REACTIONS OF MONOHALOMETHYL ARYL KETOXIMES WITH TETRASULFUR TETRANITRIDE: MUCH IMPROVED SYNTHESIS OF 3-ARYL-1,2,5-THIADIAZOLES

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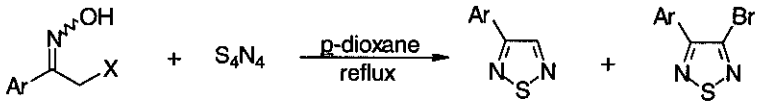
Abstract - Reactions of chloromethyl aryl ketoximes (1, X = Cl) with tetrasulfur tetranitride in p-dioxane at reflux for 4 h afforded 3-aryl-1,2,5-thiadiazoles (2) in 37-92% yields, whereas those of bromo analogs under the same conditions gave 2 and 3-aryl-4-bromo-1,2,5-thiadiazoles (3) in 48-81% and 17-31% yields, respectively. However, the compounds (3) were not formed in the presence of pyridine. α-Nitrosostyrene and its ring-substituted derivatives (4) are proposed as intermediates for the formations of 2.

In the previous papers we have shown that the reactions of monobromomethyl aryl ketones and the corresponding alkyl ketones without α-hydrogens on the alkyl group with tetrasulfur tetranitride (S_4N_4) in chloroform at reflux gave 3,5-diaroyl- or 3,5-diacyl-1,2,4-thiadiazoles as major products.[1] On the other hand, the analogous reactions of alkyl aryl ketoximes having at least two α-hydrogens on the alkyl group in p-dioxane at reflux afforded 3-substituted or 3,4-disubstituted 1,2,5-thiadiazoles.[2] The yields of the known products among the 1,2,5-thiadiazoles prepared were slightly improved in comparison with those reported.[3]

In order to understand the effects of possible synergism between the α-halogen atom and the oxime functionality in alkyl aryl ketones, the reactions of monohalomethyl aryl ketoximes (1) with S_4N_4 were investigated. The results are described herein.

A mixture of 1 (X = Cl, 4 mmol) and S_4N_4 (4 mmol) in p-dioxane (20 ml) was refluxed for 4 h until S_4N_4 had disappeared completely. During which time, the solution became cloudy and much white solids deposited. The reaction mixture was cooled to room temperature and filtered to remove the white solids, which showed no ^1H Nmr signals. Concentration of the filtrate, followed by chromatography on silica gel [230-400 mesh, hexane/benzene (3:1)] gave 3-aryl-1,2,5-thiadiazoles (2) in good yields except for the reaction with p-anisyl chloromethyl ketoxime (1e). The results are summarized in Table 1.



1
X = Cl, Br

2

3

Table 1. Synthesis of 3-Aryl-1,2,5-thiadiazoles (2) and 3-Aryl-4-bromo-1,2,5-thiadiazoles (3).

1	Ar	X	yield,* %	
			2	3
a	C_6H_5	Cl	a 87 (85)	
b	p-MeC_6H_4	Cl	b 80 (85)	
c	p-ClC_6H_4	Cl	c 88 (83)	
d	p-BrC_6H_4	Cl	d 92 (82)	
e	p-$MeOC_6H_4$	Cl	e 37 (57)	
f	C_6H_5	Br	a 61 (29)	a 29
g	p-MeC_6H_4	Br	b 48 (32)	b 31
h	p-$O_2NC_6H_4$	Br	f 81 (26)	c 17

* Isolated yield. Numbers in the parenthesis represent the yields in the presence of pyridine (1.1 equiv).

The Table shows that introduction of a chlorine atom to the methyl group of aryl methyl ketoximes causes the increase of the yields of 3-aryl-1,2,5-thiadiazoles (2a-2d) strikingly in comparison with those obtained from other reactions previously studied under various conditions.[3] In fact, no such high yields of organic products have been obtained in the reactions of S_4N_4. The low yield (37%) of 2e is not unexpected in view of the results in which the reaction of o-methoxyacetophenone oxime with S_4N_4 did not give the corresponding 1,2,5-thiadiazoles at all in spite of the formations of the corresponding 1,2,5-thiadiazoles from the ketoximes with other substituents such as o-amino-, p-amino-, o-hydroxy-, and m-hydroxy groups[2] as well as other relevant results.[4]

