Synthesis of *s*-Triazines Bearing Three Different Substituents (1)

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Reaction of *N'*-acyl-*N,N*-dimethylamidines with hydrogen sulfide in acetic acid gave *N*-thioacylbenzamides in almost quantitative yields. *S*-Ethylation of the *N*-thioacylbenzamides with iodoethane gave *N*-aroylthioimidates in excellent yields. Reaction of the *N*-aroylthioimidates with acetamidine, benzamidine, or guanidine in ethanol gave *s*-triazines in 60-93% yield.

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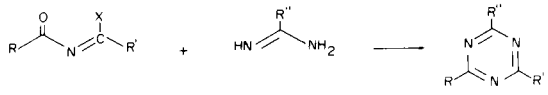
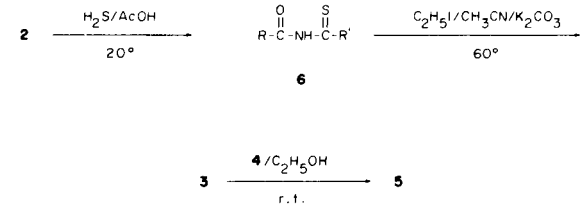
A general synthesis of *s*-triazines **5** bearing three different substituents was reported by Bader in 1965 (2). The reaction of ethyl *N*-acylimidates **1** with amidines gave *s*-triazines **5** in low yields (6-53%) because the carboxamide function of **1** completed with the ethoxy as a leaving group. It was conceivable that by replacing the ethoxy with a better leaving group such a dimethylamino moiety (in acetic acid) (3,4) or ethylthio, the yield of the reaction may be improved. Since the dimethylamino moiety of **2** was not replaceable by an amidine or guanidine in acetic acid, we found a very effective way of converting *N'*-acyl-*N,N*-dimethylamidines **2** into ethyl *N*-aroylthioimidates **3**. We now report an efficient general synthesis of *s*-triazines starting from *N'*-acyl-*N,N*-dimethylamidines **2**.



1, X = OC_2H_5
2, X = $N(CH_3)_2$
3, X = SC_2H_5

4 **5**

Reaction of *N'*-acyl-*N,N*-dimethylamidines **2** (3,4) with hydrogen sulfide in acetic acid gave *N*-thioacylbenzamides **6** in almost quantititative yields. *S*-Ethylation of the *N*-thioacylbenzamides **6** with iodoethane in acetonitrile in the presence of potassium carbonate gave *N*-aroylthioimidates **3** in excellent yields (85-97%). The monothio *N*-acylbenzamides **6** and monothio *N*-aroylimidates **3** synthesized are presented in Table I. Reaction of the *N*-aroylthioimidates **3** with acetamidine, benzamidine, or guanidine in ethanol at room temperature gave *s*-triazines **5** in 60-93% yields. The amidine or guanidine base was liberated from its hydrochloride salt with sodium methoxide in ethanol. Fourteen *s*-triazines **5** were synthesized and listed in Table II. The structure of the *s*-triazines **5** were all supported by nmr, ir, ms, and elemental analysis data.



Our procedure provides a new and effective synthesis of *N*-thioacylbenzamides **6** and their conversion to *N*-aroylthioimidates **3**. *N*-Thioacetylbenzamide (**6d**) has been prepared by the benzoylation of thioacetamide in 21% yield (5) and by the addition of methyl magnesium bromide to benzoylisothiocyanate in 31% yield (6).

As is obvious from Table II, the yield of the reaction has been dramatically improved by using ethylthio instead of ethoxy (2) as the leaving group. Thus, the present synthesis provides a general and effective way of synthesizing *s*-triazines **5** with three different substituents, in particular, three different alkyl and aryl substituents. Recently, a related reaction has been reported (7). The reaction of *N*-benzoylcarbonimidodithioic acid diethyl ester with amidines or guanidine gave *s*-triazines in 20-60% yields.

