Synthesis of Some *N*-(4,5,5-Trisubstituted-Δ^2-1,3,4-thiadiazolin-2-yl)-*N,N'*-dimethylureas

E. V. P. Tao* and G. S. Staten

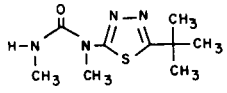
The Lilly Research Laboratories, Eli Lilly and Company,
Indianapolis, Indiana 46206

Received July 18, 1983

The synthesis of some *N*-(4,5,5-trisubstituted-Δ^2-1,3,4-thiadiazolin-2-yl)-*N,N'*-dimethylureas is described.

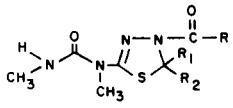
J. Heterocyclic Chem., **21**, 599 (1984).

As part of a continuing interest in the synthesis of *N*-[5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl]-*N,N'*-dimethylurea, **1** [1-3], it appeared appropriate to synthesize and determine the biological activities of some related *N*-(4,5,5-



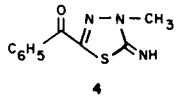
1

trisubstituted-Δ^2-1,3,4-thiadiazolin-2-yl)-*N,N'*-dimethylureas, **3**.



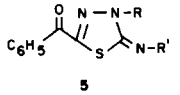
3

In 1975, Werber, *et al.* [4], reported methylation of 2-amino-5-benzoyl-1,3,4-thiadiazole with methyl iodide proceded exclusively on the ring nitrogen in position 3 giving



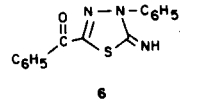
4

good yields of the thiadiazoline **4**. Werber, *et al.* [5], also reported the synthesis of some thiadiazoline derivatives **5** by oxidative cyclization of thiosemicarbazones with ferric chloride. Shawali and Abdelhamid [6] described an effi-



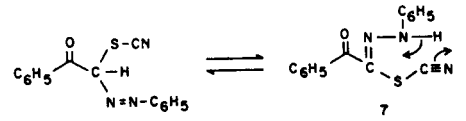
5

cient and rapid experimental procedure for the synthesis of 5-imino-4-phenyl-2-benzoyl-Δ^2-1,3,4-thiadiazoline, **6**, from the reaction of thiocyanic acid, 2-oxo-2-phenyl ethyl



6

ester with benzene diazonium chloride. They have proposed a reaction sequence which is consistent with the data. The key step in this mechanism is the formation of the hydrazone **7** which subsequently cyclizes to afford **6**.

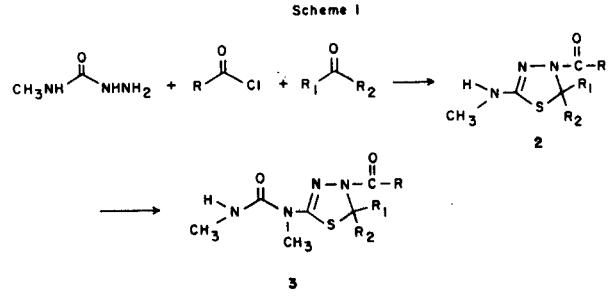


7

In 1980, Kubota, *et al.* [7] described the synthesis of 5-substituted-4-acyl-2-(acylamino)-Δ^2-1,3,4-thiadiazolines by acylation of thiosemicarbazones.

During the course of our study of the relationship of structures and biological activities of some *N*-(4,5,5-trisubstituted-Δ^2-1,3,4-thiadiazolin-2-yl)-*N,N'*-dimethylureas, we developed a synthetic method leading to 4,5,5-trisubstituted-2-methylamino-Δ^2-1,3,4-thiadiazolines, **2**. This allows the urea functionality to be introduced at the C-2 position of the thiadiazoline ring moiety. We now wish to report a convenient procedure for the preparation of **2** directly from the reaction of carbonyl compounds, 4-methyl-3-thiosemicarbazide and acyl chlorides. Conversion to **3** was subsequently effected by reaction of **2** with phosgene and methyl amine. The transformation has proven successful with a variety of carbonyl compounds and acyl chlorides (Table I). The phosgenation reaction was found to be a general procedure for the preparation of ureas, **3** (Table II). This sequence of reaction is depicted in Scheme 1.

