A Facile Synthesis of 2-Substituted-4-(substituted)phenyl-Δ^2-1,3,4-oxadiazolin-5-ones

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The title compounds, **3**, are formed at ambient temperature from 4,4-dimethyl-2-(substituted)-phenylsemicarbazides (**1**) and carboxylic acid chlorides in the presence of triethylamine. 2-Dimethylamino-4-(substituted)phenyl-Δ^2-1,3,4-oxadiazolin-5-ones are formed from **1** and dialkylcarbamoyl chlorides at elevated temperature (about 150°). Acylation of **1** with carboxylic acid anhydrides, also at elevated temperature, is accompanied by loss of dimethylamine from the intermediate 1-acyl-4,4-dimethyl-2-(substituted)phenylsemicarbazides, **2**, to give **3**.

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Δ^2-1,3,4-Oxadiazolin-5-ones have been of considerable chemical interest for many years (1,2). The earliest reported synthesis was published in 1890 by Freund and Kuh (3) who treated phenylhydrazides with phosgene under pressure and at elevated temperature. More recently, Dornow and Brunken (4) have shown that Δ^2-1,3,4-oxadiazolin-5-ones are formed more easily by the action of phosgene on acylhydrazines in aqueous solution. Recent investigators (1,2,5) have reported the preparation of Δ^2-1,3,4-oxadiazolin-5-ones of biological interest, in some cases with much difficulty, following a variety of procedures.

In an attempt to acylate 4,4-dimethyl-2-(substituted-phenyl)semicarbazides (6) (**1**) with a variety of carboxylic acid chlorides in the presence of triethylamine in tetrahydrofuran at ambient (10-25°) temperature, more extensive reaction occurred and only 2-substituted-4-(substituted-phenyl)-Δ^2-1,3,4-oxadiazolin-5-ones (**3**) were isolated, indicating that the reaction involved not only the elimination of the elements of HCl, but also those of dimethylamine. For example, treatment at ambient temperature of **1b** with chloroacetyl chloride in tetrahydrofuran and in the presence of triethylamine in the molar ratio of 1:1.1:1.1 led to the exclusive formation of **3a**, isolated in 39% yield by silica chromatography. The acylated semicarbazide, **2** ($R = CH_2Cl$, $X = 3\text{-}CF_3$), was not isolated. Similarly facile was the reaction of 1,2-dichloroacryloyl chloride with **1b** and **1c** to give **3b** and **3c** in good yields. The Δ^2-1,3,4-oxadiazolin-5-one structure was readily deduced for **3a**, **3b** and **3c** from correct elemental analysis (C,H,N), and infrared, nmr and mass spectral evidence (see Table I and data cited in the Experimental).

The reaction of **1b** with cyclopropanecarbonyl chloride to produce both 1,1-bis(cyclopropylcarbonyl)-4,4-dimethyl-2-(3-trifluoromethyl)phenylsemicarbazide (**2a**) (34%), and 2-cyclopropyl-4-(3-trifluoromethyl)phenyl-Δ^2-1,3,4-oxadiazolin-5-one (**3d**) is somewhat unusual, especially since **3d** was isolated in such low (3%) yield. The identity of **2a** is evident from its correct elemental analysis, and infrared (no apparent NH, two carbonyl bands at 1720 and 1690 cm^{-1}) and mass spectra (m/e 383 (M^+)).

2-Dialkylamino-4-(substituted)phenyl-Δ^2-1,3,4-oxadiazolin-5-ones are best obtained by reflux (about 150°) for 45-90 minutes of a solution of a **1** compound in an excess of the respective dialkylcarbamoyl chloride. In this way **3e-3h** were prepared in good yields. Attempted reaction of the **1** compounds with dimethyl- and diethylcarbamoyl chloride in refluxing tetrahydrofuran and in the presence of triethylamine led to the recovery of starting materials.