EXPERIMENTAL

All melting points were taken on a Mel-Temp apparatus. Samples for elemental analyses were dried over phosphorus pentoxide under high vacuum for 1-10 hours. Infrared spectra were measured on a Perkin-Elmer spectrophotometer (Model 21). The nmr spectra were determined with a Varian Model HA-100 spectrometer; chemical shifts (δ) are in ppm relative to internal tetramethylsilane. Mass spectra were recorded on A.E.I. MS 902.

N-Thioacetyl-*p*-anisamide (**6e**). Typical Procedure for **6a-h**.

Hydrogen sulfide was bubbled into 200 ml of acetic acid at 20° for 5 minutes. To the hydrogen sulfide solution in acetic acid was added 20.0 g (0.090 mole) of *N*-[(dimethylamino)ethylidene]-*p*-anisamide (3,4). The reaction mixture was stirred and the introduction of hydrogen sulfide was continued for another 10 minutes. After standing at room temperature for another 10 minutes and being diluted with 200 ml of water, the solution deposited 18.4 g (97%) of **6e** as yellow crystals, mp 128-130°; nmr (deuteriochloroform): δ 3.10 (s, 3H), 3.91 (s, 3H), 7.00 (d, J = 9 Hz, 2H), 7.88 (d, J = 9 Hz, 2H), 10.04 (bs, 1H).

Ethyl *N*-*p*-Anisolylthioacetimidate (**3e**). Typical Procedure for **3a-h**.

A mixture of **6e** (18.0 g, 0.093 mole), iodoethane (28.9 g, 0.186 mole), potassium carbonate (25.8 g, 0.186 mole), and acetonitrile (150 ml) was stirred at 60° for 2.5 hours and then filtered. The volatile components were removed under reduced pressure. The residue was dissolved in a mixture of 25 ml hexane and 25 ml dichloromethane, and the solution filtered. After removal of the dichloromethane and hexane, 20.1 g (91%) of **3e** as slightly yellow crystals (in the cases of **3a-d** and **3f-g**, yellow oils) were obtained, mp 52-55°; nmr (deuteriochloroform): δ 1.31 (t, J = 7.5 Hz, 3H), 2.14 (s, 3H), 2.98 (q, J = 7.5 Hz, 2H), 3.84 (s, 3H), 6.90 (d, J = 9 Hz, 2H), 7.86 (d, J = 9 Hz, 2H).

Table I

N-Thioacylbenzamides **6** and *N*-Aroylthioimidates **3**

Product	R	R′	Yield, %	Mp, °C	Formula (d)
6a	C_6H_5	H	90	122-124	C_8H_7NOS
6b	$4\text{-}(CH_3O)C_6H_4$	H	95	139-140	$C_9H_9NO_2S$
6c	$4\text{-}BrC_6H_4$	H	97	180-182	C_8H_6BrNOS
6d	C_6H_5	CH_3	90	81-82 (a)	C_9H_9NOS
6e	$4\text{-}(CH_3O)C_6H_4$	CH_3	97	128-130	$C_{10}H_{11}NO_2S$
6f	$4\text{-}BrC_6H_4$	CH_3	91	108-109	C_9H_8BrNOS
6g	$4\text{-}ClC_6H_4$	CH_3	93	101-103 (b)	C_9H_8ClNOS
6h	$4\text{-}(NO_2)C_6H_4$	CH_3	92	102-104 (c)	$C_9H_8N_2O_3S$
3a	C_6H_5	H	95	oil	$C_{10}H_{11}NOS$
3b	$4\text{-}(CH_3O)C_6H_4$	H	88	oil	$C_{11}H_{13}NO_2S$
3c	$4\text{-}BrC_6H_4$	H	76	oil	$C_{10}H_{10}BrNOS$
3d	C_6H_5	CH_3	97	oil	$C_{11}H_{13}NOS$
3e	$4\text{-}(CH_3O)C_6H_4$	CH_3	91	52-55	$C_{12}H_{15}NO_2S$
3f	$4\text{-}BrC_6H_4$	CH_3	85	oil	$C_{11}H_{12}BrNOS$
3g	$4\text{-}ClC_6H_4$	CH_3	97	oil	$C_{11}H_{12}ClNOS$
3h	$4\text{-}(NO_2)C_6H_4$	CH_3	89	60-62	$C_{11}H_{12}N_2O_3S$

(a) Lit mp 76-78° (6); 78° (5). (b) Lit (5) mp 100.5°. (c) Lit (5) mp 108°. (d) See Table III for the analytical data of all new compounds.

