AN EFFICIENT REGIOSELECTIVE SYNTHESIS OF 7-SUBSTITUTED 1,3-DIMETHYL-4-OXO-4H-1,3,4-THIADIAZOLO[2,3-c]-1,2,4-TRIAZINIUM CATIONS

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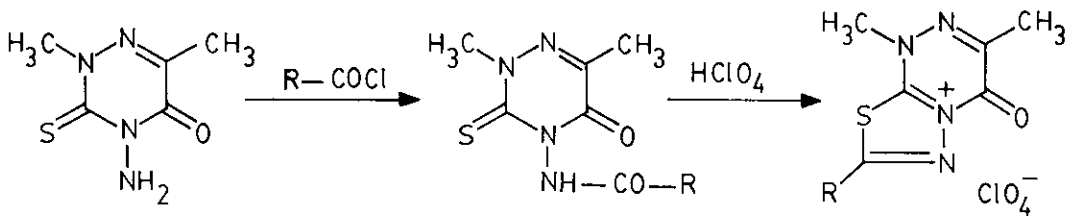
Abstract - *A number of 7-substituted 1,3-dimethyl-4-oxo-4H-1,3,4-thiadiazolo[2,3-c]-1,2,4-triazinium perchlorates 3 have been prepared by sequential treatment of 4-amino-2,6-dimethyl-5-oxo-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazine 1 with acyl chlorides and acetic anhydride/perchloric acid.*

As a part of an investigation of fused heterocycles we have reported the preparation of bridgehead nitrogen heterocycles which contain the 1,2,4-triazine moiety e.g. pyrido[2,1-f]-1,2,4-triazine[1,2], 1,2,4-thiadiazolo[5,1-c]-1,2,4-triazine[3] and imidazo[1,2-d]-1,2,4-triazine[4]. We now describe a new general method for the synthesis of derivatives of the 1,3,4-thiadiazolo[2,3-c]-1,2,4-triazine ring system which contain the 1,2,4-triazine and 1,3,4-thiadiazolo moieties.
Methods for the syntesis of 1,3,4-thiadiazolo[2,3-c]-1,2,4-triazine may be conveniently separated into two main groups: ring closure of an appropriate 4-amino-1,2,4-triazine with a carbon-inserting reagent which supplies the carbon of the 1,3,4-thiadiazole moiety, and construction of the 1,2,4-triazine portion of the fused ring system onto a preformed 1,3,4-thiadiazole nucleus. The first method involves cyclization with carbon disulfide[5], cyanogen bromide[6], aryl isothiocyanates[7] and carboxylic acids in the presence of phosphoryl chloride[8] or sulfuric acid[9]. The second one involves reaction of 1,3,4-thiadiazol-2-yl hydrazines with α-keto acids[10] to give the corresponding hydrazones which cyclize in acid to 1,3,4-thiadiazolo[2,3-c]-1,2,4-triazines. However, no generally useful procedure for the preparation of 1,3,4-thiadiazolo[2,3-c]-1,2,4-triazinium cations has hitherto been reported.

We now report here an apparently widely applicable synthesis of 7-substituted 1,3 dimethyl-4-oxo-4H-1,3,4-thiadiazolo[2,3-c]-1,2,4-triazinium perchlorates 3 in synthetically useful yields. Our approach is based on the sequential treatment of 4-amino-2,6-dimethyl-5-oxo-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazine 1, readily available from 2-methylthiocarbohydrazide[11] and pyruvic acid, with acyl chlorides and perchloric acid. The N-amino heterocycle 1 reacts with acyl chlorides in dry pyridine (method A) or in chloroform in the presence of potassium carbonate (method B) to give the corresponding N-acylamino derivatives 2 in good yields (59-80%). Compounds 2 undergo cyclization by the action of perchloric acid in acetic anhydride at 0°C to give the corresponding 1,3,4-thiadiazolo[2,3-c]-1,2,4-triazinium perchlorates 3 as crystalline solids in high yields (69-99%). The reaction of the N-amino heterocycle 1 with perchloric acid in acetic anhydride leads directly to 3g ($R=CH_3$) in good yield (62%).