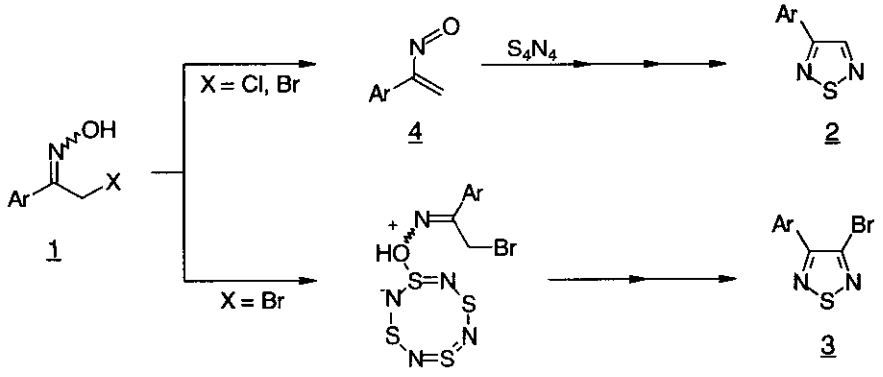
In the meantime, the analogous reactions of monobromomethyl ketoximes (1f-1h) under the same conditions as in the reactions of the monochloro analogs (1a-1e) afforded reduced yields of 2 (from 87% to 61% for 2a; from 80% to 48% for 2b) along with 3-aryl-4-bromo-1,2,5-thiadiazoles (3a-3c). The bromo-1,2,5-thiadiazoles, to our knowledge, have never been previously reported in the literature. Although the yields of 2a and 2b decreased somewhat in the reactions of monobromomethyl ketoximes (1f-1g), the total yields of two products, i.e. 2a and 3a (90%); 2b and 3b (79%), were comparable with the yields of 87% for 2a obtained from 1a and 80% for 2b obtained from 1b. The formations of 2 from chloromethyl ketoximes (1, X = Cl) but the

formations of 2 and 3 from bromomethyl ketoximes (1, X = Br) together with the comparable total yields in both reactions suggest that two competitive reactions play an important role in these reactions.

Since the bromine atom is known to be generally a better leaving group than the chlorine atom without regard to SN1 or SN2 reaction,[5] the isolations of 3 only from the reactions of bromo ketoximes (1, X = Br) imply the involvement of intermediates generated from 1 prior to the direct reactions between 1 and S_4N_4.

α-Nitrosostyrene and its ring-substituted derivatives (4) were reported to be readily formed by treatments of either α-chloro or α-bromo ketoximes with heterogeneous bases such as sodium carbonate and potassium carbonate in aprotic solvent[6] and their synthetic applications have been extensively studied.[7] With the expectation of the possible involvement of 4 as intermediates in mind, a mixture of 1g (4 mmol), S_4N_4 (4 mmol), and sodium carbonate (1.1 equiv) in p-dioxane (20 ml) was heated at reflux for 4 h. From the reaction mixture were obtained 2b and 3b in 61% and 16% yields, respectively, and the total yield (77%) of two products was close to the total yield (79%) of 2b and 3b obtained in the absence of sodium carbonate. Thus the increased yield of 2b from 48% to 61% at the expense of the yield of 3b from 31% to 16% by employing sodium carbonate as a heterogeneous base is conceived to support the assumption that 1-nitroso-1-(p-tolyl)ethylene 4 (Ar = p-MeC_6H_4) is generated more readily in these conditions than in the absence of sodium carbonate to react with S_4N_4 to give 2b.

Therefore, two pathways are tentatively proposed for the formations of 2 and 3: the formation of 4 as an intermediate, followed by the reaction with S_4N_4 to give 2 and a nucleophilic attack of a hydroxy group of 1 to an electron-deficient sulfur atom of S_4N_4, followed by a series of rearrangment to lead to 3 as proposed in the literature.[8]



The same reaction was repeated in the presence of a homogeneous base such as pyridine (3 equiv) under the same reaction conditions. Neither 2b nor 3b was detected and only an intractable mixture was obtained. The

result seems to be similar to the reported result[6] in which no adducts derived from the cyclization reactions of 4 were obtained in the presence of a homogeneous base. However, by employing 1 equiv of pyridine was isolated 2b in 32% yield along with the foregoing white solids. No 3b was detected under the conditions. Similarly no halogeno-1,2,5-thiadiazoles were detected either in the reactions of chloro- (1a-1e) or bromomethyl aryl ketoximes (1f-1h) in the presence of pyridine (1.1 equiv) as shown in Table 1.

At this moment it is rather difficult to explain the reason why the yields of 2a-2d are not much affected in the cases of α-chloromethyl aryl ketoximes (1a-1d) but those of 2a, 2b, and 2f decrease drastically in the cases of α-bromomethyl aryl ketoximes (1f-1h) in the presence of pyridine.

