.22; N, 7.71; Cl, 19.52. Found: C, 52.76; H, 2.41; N, 7.69; Cl, 19.37.

3,5-Di(*p*-bromobenzoyl)-1,2,4-thiadiazole (**2d**).

A mixture of **1d** (564 mg, 2.030 mmoles), tetrasulfur tetranitride (738 mg, 4.005 mmoles) in chlorobenzene (15 ml) was refluxed for 24 hours. Workup as in the reaction with **1a** (X = Cl) gave sulfur (119 mg, 0.464 mmole), unreacted **1d** (281 mg, 1.011 mmoles), and **2d** (69 mg, 0.185 mmole, 36%); ^{1}H nmr (deuteriochloroform, 60 MHz): δ 7.87 (d, 4H, J = 8.6 Hz), 8.38 (d, 2H, J = 8.6 Hz), 8.72 (d, 2H, J = 8.6 Hz); ^{13}C nmr (deuteriochloroform, 80 MHz): δ 129.83, 131.18, 131.86, 131.97, 132.15, 132.36, 132.40, 133.92, 171.04, 181.39, 183.08, 188.04; ir (sodium chloride): 1670 (C=O), 1648 (C=O), 1581, 1390, 1280, 1174, 1069, 1010, 998, 894, 860, 840, 750 cm^{-1}; ms: (70 eV) m/z (%) 452 (2.6) (M$^+$), 183 (100), 155 (46.1).

Anal. Calcd. for $C_{16}H_8Br_2N_2O_2S$: C, 42.51; H, 1.78; N, 6.20; Cl, 35.35. Found: C, 42.43; H, 1.89; N, 6.03; Cl, 35.48.

3,5-Di(*m*-methoxybenzoyl)-1,2,4-thiadiazole (**2e**).

A mixture of **1e** (463 mg, 2.021 mmoles), tetrasulfur tetranitride (738 mg, 4.005 mmoles) in chlorobenzene (15 ml) was refluxed for 24 hours. Workup as in the reaction with **1a** (X = Cl) gave sulfur (128 mg, 0.499 mmole), unreacted **1e** (166 mg, 0.725 mmole), and **2e** (40 mg, 0.113 mmole, 17%); ^{1}H nmr (deuteriochloroform, 60 MHz): δ 3.87 (s, 6H), 7.00-8.51 (m, 8H); ^{13}C nmr (deuteriochloroform, 80 MHz): δ 122.18, 123.86, 124.23, 129.51, 129.92, 134.68, 136.50, 159.73, 159.89, 171.64, 182.16, 184.07, 188.05; ir (sodium chloride): 1670 (C=O), 1637 (C=O), 1593, 1578, 1483, 1460, 1427, 1316, 1284, 1255, 1234, 1043, 1019, 800, 771, 749 cm^{-1}; ms: (70 eV) m/z (%) 354 (11.4) (M$^+$), 135 (100), 107 (37.5).

Anal. Calcd. for $C_{18}H_{14}N_2O_4S$: C, 61.01; H, 3.98; N, 7.90. Found: C, 60.98; H, 3.83; N, 7.93.

3,5-Di(*p*-phenylbenzoyl)-1,2,4-thiadiazole (**2f**).

A mixture of **1f** (554 mg, 2.013 mmoles), tetrasulfur tetranitride (744 mg, 4.038 mmoles) in chlorobenzene (15 ml) was refluxed for 24 hours. Workup as in the reaction with **1a** (X = Cl) gave sulfur (82 mg, 0.320 mmole), unreacted **1f** (219 mg, 0.796 mmole), and **2f** (65 mg, 0.146 mmole, 24%); ^{1}H nmr (deuteriochloroform, 60 MHz): δ 7.28-7.89 (m, 14H), 8.42 (d, 2H, J = 8.6 Hz), 8.74 (d, 2H, J = 8.6 Hz); ^{13}C nmr (deuteriochloroform, 80 MHz): δ 127.15, 127.31, 127.47, 128.47, 128.67, 128.97, 129.00, 131.56, 131.87, 132.18, 133.99, 139.36, 139.58, 146.78, 147.72, 171.22, 181.55, 183.30, 188.31; ir (sodium chloride): 1670 (C=O), 1641 (C=O), 1597, 1403, 1314, 1276, 1180, 1005, 999, 863, 756, 744, 696 cm^{-1}; ms: (70 eV) m/z (%) 446 (14.5) (M$^+$), 181 (53.0), 153 (37.3), 152 (100).