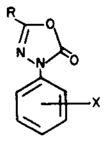
Although the foregoing procedure is useful for many 2-substituted-4-aryl-Δ^2-1,3,4-oxadiazolin-5-ones, the applicability is limited owing to diacylation of the NH_2 group of **1**. Therefore, the reaction of **1** with carboxylic acid anhydrides was investigated. This synthesis could be modified (by elimination of solvent and triethylamine) to afford a convenient variation on the above synthesis of **3**. For example, the semicarbazide **1c** underwent ready reaction when heated briefly (25 minutes) to reflux with an excess of acetic anhydride to give **3i** in 72% yield. The results of a number of similar preparations (**3j-3p**) are summarized in Chart 1 and Table I.

The fate of the dimethylamino moiety in these reactions was established by the following experiment: Treatment of **1b** with pivalic anhydride proceeded smoothly at 150° (5 minutes) to give an 83.5% yield of **3l**. When the mother liquor from this reaction was subjected to alkaline hydrolysis, a dark yellow liquid was obtained. Molecular weight determination (129 from mass spectrum) and nmr measurements (δ 1.3 (9, $(CH_3)_3C$) and 3.0 ppm (6, $(CH_3)_2N$)) established it to be *N,N*-dimethylpivalamide, $(CH_3)_3CC(=O)N(CH_3)_2$.

That the formation of the **3** compounds by acylation of **1** occurs stepwise was indicated in the following manner. When **1b** was allowed to react with two molar equivalents of trifluoroacetic anhydride at 5-15° (external cooling was necessary), there were obtained two compounds separated by silica chromatography and identified as 4,4-dimethyl-1-trifluoroacetyl-2-(3-trifluoromethyl)phenylsemicarbazide, **2b** (18.5%), and 2-trifluoromethyl-4-(3-trifluoromethyl-4-(3-trifluoromethyl)phenyl-Δ^2-1,3,4-oxadiazolin-5-one (**3m**) (34%). When **2b** was refluxed in trifluoro-

Table I

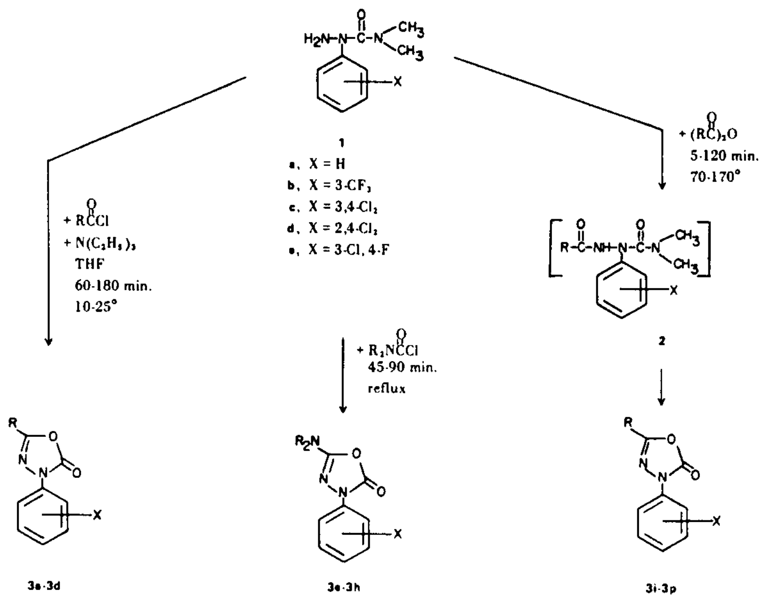
2-Substituted-4-(substituted-phenyl)-Δ^2-1,3,4-oxadiazolin-5-ones, **3**