EXPERIMENTAL

Tetrasulfur tetranitride (S_4N_4) was prepared by the reaction of sulfur monochloride with ammonia gas at room temperature.[10] α-Monohalomethyl aryl ketones were converted to the corresponding oximes according to the known procedures.[11] p-Dioxane was purchased from Duck San Inc. and distilled prior to use. Petroleum ether (bp 30-60°C) was purchased from Duck San Inc. Ir spectra were obtained on a Perkin-Elmer Model 283 spectrometer. ^{1}H Nmr spectra were determined on a Bruker 80 MHz spectrometer using tetramethylsilane as an internal standard. Mass spectra were obtained by electron impact at 70 eV on a Varian MAT 711. Elemental analyses were determined by Korea Basic Science Center. Melting points were measured on a Fisher-Johns melting point apparatus and are uncorrected. Column chromatography was performed on a silica gel (Merck 230-400 mesh, ASTM).

General Procedure for the Reaction of α-Monohalomethyl Aryl Ketoximes with S_4N_4. (i) A mixture of α-monohalomethyl aryl ketoxime (4 mmol) and S_4N_4 (4 mmol) in p-dioxane (20 ml) was refluxed for 4 h and then cooled to room temperature. Filtration of the white solid formed, followed by evaporation of the solvent gave a residue, which was chromatographed on silicagel (2 × 12 cm). Sulfur was removed first by elution with petroleum ether (100 ml) and then appropriate solvents were used for the elution of other products. (ii) The reactions performed in the presence of pyridine were worked up in the same manner as described in (i).

3-Phenyl-1,2,5-thiadiazole (2a): (i) Chromatography of the reaction mixture obtained from the reaction of α-chloromethyl phenyl ketoxime (1a) (683 mg, 4.03 mmol) with S_4N_4 (747 mg, 4.05 mmol) using carbon tetrachloride (200 ml) gave 2a (567 mg, 3.50 mmol, 87%): mp 42-43°C (from Et_2O) (lit.,[12] 42-44°C). (ii)

Chromatography of the reaction mixture obtained from the reaction of 1a (681 mg, 4.02 mmol) with S_4N_4 (741 mg, 4.02 mmol) in the presence of pyridine (0.35 ml) using a mixture of n-hexane and carbon tetrachloride (4:1, 150 ml) gave unreacted S_4N_4 (42 mg, 0.228 mmol, 6%). Elution next with a mixture of n-hexane and benzene (3:1, 200 ml) gave 2a (552 mg, 3.40 mmol, 85%). (iii) Chromatography of the reaction mixture obtained from the reaction of α-bromomethyl phenyl ketoxime 1f (643 mg, 3.00 mmol) with S_4N_4 (553 mg, 3.00 mmol) using a mixture of n-hexane and carbon tetrachloride (4:1, 80 ml) gave 3-bromo-4-phenyl-1,2,5-thiadiazole (3a) (209 mg, 0.867 mmol, 29%): mp 56-57°C (from n-hexane): Ir (film) (ν, cm^{-1}) 1440, 1352, 1143, 963, 832, 818, 773, 716, 698; ^1H nmr ($CDCl_3$, δ, ppm) 7.40-7.58 (3 H, m, ArH), 7.81-8.03 (2 H, m, ArH); ms (m/z) 242 ($M^+ + 2$, 50.3), 240 (M^+, 46.6), 135 (100, M^+ - BrCN), 103 (12.9, M^+ - BrCNS). Anal. Calcd for $C_8H_5N_2BrS$: C, 39.85; H, 2.09; N, 11.62; S, 13.30. Found: C, 39.76; H, 2.13; N, 11.60; S, 13.33. Elution next with carbon tetrachloride (200 ml) gave 2a (298 mg, 1.84 mmol, 61%). (iv) Chromatography of the reaction mixture obtained from the reaction of 1f (644 mg, 3.01 mmol) with S_4N_4 (554 mg, 3.01 mmol), in the presence of pyridine (0.26 ml) using a mixture of n-hexane and carbon tetrachloride (4:1, 100 ml) gave 2a (142 mg, 0.875 mmol, 29%). Elution next with carbon tetrachloride (200 ml) gave unreacted S_4N_4 (92 mg, 0.499 mmol, 17%).