1 2 3

Structural elucidation of 2 and 3 is accomplished on the basis of spectral and microanalytical data. The ir spectra of all N-acylamino derivatives 2 show two strong absorption bands in the region 1730-1710 cm^{-1} attributable to the exocyclic and endocyclic carbonyl groups respectively; the presence of the NH group in compounds 2 is confirmed by the absorption band in the region 3500-3100 cm^{-1}, while in the ir spectra of compounds 3 this band is absent; furthermore the exocyclic carbonyl group in 3 appears in the region 1754-1738 cm^{-1} being these wavenumbers higher than those corresponding to the absorption of the same carbonyl group in the N-acylamino derivatives 2; bands are also found in the ir spectra of 3 due to the perchlorate anion. In the ^1H-nmr spectra of 2 the chemical shifts of $N-CH_3$ and C_3-CH_3 groups are characteristic at δ 4.10-3.95 and δ 2.35-2.25 ppm respectively, while in the ^1H-nmr spectra of compounds 3 these groups appear at δ 4.40-4.30 and δ 2.75-2.55 ppm respectively.

This conversion is a useful procedure for the preparation of 1-methylthiadiazolo[2,3-c]-1,2,4-triazinium cations since the methylation of the neutral bicyclic system, e.g. compound 4 takes place mainly at N_2. Thus, the bicyclic compound 7-phenyl-3-methyl-4-oxo-4H-1,3,4-thiadiazolo[2,3-c]-1,2,4-triazine 4, available from 1 and benzoic acid[9], reacts with methyl trifluoromethanesulfonate in dry

TABLE 1. Preparation of N-Acylamino Derivatives 2.

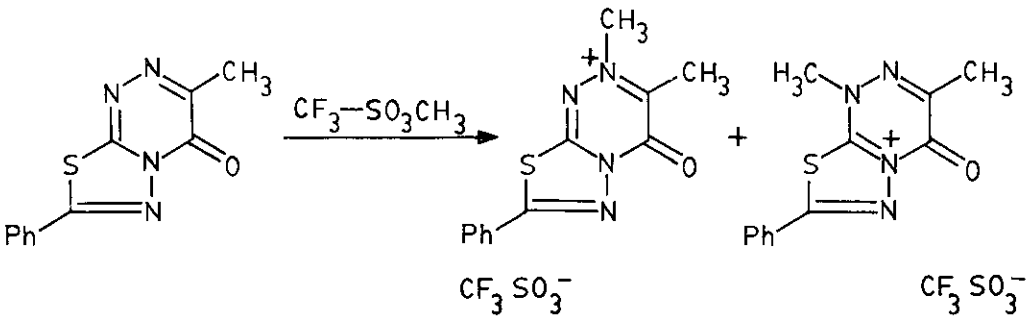
Entry	R	Mp(°C)	Yield[a] (%)	Crystal form	Found C	Found H	Found N	Molecular Formula	Required C	Required H	Required N
a	C_6H_5	227-228	63	Yellow prisms	51.96	4.24	20.18	$C_{12}H_{12}N_4O_2S$	52.16	4.38	20.27
b	4-H_3C-C_6H_4	191-193	66	Yellow prisms	53.67	4.72	19.17	$C_{13}H_{14}N_4O_2S$	53.78	4.86	19.30
c	α-$C_{10}H_7$	209-210	59	Yellow prisms	58.71	4.17	16.98	$C_{16}H_{14}N_4O_2S$	58.88	4.32	17.17
d	4-Br-C_6H_4	205-207	63	Colourless prisms	40.37	2.98	15.64	$C_{12}H_{11}N_4BrO_2S$	40.58	3.12	15.77
e	4-Cl-C_6H_4	207-209	80	Colourless prisms	46.22	3.40	17.83	$C_{12}H_{11}N_4ClO_2S$	46.38	3.57	18.03
f	C_6H_5-CH=CH	220-221	78	Colourless prisms	55.49	4.53	18.51	$C_{14}H_{14}N_4O_2S$	55.61	4.67	18.53

[a] Compounds 2a-2c were obtained by the experimental Method A, whereas 2d-2f were obtained by the Method B.