Anal. Calcd. for $C_{28}H_{18}N_2O_2S$: C, 75.32; H, 4.06; N, 6.27. Found: C, 75.17; H, 4.02; N, 6.31.

3,5-Di(2-thiophenecarbonyl)-1,2,4-thiadiazole (**2g**).

A mixture of **1g** (414 mg, 2.019 mmoles), tetrasulfur tetranitride (741 mg, 4.021 mmoles) in chlorobenzene (15 ml) was heated for 16 hours. Workup as in the reaction with **1a** (X = Cl) gave sulfur (103 mg, 0.402 mmole), unreacted **1g** (239 mg, 1.165 mmoles), and **2g** (41 mg, 0.149 mmole, 35%); ^{1}H nmr (deuteriochloroform, 80 MHz): δ 7.17-7.34 (m, 2H), 7.78-7.97 (m, 2H), 8.47 (dd, 1H, J = 4.0, 0.8 Hz), 8.82 (dd, 1H, J = 4.0, 0.8 Hz); ir (sodium chloride): 1647 (C=O), 1623 (C=O), 1404, 1352, 1270, 1228, 1202, 1048, 775, 730 cm^{-1}; ms: (70 eV) m/z (%) 306 (6.6) (M$^+$), 111 (100), 83 (8.5).

Anal. Calcd. for $C_{12}H_6N_2O_2S_3$: C, 47.04; H, 1.97; N, 9.14. Found: C, 47.16; H, 2.15; N, 9.31.

3,5-Di(1-Adamanecarbonyl)-1,2,4-thiadiazole (**2h**).

A mixture of **1h** (515 mg, 2.003 mmoles), tetrasulfur tetranitride (743 mg, 4.032 mmoles) in chlorobenzene (15 ml) was heated for 24 hours. Workup as in the reaction with **1a** (X = Cl) gave sulfur (137 mg, 0.534 mmole), unreacted **1h** (280 mg, 1.089 mmoles), and **2h** (48 mg, 0.118 mmole, 26%); ^{1}H nmr (deuteriochloroform, 60 MHz): δ 1.75 (s, 12H), 1.85-2.45 (broad, 18H); ir (sodium chloride): 1687 (C=O), 1671 (C=O), 1445, 1336, 1262, 1228, 1184, 1142, 1100, 1005, 910, 660 cm^{-1}; ms: (70 eV) m/z (%): 410 (4.4) (M^+), 135 (100).

Anal. Calcd. for $C_{24}H_{30}N_2O_2S$: C, 70.21; H, 7.37; N, 6.82. Found: C, 70.15; H, 7.43; N, 6.79.

General Procedure for the Reaction of Tetrasulfur Tetranitride with Halomethyl Ketones **1** Without the Solvent.

A mixture of **1** (25 mmoles) and tetrasulfur tetranitride (5 mmoles) was slowly heated until 115°. During which time, the solid **1** melted and tetrasulfur tetranitride was dissolved in it. Heating was continued for 3 hours to give a dark mixture, which was cooled to room temperature. The mixture was dissolved in benzene (5 ml), which was filtered to give a dark solution. Evaporation of the solvent gave a residue, which was chromatographed on silica gel (2 x 12 cm). Elution with *n*-hexane (100 ml) gave sulfur. Elution next with a mixture of *n*-hexane and benzene (v:v, 1:1, 150 ml) gave unreacted **1**. Elution with benzene (150 ml) gave **2**. The amounts of reactants and reaction time of each reaction are described below:

2a from **1a** (X = Cl).

A mixture of **1a** (X = Cl) (4,000 mg, 25.87 mmoles) and tetrasulfur tetranitride (1,000 mg, 5.427 mmoles) was heated for 3 hours. From the benzene fraction there was obtained **2a** (298 mg, 1.012 mmoles, 9%).

2a from **1a** (X = Br).

A mixture of **1a** (X = Br) (4,000 mg, 22.10 mmoles) and tetrasulfur tetranitride (1,000 mg, 5.427 mmoles) was heated for 3 hours. From the benzene fraction there was obtained **2a** (159 mg, 0.540 mmole, 5%).

2a from **1a** (X = I).

A mixture of **1a** (X = I) (2,039 mg, 8.287 moles) and tetrasulfur tetranitride (527 mg, 2.860 mmoles) was heated for 2.5 hours. From the benzene fraction there was obtained **2a** (95 mg, 0.323 mmole, 6%).

2b.

A mixture of **1b** (4,000 mg, 18.77 mmoles) and tetrasulfur tetranitride (1,000 mg, 5.427 mmoles) was heated for 7 hours. From the benzene fraction there was obtained **2b** (213 mg, 0.661 mmole, 6%).