Scheme I



3

EXPERIMENTAL

Compounds **2a-l** were prepared either by method A or B depending on the availability of the carbonyl compounds. Melting points, yields and elemental analyses are shown in Table I. Satisfactory spectroscopic data (ms, nmr) were obtained for all substances. The melting points, yields and elemental analyses of compounds **3a-l** are shown in Table II. All compounds possessed satisfactory spectral data (ms, nmr).

Table I

4,5,5-Substituted-2-methylamino-Δ^2-1,3,4-thiadiazolines

Compound	R	R_1	R_2	Method	Yield, %	Mp °C	Analyses Calculated C	H	N	Found C	H	N
2a	*t*-butyl	CH_3	CH_3	A	79.0	162-164	52.37	8.35	18.32	52.17	8.66	18.05
2b	*t*-butyl	CH_3	H	B	38.6	102-103	50.44	7.53	19.67	50.29	7.57	19.44
2c	*t*-butyl	C_2H_5	H	B	60.2	78.5-80	52.60	7.95	18.40	52.39	7.94	18.20
2d	*t*-butyl	C_2H_5	CH_3	A	62.0	132-136	54.29	8.70	17.27	54.06	8.61	17.33
2e	*t*-butyl	$-CH_2CH_2CH_2CH_2CH_2-$		B	47.6	157-158	57.96	8.61	15.60	57.81	8.47	15.48
2f	CH_3	CH_3	CH_3	A	56.1	114-115.5	44.90	7.00	22.44	44.75	6.83	22.20
2g	C_6H_5	CH_3	CH_3	A	31.8	130-135	57.81	6.06	16.85	57.82	6.12	16.91
2h	*o*-F-C_6H_4	CH_3	CH_3	A	62.2	135.5-138.5	53.92	5.28	15.72	53.66	5.13	15.52
2i	*p*-F-C_6H_4	CH_3	CH_3	A	74.1	156-158	53.92	5.28	15.72	53.68	5.47	15.71
2j	*o*-CF_3-C_6H_4	CH_3	CH_3	A	55.2	164-169	49.21	4.44	13.24	49.35	4.36	13.22
2k	*m*-CF_3-C_6H_4	CH_3	CH_3	A	61.1	111-115	49.21	4.44	13.24	49.31	4.36	13.32
2l	*p*-CF_3-C_6H_4	CH_3	CH_3	A	53.3	107-112	49.21	4.44	13.24	49.02	4.17	13.06

Table II

N-(4,5,5-Substituted-Δ^2-1,3,4-thiadiazolin-2-yl-*N,N'*-dimethylureas

Compound	R	R_1	R_2	Yield, %	Mp °C	Analyses Calculated C	H	N	Found C	H	N
3a	*t*-butyl	CH_3	CH_3	80.4	128-130	50.33	7.44	19.56	50.14	7.82	19.59
3b	*t*-butyl	CH_3	H	77.2	168-169	48.51	7.40	20.57	48.52	7.31	20.37
3c	*t*-butyl	C_2H_5	H	64.6	144-146	50.33	7.74	19.56	50.12	7.55	19.45
3d	*t*-butyl	C_2H_5	CH_3	47.6	124-126.5	51.97	8.05	18.65	51.74	7.95	18.38
3e	*t*-butyl	$-CH_2CH_2CH_2CH_2CH_2-$		89.7	195-196	55.19	8.03	17.16	55.39	7.87	16.98
3f	CH_3	CH_3	CH_3	70.6	154-155.5	44.25	6.60	22.93	44.32	6.84	23.24
3g	C_6H_5	CH_3	CH_3	58.8	150-152	54.88	5.92	18.29	55.10	5.63	18.17
3h	*o*-F-C_6H_4	CH_3	CH_3	82.1	120-123	51.84	5.28	17.27	51.78	5.02	17.42
3i	*p*-F-C_6H_4	CH_3	CH_3	65.7	151-153	51.84	5.28	17.27	52.00	5.35	17.36
3j	*o*-CF_3-C_6H_4	CH_3	CH_3	64.2	128-130	48.12	4.58	14.97	48.19	4.64	15.04
3k	*m*-CF_3-C_6H_4	CH_3	CH_3	48.0	145-148	48.12	4.58	14.97	47.91	4.84	15.23
3l	*p*-CF_3-C_6H_4	CH_3	CH_3	37.8	141-144	48.12	4.58	14.97	47.98	4.58	14.75

Method A. 5,5-Dimethyl-4-(trifluoromethylbenzoyl)-2-methylamino-Δ^2-1,3,4-thiadiazoline (**2k**).