Compound	R	X	Yield (%)	M.p., °C	Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
3a	CH_2Cl	3-CF_3	39	(a)	$C_{10}H_6ClF_3N_2O_2$	43.1	43.5	2.2	2.5	10.1	9.8
3b	$ClCH=C(Cl)$	3-CF_3	46	80-82	$C_{11}H_5Cl_2F_3N_2O_2$	40.6	40.6	1.5	1.5	8.6	8.8
3c	$ClCH=C(Cl)$	3,4-Cl_2	41	144-145	$C_{10}H_4Cl_4N_2O_2$	36.8	37.0	1.2	1.3	8.6	8.8
3d		3-CF_3	3	(a)	$C_{12}H_9F_3N_2O_2$	53.3	53.1	3.3	3.3	10.3	9.9
3e	$(CH_3)_2N$	3,4-Cl_2	58	116-119	$C_{10}H_9Cl_2N_3O_2$	43.8	43.8	3.3	3.4	15.3	15.2
3f	$(CH_3)_2N$	3-CF_3	71	76-79	$C_{11}H_{10}F_3N_3O_2$	48.3	48.3	3.7	3.7	15.4	15.5
3g	$(CH_3)_2N$	2,4-Cl_2	75.6	125-127	$C_{10}H_9Cl_2N_3O_2$	43.8	43.9	3.3	3.3	15.3	15.4
3h	$(C_2H_5)_2N$	2,4-Cl_2	28.9	73-76	$C_{12}H_{13}Cl_2N_3O_2$	47.7	47.6	4.3	4.3	13.9	14.0
3i	CH_3	3,4-Cl_2	72	136-137	$C_9H_6Cl_2N_2O_2$	44.2	44.1	2.5	2.4	11.5	11.7
3j	$(CH_3)_3C$	3,4-Cl_2	35	102-103 (b)	$C_{12}H_{12}Cl_2N_2O_2$	50.2	50.2	4.2	4.2	9.3	9.5
3k	$(CH_3)_3C$	3-Cl, 4-F	52	93-95	$C_{12}H_{12}ClFN_2O_2$	53.2	53.3	4.4	4.5	10.3	10.4
3l	$(CH_3)_3C$	3-CF_3	83.5	110-111	$C_{13}H_{13}F_3N_2O_2$	54.6	54.5	4.5	4.5	9.8	9.9
3m	CF_3	3-CF_3	34	(a)	$C_{10}H_4F_6N_2O_2$	40.3	40.6	1.3	1.5	9.3	9.4
3n	C_2F_5	2,4-Cl_2	86	(a)	$C_{10}H_3Cl_2F_5N_2O_2$	34.4	34.2	0.9	1.0	8.0	7.6
3o	n-C_3F_7	2,4-Cl_2	96	(a)	$C_{11}H_3Cl_2F_7N_2O_2$	33.1	33.5	0.8	0.8	7.0	7.0
3p	n-C_7F_{15}	2,4-Cl_2	50	54-56	$C_{15}H_3CL_2F_{15}N_2O_2$	30.1	30.1	0.5	0.5	4.7	4.8

(a) Failed to crystallize at room temperature. (b) Lit. (5) m.p. 105-106°.

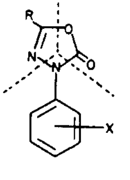
Chart I



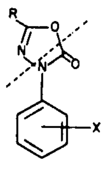
acetic anhydride for 30 minutes, the only product detected in the reaction mixture was **3m** as evidenced by identical retention time and R_f-value with an authentic sample of **3m**. Furthermore, when **1a** and **1c** were allowed to react with one molar equivalent of trifluoroacetic anhydride in acetonitrile at 20-40°, the respective trifluoroacetylated semicarbazides, **2c** and **2d**, were isolated in good yields (Table II).

The infrared spectra of all **3** compounds show strong absorptions in the 1820-1750 cm^{-1} range (C=O stretching) and absorption of intermediate intensity at 1675-1650 cm^{-1} due to the C=N stretching vibration. These values correspond closely to values assigned to carbonyl absorptions in γ-lactams (1750-1700 cm^{-1}) and to the C=N stretching vibration in Schiff bases (1670-1630 cm^{-1}).