2c.

A mixture of **1c** (4,000 mg, 17.13 mmoles) and tetrasulfur tetranitride (1,000 mg, 5.427 mmoles) was heated for 10 hours. From the benzene fraction there was obtained **2c** (379 mg, 1.043 mmoles, 10%).

2d.

A mixture of **1d** (4,000 mg, 14.39 mmoles) and tetrasulfur tetranitride (1,000 mg, 5.427 mmoles) was heated for 10 hours. From the benzene fraction there was obtained **2d** (361 mg, 0.798 mmole, 7%).

2e.

A mixture of **1e** (4,000 mg, 17.46 mmoles) and tetrasulfur tetranitride (1,000 mg, 5.427 mmoles) was heated for 10 hours. From the benzene fraction there was obtained **2e** (228 mg, 0.643 mmole, 6%).

2f.

A mixture of **1f** (4,000 mg, 14.54 moles) and tetrasulfur tetranitride (1,000 mg, 5.427 mmoles) was heated at 135° for 6 hours. From the benzene fraction there was obtained **2f** (645 mg, 1.444 mmoles, 13%).

2g.

A mixture of **1g** (4,000 mg, 19.51 mmoles) and tetrasulfur tetranitride (1,000 mg, 5.427 mmoles) was heated at 95° for 3 hours. From benzene fraction there was obtained **2g** (161 mg, 0.526 mmole, 5%).

2h.

A mixture of **1h** (2,002 mg, 7.785 mmoles) and tetrasulfur tetranitride (502 mg, 2.724 mmoles) was heated for 10 hours. From the benzene fraction there was obtained **2h** (120 mg, 0.292 mmole, 5%).

Reaction of a Mixture of **1b** and **1e** with Tetrasulfur Tetranitride.

A mixture of **1b** (2,121 mg, 9.954 mmoles) and **1e** (2,301 mg, 10.05 mmoles) and tetrasulfur tetranitride (922 mg, 5.004 mmoles) was heated at 115° for 10 hours. The mixture was worked up as described in the general procedure involving no solvent. After removal of sulfur using *n*-hexane (150 ml), unreacted **1b** and **1e** were eluted with a mixture of *n*-hexane and benzene (v:v, 1:1, 200 ml). Elution next with benzene (170 ml) gave a mixture (261 mg), which was rechromatographed on silica gel (2 x 12 cm). Elution with a mixture of *n*-hexane and benzene (v:v, 1:4, 50 ml) gave **1e** (76 mg, 0.332 mmole). Next fraction of the same solvent mixture (150 ml) gave **2b** (68 mg, 0.211 mmole, 2%). Elution next with benzene (120 ml) gave a mixture of **3** and **4** (78 mg, 2%). Continuous elution with benzene (120 ml) gave **2e** (45 mg, 0.127 mmole, 1%).

General Procedure for the Hydrolysis of **2**.

To a solution of **2** in a mixture of ethanol (4 ml), ethyl acetate (2 ml), and water (1 ml) was added sodium hydroxide, which was stirred for 16 hours at 75° to 85°. The mixture was cooled to room temperature, followed by the addition of 5% aqueous hydrochloric acid and then extracted with ethyl acetate (30 ml x 3). The combined organic layer was washed with water (30 ml x 3) and dried (magnesium sulfate). Removal of the solvent *under vacuo* gave a residue, which was chromatographed on silica gel (2 x 10 cm).

3-Benzoyl-1,2,4-thiadiazole (**5a**).

A solution of **2a** (187 mg, 0.635 mmole) in the solvent mixture was treated with sodium hydroxide (102 mg, 2.550 mmoles). Elution with benzene (100 ml) gave **2a** (60 mg. 0.204 mmole, 32%). Elution next with ethyl acetate (100 ml) afforded **5a** (73 mg, 0.384 mmole, 60%), recrystallized from carbon tetrachloride, mp

99.5-100°; ^{1}H nmr (deuteriochloroform, 80 MHz): δ 7.26-7.66 (m, 3H), 8.19-8.31 (m, 2H), 9.99 (s, 1H); ir (potassium bromide): 1665 (C=O), 1595, 1450, 1363, 1240, 893, 869, 743, 690, 681 cm^{-1}; ms: (70 eV) m/z (%) 190 (39.9) (M$^+$), 105 (88.4), 77 (100).

Anal. Calcd. for $C_9H_6N_2OS$: C, 56.83; H, 3.18; N, 14.73. Found: C, 56.66; H, 3.02; N, 14.69.