TABLE 2. Preparation of 1,3,4-Thiadiazolo[2,3-c]-1,2,4-triazinium Perchlorates 3.

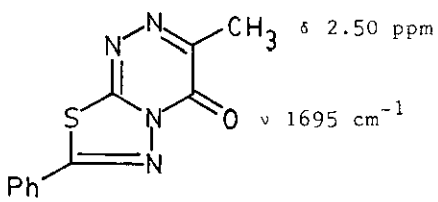
Entry	R	Mp(°C)	Yield (%)	Crystal form	Found C	Found H	Found N	Molecular Formula	Required C	Required H	Required N
a	C_6H_5	240-241	69	Yellow prisms	33.99	2.99	15.50	$C_{12}H_{11}N_4ClO_5S$	40.17	3.09	15.62
b	4-H_3C-C_6H_4	269-270	78	Yellow prisms	41.78	3.46	14.89	$C_{13}H_{13}N_4ClO_5S$	41.88	3.51	15.03
c	α-$C_{10}H_7$	115-117	80	Yellow prisms	46.86	3.09	13.60	$C_{16}H_{13}N_4ClO_5S$	47.01	3.20	13.70
d	4-Br-C_6H_4	320-321	95	Colourless prisms	32.87	2.30	12.80	$C_{12}H_{10}N_4BrClO_5S$	32.93	2.30	12.80
e	4-Cl-C_6H_4	307-308	99	Colourless prisms	36.54	2.49	14.17	$C_{12}H_{10}N_4Cl_2O_5S$	36.65	2.56	14.25
f	C_6H_5-CH=CH	272-274	79	Yellow prisms	43.58	3.26	14.50	$C_{14}H_{13}N_4ClO_5S$	43.70	3.40	14.56
g	CH_3	224-225	62	Colourless prisms	28.19	2.96	18.71	$C_7H_9N_4ClO_5S$	28.34	3.06	18.88

dichloromethane at room temperature to give a mixture of 7-phenyl-1,3-dimethyl-4-oxo-4H-1,3,4-thiadiazolo[2,3-c]-1,2,4-triazinium trifluoromethanesulfonate 3 and 7-phenyl-2,3-dimethyl-4-oxo-4H-1,3,4-thiadiazolo[2,3-c]-1,2,4-triazinium trifluoromethanesulfonate 5 in a 1:3 ratio, as is shown in its ^{1}H-nmr spectrum. From the above mixture only compound 5 could be isolated in pure form.



4 5 3

The structure of compound 5 is assigned on the basis of spectral and microanalytical data; in its ^{1}H-nmr spectrum the C_3-CH_3 protons appears at low field, δ 3.00 ppm, due to the deshielding effect of the quaternized nitrogen atom at position 2. Salient features of the spectral data of compounds 3, 4 and 5 are given below.



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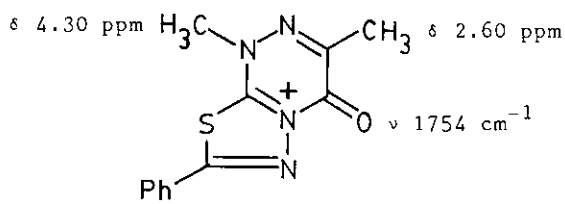

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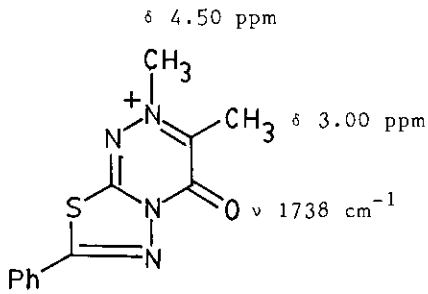

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TABLE 3. Spectral Data of Compounds 2 and 3