A common feature of the mass spectra of **3d**, **3i** and **3l** is that the molecular ions are prominent peaks indicating a stable Δ^2-1,3,4-oxadiazolin-5-one ring system. The base peaks of all three compounds are due to the substituted-phenyl-*N*-moiety with two major fragmentation modes occurring (path a and path b). These involve cleavage of the N-CO (path a) and of the O-CO bond (path b). Fission of the N-CO bond is followed by the loss of CO_2 giving rise to the observed fragment M^+-44, followed by cleavage of the N-N bond to give fragment X-C_6H_4-N (base peak). Cleavage of the O-CO bond is followed by rupture of the N-N bond giving rise to the fragment X-C_6H_4-N=C=O.



path a



path b

EXPERIMENTAL

Representative methods of synthesis are described for **3b**, **2a** and **3d**, **3e**, **2b** and **3m**, and **3l**.

2-(1,2-Dichlorovinyl)-4-(3-trifluoromethyl)phenyl-Δ^2-1,3,4-oxadiazolin-5-one (**3b**).

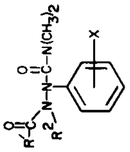
To a solution of 9.9 g. (0.044 mole) of **1b** and 4.5 g. (0.044 mole) of triethylamine in 150 ml. of tetrahydrofuran was added dropwise, with stirring at 10-15°, 6.7 g. (0.042 mole) of 1,2-dichloroacryloyl chloride. The reaction mixture was stirred for 2 hours, poured into ice water, and extracted with ether. The extract was dried and concentrated to an almost colorless residue, which thin layer chromatography (tlc) revealed to consist of two substances. The less mobile material was the major component (R_f = 0.4 in solvent No. 3 (7)). The minor component had R_f = 0.7 in solvent No. 3. Attempted separation by silica chromatography was unsuccessful as the less mobile component, presumably **2** (X = 3-CF_3, R = CHCl=CCl-), was converted into the more mobile component, **3b**, during this operation. Work-up of the eluent gave 6.0 g. (46%) of **3b** as a colorless crystalline solid, m.p. 80-82° (from hexane); ir (potassium bromide pellet): 3190 (CH=), 1805 (C=O) and 1140 cm^{-1} (C-O-); nmr (deuteriochloroform): δ 7.35 (1, s, CH=) and 7.8 and 8.1 ppm (4, m, C_6H_4); ms: (70 eV) 324 (M^+), 305 (M^+-F), 280 (M^+-CO_2), 245 (M^+-(CO_2+Cl)), 217 (M^+-(C_3HCl_2)), 187 ($CF_3 \cdot C_6H_4NCO^+$) (base peak), 145 ($CF_3 \cdot C_6H_5^+$), 139, 109, 95, 90, 69, 44, 36.

1,1-Bis(Cyclopropylcarbonyl)-4,4-dimethyl-2-(3-trifluoromethyl)-phenyl Semicarbazide (**2a**) and 2-Cyclopropyl-4-(3-trifluoromethyl)phenyl-Δ^2-1,3,4-oxadiazolin-5-one (**3d**).

A solution of 9.9 g. (0.04 mole) of **1b** and 4.5 g. (0.044 mole) of triethylamine in 150 ml. of tetrahydrofuran was treated with

Table II

Acylated 4,4-Dimethyl-2-(substituted-phenyl) Semicarbazides, 2



Compound	R¹	R²	X	Yield (%)	M.p., °C	Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
2a			3-CF₃	34.2	98-100	$C_{18}H_{20}F_3N_3O_3$	56.3	56.4	5.2	5.4	11.0	11.0
2b	CF_3	H	3-CF₃	18.5	118-121	$C_{12}H_{11}F_6N_3O_2$	42.0	42.0	3.2	3.2	12.2	11.8
2c	CF_3	H	H	58	151-154	$C_{11}H_{12}F_3N_3O_2$	48.0	48.1	4.3	4.3	15.3	15.3
2d	CF_3	H	3,4-Cl₂	29	146-148	$C_{11}H_{10}Cl_2F_3N_3O_2$	38.4	38.1	2.9	3.1	12.2	12.2