3-(*p*-Methylbenzoyl)-1,2,4-thiadiazole (**5b**).

A solution of **2b** (254 mg, 0.788 mmole) in the solvent mixture was treated with sodium hydroxide (126 mg, 3.150 mmoles). Elution with a mixture of *n*-hexane and ethyl acetate (v:v, 1:1, 80 ml) gave **5b** (127 mg, 0.622 mmole, 79%), recrystallized from carbon tetrachloride, mp 102-104°; ^{1}H nmr (deuteriochloroform, 80 MHz): δ 2.43 (s, 3H), 7.30 (d, 2H, J = 8.0 Hz), 8.13 (d, 2H, J = 6.6 Hz), 9.98 (s, 1H); ir (sodium chloride): 1659 (C=O), 1604, 1361, 1270, 1239, 1178, 900, 895, 867, 774 cm^{-1}; ms: (70 eV) m/z (%) 204 (38.9) (M$^+$), 119 (100), 91 (61.4).

Anal. Calcd. for $C_{10}H_8N_2OS$: C, 58.81; H, 3.95; N, 13.72. Found: C, 58.97; H, 4.03; N, 13.69.

Final elution with ethyl acetate (100 ml) gave *p*-toluic acid (60 mg, 0.443 mmole).

3-(*p*-Chlorobenzoyl)-1,2,4-thiadiazole (**5c**).

A solution of **2c** (222 mg, 0.677 mmole) in the solvent mixture was treated with sodium hydroxide (98 mg, 2.450 mmoles). Elution with a mixture of *n*-hexane and ethyl acetate (v:v, 3:1, 100 ml) gave **5c** (120 mg, 0.534 mmole, 79%), recrystallized from carbon tetrachloride, mp 98.5-99.5°; ^{1}H nmr (deuteriochloroform, 80 MHz): δ 7.50 (d, 2H, J = 8.8 Hz), 8.26 (d, 2H, J = 8.8 Hz), 10.03 (s, 1H); ir (sodium chloride): 1665 (C=O), 1582, 1400, 1378, 1358, 1250, 1240, 1169, 1090, 900, 890, 870, 865, 843, 775, 756 cm^{-1}; ms: (70 eV) m/z (%) 224 (21.1) (M$^+$), 226 (18.3) (M$^+$+2), 141 (32.2), 139 (100), 113 (56.9), 111 (23.0).

Anal. Calcd. for $C_9H_5ClN_2OS$: C, 48.12; H, 2.24; N, 12.47; Cl, 15.78. Found: C, 48.05; H, 2.18; N, 12.44; Cl, 15.59.

Final elution with ethyl acetate (100 ml) gave *p*-chlorobenzoic acid (60 mg, 0.383 mole).

3-(*p*-Bromobenzoyl)-1,2,4-thiadiazole (**5d**).

A solution of **2d** (128 mg, 0.344 mmole) in the solvent mixture was treated with sodium hydroxide (45 mg, 1.125 mmoles). Elution with a mixture of *n*-hexane and ethyl acetate (v:v, 1:2, 100 ml) gave **5d** (59 mg, 0.219 mmole, 64%), recrystallized from a mixture of *n*-hexane and carbon tetrachloride, mp 104-105°; ^{1}H nmr (deuteriochloroform, 80 MHz): δ 7.67 (d, 2H, J = 8.8 Hz), 8.18 (d, 2H, J = 8.8 Hz), 9.99 (s, 1H); ir (sodium chloride): 1664 (C=O), 1579, 1395, 1375, 1251, 1237, 1171, 1069, 1009, 974, 892, 868, 763 cm^{-1}; ms: (70 eV) m/z (%) 269 (14.2) (M$^+$), 183 (30.0), 185 (24.2), 157 (35.0), 155 (25.0).

Anal. Calcd. for $C_9H_5BrN_2OS$: C, 40.17; H, 1.87; N, 10.41; Br, 29.69. Found: C, 40.09; H, 1.73; N, 10.39; Br, 29.56.

Elution with ethyl acetate (100 ml) gave *p*-bromobenzoic acid 30 mg, 0.150 mmole).

3-(*m*-Methoxybenzoyl)-1,2,4-thiadiazole (**5e**).