3-(p-Tolyl)-1,2,5-thiadiazole (2b): (i) Chromatography of the reaction mixture obtained from the reaction of α-chloromethyl p-totyl ketoxime (1b) (736 mg, 4.01 mmol) with S_4N_4 (752 mg, 4.08 mmol) using a mixture of n-hexane and benzene (3:1, 200 ml) gave 2b (564 mg, 3.20 mmol, 80%): mp 56-57°C (from n-hexane) (lit.,[12] 56-57°C). (ii) Chromatography of the reaction mixture obtained from the reaction of 1b (712 mg, 3.88 mmol) with S_4N_4 (724 mg, 3.93 mmol) in the presence of pyridine (0.35 ml) using a mixture of n-hexane and carbon tetrachloride (4:1, 150 ml) gave unreacted S_4N_4 (48 mg, 0.260 mmol, 7%). Elution next with a mixture of n-hexane and benzene (3:1, 200 ml) gave 2b (583 mg, 3.31 mmol, 85%). (iii) Chromatography of the reaction mixture obtained from the reaction of α-bromomethyl p-totyl ketoxime (1g) (690 mg, 3.03 mmol) with S_4N_4 (556 mg, 3.02 mmol) using a mixture of n-hexane and carbon tetrachloride (4:1, 100 ml) gave 3-bromo-4-(p-totyl)-1,2,5-thiadiazole (3b) (242 mg, 0.949 mmol, 31%): mp 25°C (from MeOH): Ir (film) (ν, cm^{-1}) 1615, 1451, 1349, 1160, 1141, 982, 963, 820, 735; ^1H nmr ($CDCl_3$, δ, ppm) 2.42 (3 H, s, Me), 7.29 (2 H, 2 d, J = 8.0 Hz, ArH), 7.82 (2H, d, J = 8.0 Hz, ArH); ms (m/z) 256 ($M^+ + 2$, 44), 254 (M^+, 57.2), 149 (100, M^+ - BrCN), 117 (19.3, M^+ - BrCNS). Anal. Calcd for $C_9H_7N_2BrS$: C, 42.37; H, 2.77; N, 10.98; S, 12.57. Found: C, 42.29; H, 2.71; N, 10.92; S, 12.60. Elution next with carbon tetrachloride (200 ml) gave 2b (255 mg, 1.45 mmol, 48%). (iv) Chromatography of the reaction

mixture obtained from the reaction of 1g (690 mg, 3.03 mmol) with S_4N_4 (558 mg, 3.03 mmol) in the presence of pyridine (0.26 ml) using a mixture of n-hexane and carbon tetrachloride (3:1, 100 ml) gave 2b (170 mg, 0.965 mmol , 32%). Elution next with carbon tetrachloride (150 ml) gave unreacted S_4N_4 (123 mg, 0.668 mmol, 22%).

3-(p-Chlorophenyl)-1,2,5-thiadiazole (2c): (i) Chromatography of the reaction mixture obtained from the reaction of α-chloromethyl p-chlorophenyl ketoxime 1c (820 mg, 4.02 mmol) with S_4N_4 (742 mg, 4.03 mmol) using a mixture of n-hexane and benzene (3:1, 200 ml) gave 2c (697 mg, 3.54 mmol, 88%): mp 101-102°C (from n-hexane) (lit.,[12] 101-102°C). (ii) Chromatography of the reaction mixture obtained from the reaction of 1c (821 mg, 4.02 mmol) with S_4N_4 (741 mg, 4.02 mmol) in the presence of pyridine (0.35 ml) using a mixture of n-hexane and carbon tetrachloride (4:1, 150 ml) gave unreacted S_4N_4 (87 mg, 0.472 mmol, 12%). Elution next with a mixture of n-hexane and benzene (2:1, 200 ml) gave 2c (657 mg, 3.34 mmol, 83%).

3-(p-Bromophenyl)-1,2,5-thiadiazole (2d): (i) Chromatography of the reaction mixture obtained from the reaction of α-chloromethyl p-bromophenyl ketoxime (1d) (995 mg, 4.00 mmol) with S_4N_4 (742 mg, 4.03 mmol) using a mixture of n-hexane and benzene (1:1, 200 ml) gave 2d (891 mg, 3.70 mmol, 92%): mp 119-120°C (from CCl_4) (lit.,[12] 120-121°C). (ii) Chromatography of the reaction mixture obtained from the reaction of 1d (1,011 mg, 4.07 mmol) with S_4N_4 (748 mg, 4.06 mmol) in the presence of pyridine (0.35 ml) using a mixture of n-hexane and carbon tetrachloride (4:1, 100 ml) gave unreacted S_4N_4 (94 mg, 0.510 mmol, 13%). Elution next with a mixture of n-hexane and benzene (1:1, 200 ml) gave 2d (802 mg, 3.33 mmol, 82%).