Compound No.	IR ν (cm^{-1})	^1H-NMR[a] δ (ppm)
2a	3234,1721,1659,1529,1314,1280,1189, 1189,1132,1053,1036,906,749,719.	11.70(1H,s); 8.1-7.5(5H,m); 3.95(3H,s); 2.30(3H,s).
2b	3251,1710,1693,1614,1495,1325,1268, 1189,1132,1121,1093,906,826,753, 742,691.	12.00(1H,s,broad); 8.4-7.6(4H,dd); 4.10(3H,s); 2.50(3H,s); 2.35(3H,s).
2c	3222,1713,1697,1667,1591,1537,1508, 1439,1319,1287,1257,1188,1140,1105, 1049,959,905,868,804,783,746,725, 683,658,633.	12.25(1H,s,broad); 8.8-7.4(7H,m); 4.10(3H,s); 2.25(3H,s).
2d	3246,1723,1695,1593,1462,1335,1262, 1182,1128,1117,1088,1013,891,845, 754,743,721,684.	12.10(1H,s,broad); 7.95(4H,s); 3.95(3H,s); 2.25(3H,s).
2e	3256,1721,1693,1596,1511,1336,1262, 1226,1190,1092,1013,894,849,756, 744,684.	12.00(1H,s,broad); 8.2-7.6(4H,m); 3.95(3H,s); 2.30(3H,s).
2f	3190,1719,1672,1630,1530,1346,1313, 1277,1202,1184,1070,1030,980,897, 864,775,764,713,628,625.	11.50(1H,s); 7.9-7.4(6H,m); 7.00(2H,d); 3.95(3H,s); 2.25(3H,s).
3a	1754,1602,1561,1526,1385,1260,1094, 1026,986,895,839,775,740,690,623, 605.	8.4-7.7(5H,m); 4.30(3H,s); 2.60(3H,s).
3b	1744,1602,1529,1501,1387,1306,1263, 1122,1098,1018,989,897,810,744,704, 625,608.	8.3-7.6(4H,m); 4.40(3H,s); 2.70(3H,s); 2.55(3H,s).
3c	1738,1653,1647,1600,1558,1524,1388, 1364,1311,1273,1250,1097,893,793, 768,742,698,625.	9.2-7.5(7H,m); 4.40(3H,s); 2.75(3H,s).

TABLE 3. Continued

3d	1749,1602,1595,1558,1525,1487,1388, 1306,1288,1259,1090,1013,988,899, 833,820,744,704,625,604.	8.5-7.6(4H,m); 4.35(3H,s); 2.70(3H,s).
3e	1749,1605,1589,1559,1525,1390,1304, 1259,1094,1011,980,897,852,818,744, 704,625,602.	8.00(4H,s); 4.40(3H,s); 2.70(3H,s).
3f	1738.1732,1628,1602,1555,1506,1489, 1308,1258,1180,1092,959,910,849,756, 744,729,692,671,625,608.	8.4-7.3(7H,m); 4.40(3H,s); 2.70(3H,s).
3g	1738,1602,1540,1433,1393,1302,1274, 1217,1189,1093,894,747,696,645,622.	4.40(3H,s); 3.05(3H,s); 2.60(3H,s).

[a] Obtained as solutions in DMSO-d^6, except for compounds 3a-3f which were recorded in $CDCl_3$+CF_3COOH.

EXPERIMENTAL

Melting points were obtained on a Kofler hot-stage apparatus and are uncorrected. Ir spectra were run using NaCl plates on a Nicolet FT-5DX spectrophotometer in Nujol emulsions. ^{1}H-nmr spectra were obtained on a Varian EM-360A spectrometer at 60 MHz. Mass spectra were recorded on a Hewlett-Packard 5993 C spectrometer. Elemental analyses were performed with a Perkin-Elmer 240 C instrument.