A solution of **2e** (73 mg, 0.206 mmole) in the solvent mixture was treated with sodium hydroxide (33 mg, 0.825 mmole). Elution with benzene (60 ml) gave a small amount of yellow liquid. Elution next with a mixture of *n*-hexane and ethyl acetate (v:v, 3:1, 80 ml) gave a unidentified compound (38 mg). Elution with a mixture of *n*-hexane and ethyl acetate (v:v, 1:1, 100 ml) gave **5e** (18 mg, 0.082 mmole, 40%), recrystallized from a mixture of *n*-hexane and carbon tetrachloride, mp 96-97°; ^{1}H nmr (deuteriochloroform, 80 MHz): δ 3.87 (s, 3H), 7.16-7.88 (m, 4H), 9.99 (s, 1H); ir (sodium chloride): 1685 (C=O), 1678, 1581, 1439, 1415, 1307, 1281, 1235, 1049, 748 cm^{-1}; ms: (70 eV) m/z (%) 220 (36.7) (M$^+$), 135 (100), 107 (47.9), 92 (35.2), 77 (56.8).

Anal. Calcd. for $C_{10}H_8N_2O_2S$: C, 54.53; H, 3.66; N, 12.72. Found: C, 54.38; H, 3.63; N, 12.68.

3-(*p*-Phenylbenzoyl)-1,2,4-thiadizole (**5f**).

A solution of **2f** (400 mg, 0.896 mmole) in the solvent mixture was treated with sodium hydroxide (143 mg, 3.575 mmoles). Elution with a mixture of *n*-hexane and ethyl acetate (v:v, 2:1, 100 ml) gave **5f** (169 mg, 0.635 mmole, 71%), recrystallized from a mixture of *n*-hexane and carbon tetrachloride, mp 137-138°; ^{1}H nmr (deuteriochloroform, 80 MHz): δ 7.39-7.80 (m, 7H), 8.34 (d, 2H, J = 8.7 Hz), 9.97 (s, 1H); ir (sodium chloride): 1658 (C=O), 1597, 1240, 1175, 972, 897, 856, 754, 690 cm^{-1}; ms: (70 eV) m/z (%) 266 (36.5) (M$^+$), 181 (100), 153 (49.1), 152 (89.3).

Anal. Calcd. for $C_{15}H_{10}N_2OS$: C, 67.65; H, 3.78; N, 10.52. Found: C, 67.61; H, 3.66; N, 10.48.

3-(2-Thiophenecarbonyl)-1,2,4-thiadiazole (**5g**).

A solution of **2g** (102 mg, 0.372 mmole) in the solvent mixture was treated with sodium hydroxide (54 mg, 1.350 mmoles). Elution with benzene (100 ml) gave a small amount of unidentified mixture. Elution with a mixture of *n*-hexane and ethyl acetate (v:v, 3:1, 100 ml) gave **5g** (25 mg, 0.127 mmole, 34%), recrystallized from a mixture of *n*-hexane and carbon tetrachloride, mp 124-125°; ^{1}H nmr (deuteriochloroform, 80 MHz): δ 7.23 (dd, 2H, J = 5.0, 3.9 Hz), 7.81 (dd, 1H, J = 5.0, 1.2 Hz), 8.48 (dd, 1H, J = 3.8, 1.2 Hz), 9.98 (s, 1H); ir (sodium chloride): 1646 (C=O), 1635, 1514, 1507, 1418, 1406, 1395, 1388, 1356, 1314, 1254, 1060, 977, 893, 876, 855, 836, 809, 773, 745, 724 cm^{-1}; ms: (70 eV) m/z (%) 196 (17.1) (M$^+$), 111 (100), 83 (10.7).

Anal. Calcd. for $C_7H_4N_2OS_2$: C, 42.84; H, 2.05; N, 14.27. Found: C, 42.73; H, 1.98; N, 14.09.

3-(1-Adamantanecarbonyl)-1,2,4-thiadiazole (**5h**).

A solution of **2h** (214 mg, 0.526 mmole) in the solvent mixture was treated with sodium hydroxide (83 mg, 2.083 mmoles). Elution with benzene (180 ml) gave a mixture of oily compound and white solids. Elution with a mixture of *n*-hexane and ethyl acetate (v:v, 3:1, 80 ml) gave **5h** (22 mg, 0.089 mmole, 17%), recrystallized from *n*-hexane, mp 134-135°; ^{1}H nmr (deuteriochloroform, 80 MHz): δ 1.78 (s, 6H), 1.99-2.21 (broad, 9H), 9.85 (s, 1H); ir (sodium chloride): 1680 (C=O), 1370, 1342, 1240, 1134, 994, 912, 858 cm^{-1}; ms: (70 eV) m/z (%) 248 (16.1) (M$^+$), 135 (100).

Anal. Calcd. for $C_{13}H_{16}N_2OS$: C, 62.87; H, 6.49; N, 11.28. Found: C, 62.74; H, 6.57; N, 11.31.

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