3-(p-Methoxyphenyl)-1,2,5-thiadiazole (2e): (i) Chromatography of the reaction mixture obtained from the reaction of α-chloromethyl p-methoxyphenyl ketoxime (1e) (799 mg, 4.00 mmol) with S_4N_4 (746 mg, 4.05 mmol) using a mixture of n-hexane and carbon tetrachloride (4:1, 100 ml) gave unchanged S_4N_4 (72 mg, 0.391 mmol, 10%). Elution next with a mixture of n-hexane and benzene (2:1, 150 ml) gave 2e (284 mg, 1.48 mmol, 37%): mp 71-72°C (from n-hexane): Ir (film) (ν, cm^{-1}) 1620, 1528, 1477, 1348, 1310, 1289, 1255, 1227, 1183, 1028, 933, 898, 840, 790, 740; ^1H nmr ($CDCl_3$, δ, ppm) 3.86 (3 H, s, MeO), 7.00 (2 H, d, J = 9.0 Hz, ArH), 7.93 (2 H, d, J = 9.0 Hz, ArH), 8.82 (1 H, s, HC=N); ms (m/z) 192 (M^+, 100), 165 (M^+ - HCN), 133 (M^+ - HCNS). Anal. Calcd for $C_9H_8N_2OS$: C, 56.23; H, 4.19; N, 14.57; S, 16.68. Found: C, 56.27; H, 4.20; N, 14.61; S, 16.70. (ii) Chromatography of the reaction mixture obtained from the reaction of 1e (807 mg, 4.04 mmol) with S_4N_4 (748 mg, 4.06 mmol) in the presence of pyridine (0.35

ml) using a mixture of n-hexane and carbon tetrachloride (4:1, 200 ml) gave unreacted S_4N_4 (150 mg, 0.814 mmol, 20%). Elution next with a mixture of n-hexane and benzene (3:1, 150 ml) gave 2e (444 mg, 2.31 mmol, 57%).

3-(p-Nitrophenyl)-1,2,5-thiadiazole (2f) (i) Chromatography of the reaction mixture obtained from the reaction of α-bromomethyl p-nitrophenyl ketoxime (1h) (778 mg, 3.00 mmol) with S_4N_4 (553 mg, 3.00 mmol) using a mixture of n-hexane and carbon tetrachloride (3:1, 100 ml) gave 3-bromo-4-(p-nitrophenyl)-1,2,5-thiadiazole (3c) (145 mg, 0.507 mmol, 17%): mp 101-102°C (from n-hexane): Ir (KBr) (ν, cm^{-1}) 1611, 1525, 1355, 1156, 979, 871, 840, 726; ^1H Nmr ($CDCl_3$, δ, ppm) 8.16 (2 H, d, J = 9.6 Hz, ArH), 8.38 (2 H, d, J = 9.6 Hz, ArH); ms (m/z) 287 ($M^+ + 2$), 96.4), 285 (M^+, 100), 257 (36.4), 255 (36.9). Anal. Calcd for $C_8H_4N_3O_2BrS$: C, 33.58; H, 1.41; N, 14.69; S, 11.21. Found: C, 33.55; H, 1.45; N, 14.70; S, 11.27. Elution next with benzene (200 ml) gave 2f (505 mg, 2.44 mmol, 81%): mp 172°C (from CCl_4): Ir (KBr) (ν, cm^{-1}) 1601, 1510, 1330,1110, 1084, 930, 890, 859, 791, 758, 695; ^1H nmr ($CDCl_3$, δ, ppm) 8.17 (2 H, d, J = 9.6 Hz, ArH), 8.38 (2 H, d, J = 9.6 Hz, ArH), 9.00 (1 H, s, HC=N); ms (m/z) 207 (M^+, 100), 180 (6.8, M^+ - HCN), 177 (36, M^+ - NO), 134 (45.4), 122 (17.2). Anal. Calcd for $C_8H_5N_3O_2S$: C, 46.37; H, 2.43; N, 20.28; S, 15.47. Found: C, 46.40; H, 2.40; N, 20.31; S, 15.44. (ii) Chromatography of the reaction mixture obtained from the reaction of 1h (781 mg, 3.02 mmol) with S_4N_4 (561 mg, 3.04 mmol) in the presence of pyridine (0.26 ml) using a mixture of n-hexane and carbon tetrachloride (4:1, 200 ml) gave unreacted S_4N_4 (57 mg, 0.309 mmol, 10%). Elution next with carbon tetrachloride (200 ml) gave 2f (161 mg, 0.777 mmol, 26%).

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