4-Methyl-3-thiosemicarbazide (42 g, 0.4 mole) and pyridine (32 g) were added to acetone (200 ml), and the mixture was stirred at ambient temperature for fifteen minutes. 3-Trifluoromethylbenzoyl chloride (83.6 g, 0.4 mole) was added dropwise at 20-25° (external cooling required). After being stirred at room temperature for three hours, water (200 ml) was added and the mixture was cooled to 5°. The resulting precipitate was removed by filtration and recrystallized from nitromethane to give 77.5 g (61%) of **2k**, mp 111-115°; nmr (DMSO-d_6): δ 2.18 (s, 6, 5-CH_3), 2.65 (d, 3, J = 5 Hz, N-CH_3), 6.98 (q, 1, J = 5 Hz, N-*H*), 7.9 (m, 4, aromatic protons).

Method B. 5-methyl-4-(pivaloyl)-2-methylamino-Δ^2-1,3,4-thiadiazoline (**2b**).

Pivaloyl chloride (12.1 g, 0.1 mole) was added dropwise between 20-25° with cooling to a stirred mixture containing toluene (200 ml), 4-methyl-3-thiosemicarbazide (10.5 g, 0.1 mole), acetaldehyde (4.4 g, 0.1 mole) and pyridine (7.9 g, 0.1 mole). After being stirred at ambient temperature for three hours, water (50 ml) was added. The layers were separated, and the organic layer was washed with water. Toluene was removed under vacuum, and the resulting oil was recrystallized from nitromethane to afford 8.3 g (38.6%) of **2b**, mp 102-103°; nmr (deuteriochloroform): δ 1.32 (s, 9, *t*-butyl), 1.50 (d 3, J = 6.2 Hz, 5-CH_3), 2.98 (d, 3, J = 5 Hz, N-CH_3), 4.68 (s, 1, N-H), 6.22 (q, 1, J = 6.2 Hz, C-*H*).

N-(4-Pivaloyl-5,5-dimethyl-Δ^2-1,3,4-thiadiazolin-2-yl)-*N,N'*-dimethylurea (**3a**).

A hot solution of 4-pivaloyl-5,5-dimethyl-2-methylamino-Δ^2-1,3,4-thiadiazoline (**2a**) (22.9 g, 0.1 mole) in toluene (150 ml) was added dropwise to a solution of phosgene (8 ml) and triethylamine (14 ml) in toluene (150 ml) while the reaction temperature was maintained between −10° and −5° with cooling. The reaction mixture was allowed to come to room temperature and was heated to 30°. It was then washed with water (125 ml). Aqueous methylamine (40%, 75 ml) was added dropwise in toluene solution between 0-10° with cooling. The reaction mixture was stirred at room temperature for two hours, and the layers were separated. Toluene

was removed under vacuum, and the resulting residue was slurried into 12.5 ml of water. The product was removed by filtration and washed with water. Recrystallization from acetone-water and vacuum drying at 50° afforded 23 g (80%) of **3a**, mp 128-130°; nmr (DMSO-d_6): δ 1.25 (s, 9, *t*-butyl), 1.82 (s, 6, CH_3), 2.65 (d, 3, J = 5 Hz, N-CH_3), 3.38 (s, 3, N-CH_3), 7.42 (q, 1, J = 5 Hz, N-*H*).

REFERENCES AND NOTES

[1] E. V. P. Tao, *Synth. Commun.*, **4**, 249 (1974).

[2] E. V. P. Tao and C. F. Christie, Jr., *Org. Prep. Proced. Int.*, **7**, 179 (1975).

[3] British Patent, 1,266,172 (1969); *Chem. Abstr.*, **72**, 100717u (1970).

[4] G. Werber, F. Buccheri and N. Vivona, *J. Heterocyclic Chem.*, **12**, 841 (1975).

[5] G. Werber, F. Buccheri and M. L. Marino, *ibid.*, **12**, 581 (1975).

[6] A. S. Shawali and A. O. Abdelhamid, *Tetrahedron Letters*, 163 (1975).

[7] S. Kubota, Y. Ueda, K. Fujikane, K. Toyooka and M. Shibuya, *J. Org. Chem.*, **45**, 1473 (1980).