Table II

s-Triazines **5**

Product	R	R′	R″	Yield %	Mp, °C	Formula (c)
5a	$4\text{-}(CH_3O)C_6H_4$	CH_3	CH_3	60	83-85	$C_{12}H_{13}N_3O$
5b	$4\text{-}(CH_3O)C_6H_4$	CH_3	C_6H_5	93	105-107	$C_{17}H_{15}N_3O$
5c	$4\text{-}(CH_3O)C_6H_4$	CH_3	NH_2	72	210-212	$C_{11}H_{12}N_4O$
5d	$4\text{-}(CH_3O)C_6H_4$	H	CH_3	60	100-102	$C_{11}H_{11}N_3O$
5e	$4\text{-}(CH_3O)C_6H_4$	H	C_6H_5	73	135-137	$C_{16}H_{13}N_3O$
5f	$4\text{-}(CH_3O)C_6H_4$	H	NH_2	86	225-228	$C_{10}H_{10}N_4O$
5g	$4\text{-}BrC_6H_4$	CH_3	CH_3	61	135-136	$C_{11}H_{10}BrN_3$
5h	$4\text{-}BrC_6H_4$	CH_3	C_6H_5	71	124-125	$C_{16}H_{12}BrN_3$
5i	$4\text{-}BrC_6H_4$	H	NH_2	69	242-244	$C_9H_7BrN_4$
5j	C_6H_5	CH_3	C_6H_5	70	113-115 (a)	$C_{16}H_{13}N_3$
5k	$4\text{-}(NO_2)C_6H_4$	CH_3	C_6H_5	86	150-153	$C_{16}H_{12}N_4O_2$
5ℓ	$4\text{-}ClC_6H_4$	CH_3	CH_3	62	133-134.5 (b)	$C_{11}H_{10}ClN_3$
5m	$4\text{-}ClC_6H_4$	CH_3	C_6H_5	70	130.5-132	$C_{16}H_{12}ClN_3$
5n	$4\text{-}ClC_6H_4$	CH_3	NH_2	80	250-252	$C_{10}H_9ClN_4$

(a) Lit mp 110° (8); 105° (9). (b) Lit (9) mp 133.1°. (c) See Table III for the analytical data of all new compounds.

2-(4-Methoxyphenyl-4-methyl-6-phenyl-1,3,5-triazine (**5b**). Typical Procedure for **5c** and **5e-n**.

A mixture of 2.35 g (0.0150 mole) of benzamidine hydrochloride X H_2O and 0.81 g (0.0150 mole) of sodium methoxide in 30 ml of absolute ethanol was stirred at room temperature for 15 minutes and filtered. To the filtrate was added 1.20 g (0.0050 mole) of ethyl *N*-*p*-anisoylthioacetimidate (**3e**). Thirty minutes later, colorless crystals began to precipitate out from the reaction mixture. After standing at room temperatue for 44 hours and then in the refrigerator for 2 hours, the reaction mixture deposited 1.30 g (93%) (10) of **5b** as colorless crystals, mp 105-107°; ms: m/e 277 (M^+); nmr (DMSO-d_6): δ 2.67 (s, 3H), 3.88 (s, 3H), 7.15 (d, J = 8.5 Hz, 2H), 7.4-7.7 (m, 3H), 8.4-8.7 (m, 4H); ir (potassium bromide): 1615, 1595, 1530, 1425, 1390, 1370, 1320, 1260, 1190, 1160, 1030, 850, 830, 780 cm^{-1}.

2-(4-Methoxyphenyl)-4,6-dimethyl-1,3,5-triazine (**5a**). Typical Procedure for **5d**.