4-Amino-2,6-dimethyl-5-oxo-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazine 1. To a hot solution of 2-methylthiocarbohydrazide (2 g, 16.7 mmol) in water (100 ml), pyruvic acid (1.48 g, 16.7 mmol) was added. The reaction mixture was stirred at reflux temperature for 24 h . After cooling, the precipitated solid was collected by filtration and recrystallised from ethanol to give 1 (2 g, 70%) as colourless prisms, mp 120°C (Found: C, 34.71; H, 4.50; N, 32.64. $C_5H_8N_4OS$ requires C, 34.87; H, 4.68; N, 32.53); Ir ν max. (Nujol) 3330, 3222, 1676, 1535, 1467, 1410, 1283, 1166, 1098, 1070, 889, 843, 747, 725, 679 cm^{-1}; ^{1}H-nmr δ($CDCl_3$) 6.50 (2H,s,broad) 4.05 (3H,s), 2.35 (3H,s); m/z(%) 173(10), 172(M^+, 100), 102(14), 74(54), 73(15), 72(19), 70(17), 69(21), 58(10), 45(11), 42(31), 40(10).

General Procedure for the Formation of N-Acylamino Derivatives 2.
Method A. To a solution of 4-amino-2,6-dimethyl-5-oxo-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazine 1 (0.50 g, 2.9 mmol) in dry pyridine (7 ml) the appropriate acyl chloride (3.5 mmol) was added. The reaction mixture was stirred at reflux temperature for 1/2 h. After cooling, the solution was poured into ice-water (90 ml), the precipitated solid was collected by filtration, washed with water, dried and recrystallised from ethanol to give 2a-2c (see Table 1).
Method B. To a solution of 1 (0.50 g, 2.9 mmol) in dry chloroform (15 ml), the appropriate acyl chloride (3.5 mmol) and anhydrous potassium carbonate (0.40 g, 2.9 mmol) were added. The resultant mixture was stirred at reflux temperature for 15 h. After cooling, the inorganic salts were separated by filtration and the filtrate concentrated to dryness to afford a crude product which recrystallised from ethanol to give 2d-2f (see Table 1).

General Procedure from the Formation of 1,3,4-Thiadiazolo[2,3-c]-1,2,4-triazinium Perchlorates 3. To a cooled solution of N-acylamino derivative 2 (2 mmol) in acetic anhydride (5 ml), 70% perchloric acid (1 ml) was added dropwise with stirring. The reaction mixture was stirred at 0°C for 1 h and allowed to warm to room temperature; after 14 h the precipitated solid was collected by filtration, washed with ether (3x5 ml), dried and recrystallised from ethanol/ether (2:1) to give 3 (see Table 2).
Compound 3f was prepared by the above procedure using the N-aminoheterocycle 1 as starting material.

Reaction of 7-Phenyl-3-methyl-4-oxo-4H-1,3,4-thiadiazolo[2,3-c]-1,2,4-triazine 4 with Methyl Trifluoromethanesulfonate. To a solution of 7-phenyl-3-methyl-4-oxo-4H-1,3,4-thiadiazolo[2,3-c]-1,2,4-triazine 4 (0.5 g, 2 mmol) in dry dichloromethane (15 ml), methyl trifluoromethanesulfonate (0.37 g, 2.25 mmol) was added. The reaction mixture was stirred at room temperature for 30 min and the precipitated solid was collected by filtration, washed with ether and recrystallised from ethanol/ether (1:1) to give 7-phenyl-2,3-dimethyl-4-oxo-4H-1,3,4-thiadiazolo [2,3-c]-1,2,4-triazinium trifluoromethanesulfonate 5 (0.54 g, 65%) as green prisms, mp 218°C (Found: C, 38.15; H, 2.66; N, 13.54. $C_{13}H_{11}N_4F_3O_4S_2$ requires C, 38.25; H, 2.71; N, 13.72); Ir ν max. (Nujol) 1738, 1580, 1540, 1523, 1489, 1348, 1274, 1223, 1161, 1059, 1030, 951, 770, 736, 696, 685, 639 cm^{-1}; ^{1}H-nmr δ ($CDCl_3$-CF_3COOH) 8.3-7.6 (5H,m), 4.50 (3H,s), 3.00 (3H,s).

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