A mixture of 1.42 g (0.150 mole) of acetamidine hydrochloride and 0.81 g (0.0150 mole) of sodium methoxide in 30 ml of absolute ethanol was stirred at room temperature for 15 minutes and filtered. To the filtrate was added 1.20 g (0.0050 mole) of ethyl *N*-*p*-anisolylthioacetimidate (**3e**). The reaction mixture was allowed to stand at room temperature for 90 hours. After removal of the ethanol under reduced pressure without heating, the residue was dissolved in 50 ml of methylene chloride. The methylene chloride solution was washed with 10 ml of saturated sodium bicarbonate solution and 10 ml of water and dried over sodium sulfate. After removal of the methylene chloride, the residue was recrystallized from 15 ml of hexane to give 0.64 g (60%) of **5a** as colorless crystals, mp 83-85°; ms: m/e 215 (M^+); nmr (deuteriochloroform): δ

Table III

Analytical Data of All New Compounds Reported

Compound	C		H		N		S		X	
	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
3a	62.1	62.1	5.74	5.81	7.25	7.13	16.6	16.4	-	-
3b	59.2	58.9	5.87	6.18	6.27	6.12	14.4	14.4	-	-
3c	44.1	44.0	3.70	3.84	5.15	5.43	11.8	11.6	29.4	29.2
3d	63.7	63.8	6.32	6.33	6.76	6.49	15.5	15.3	-	-
3e	60.7	60.7	6.37	6.33	5.90	5.78	13.5	13.7	-	-
3f	46.2	46.2	4.23	4.25	4.89	5.31	11.20	10.9	27.9	27.6
3g	54.6	54.7	5.00	5.02	5.80	5.74	13.3	13.3	14.7	14.8
3h	52.4	52.6	4.80	4.94	11.1	11.0	12.7	13.0	-	-
5a	67.0	66.8	6.09	6.02	19.5	19.5	-	-	-	-
5b	73.6	73.4	5.45	5.39	15.2	15.1	-	-	-	-
5c	61.1	61.1	5.59	5.42	25.9	26.1	-	-	-	-
5d	65.7	65.4	5.51	5.57	20.9	20.9	-	-	-	-
5e	73.0	72.6	4.98	4.90	16.0	15.9	-	-	-	-
5f	59.4	59.4	4.98	5.04	27.7	27.8	-	-	-	-
5g	50.0	49.9	3.82	3.75	15.9	15.9	-	-	30.3	30.5
5h	58.9	58.8	3.71	3.70	12.9	13.0	-	-	24.5	24.7
5i	43.0	42.9	2.81	2.80	22.3	22.4	-	-	31.8	31.8
5k	65.7	65.8	4.14	3.93	19.2	19.0	-	-	-	-
5m	68.2	68.6	4.29	4.36	14.9	15.0	-	-	-	-
6a	58.2	58.3	4.27	4.30	8.48	8.24	19.4	19.3	-	-
6b	55.4	55.3	4.65	4.63	7.18	6.99	16.4	16.7	-	-
6c	39.4	39.4	2.48	2.41	5.74	5.76	13.1	13.1	32.7	32.7
6e	57.4	57.3	5.30	5.32	6.69	6.58	15.3	15.5	-	-
6f	41.9	41.7	3.12	2.97	5.43	5.24	12.4	12.4	31.0	30.8

2.65 (s, 6H), 3.90 (s, 3H), 7.00 (d, J = 8.0 Hz, 2H), 8.50 (d, J = 8.0 Hz, 2H); ir (potassium bromide): 1600, 1580, 1540, 1460, 1420, 1370, 1300, 1255, 1170, 1135, 1110, 1025, 870, 850, 800 cm^{-1}.

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REFERENCES AND NOTES

(1) The work was presented at the 1981 Gordon Conference on the Chemistry of Heterocyclic Compounds on July 8, 1981. After the submission of our work, a synthesis of *s*-triazines by the reaction of *N*-benzoylthioimidates with amidines has been recently reported: L. L. Whitfield and E. P. Papadopoulos; *J. Heterocyclic Chem.*, **18**, 1197 (1981). We think our reactions were carried out in better reaction conditions.

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