cyclopropanecarbonyl chloride, 5.0 g. (0.048 mole), in an identical manner to that used for **3b**. The mixture was stirred for three hours at room temperature and heated to reflux for one hour. Two resulting products were separated by silica chromatography. The more mobile component, **3d**, 0.3 g. (3%), is an amber liquid; ir: no apparent NH, 1795 (C=O) and 1150 cm^{-1} (CF_3); nmr (deuteriochloroform): δ 1.0-1.3 (m, 4, $-CH_2-CH_2-$), 1.7-2.1 (m, 1, CH) and 7.2-8.2 ppm (m, 4, C_6H_4); ms: (70 eV) 270 (M^+), 251 (M^+-F), 225, 199, 187 (CF_3-C_6H_4NCO), 159 (CF_3-C_6H_4-N^+) (base peak), 145, 139, 132, 113, 109, 95, 90, 69, 63, 44, 41.

The less mobile component, **2a**, 2.6 g. (34%), is a colorless crystalline solid, m.p. 98-100°; ir: no apparent NH, 1720 and 1690 (C=O), 1175 cm^{-1} (CF_3); ms: (70 eV) 383 (M^+), 314 (M^+-C_3H_5CO), 297 (M^+-(C_3H_5CO+OH)), 245 ($CF_3C_6H_4$-N_2CON-$(CH_3)_2^+$), 226 (245-F), 159 ($CF_3C_6H_4N^+$), 145 ($CF_3C_6H_5^+$), 69 (CF_3^+) (base peak), 41 ($C_3H_5^+$).

4-(3,4-Dichlorophenyl)-2-dimethylamino-Δ^2-1,3,4-oxadiazolin-5-one (**3e**).

To a solution of **1c**, 6.2 g. (25 mmoles), and triethylamine, 2.6 g. (26 mmoles), in 100 ml. of tetrahydrofuran was added dropwise dimethylcarbamoyl chloride, 2.7 g. (28 mmoles). The mixture was heated to reflux for two hours. Tlc revealed no change. However, treatment of **1c**, 12.4 g. (0.05 mole), with dimethylcarbamoyl chloride, 20 ml., at 167° (reflux, 1 hour) brought about complete conversion to a more mobile component. The reaction mixture was poured into water, extracted with ether, dried, charcoaled, filtered, concentrated to 250 ml. and cooled. Filtration gave 8.0 g. (58%) of **3e** as a colorless crystalline solid, m.p. 116-119°; ir (potassium bromide): 3450 (carbamate), 1780 (O-C-O, lactone), and 1670 cm^{-1} (C=O); nmr (deuteriochloroform): δ 3.0 (6, s, $(CH_3)_2N$) and 7.3-8.0 ppm (3, m, C_6H_3).

2-Trifluoromethyl-4-(3-trifluoromethyl)phenyl-Δ^2-1,3,4-oxadiazolin-5-one (**3m**) and 4,4-Dimethyl-1-(trifluoroacetyl)-2-(3-trifluoromethyl)phenyl Semicarbazide (**2b**).

Trifluoroacetic anhydride, 21.0 g. (0.1 mole), was added dropwise with stirring to **1b**, 12.35 g. (0.05 mole). As this addition was very exothermic, the temperature was maintained at 5-15° by external cooling throughout the addition. The reaction mixture was stirred for two hours at ambient temperature and concentrated under reduced pressure. Tlc of the resulting residue revealed that two substances were present; the less mobile material was the major component. The oily residue was resolved into its two components by column chromatography over silica gel to give 5.1 g. (34%) of **3m**, a light yellow mobile liquid; ir: 1890, 1820 (C=O), 1650, 1620 and 1605 (C=), 1180 (CF_3); nmr (deuteriochloroform): δ 7.5-8.0 ppm (m, C_6H_4).

The second compound which emerged from the column was **2b**, a colorless crystalline solid, 3.2 g. (18.5%), m.p. 118-121° (from hexane); ir: 3200 (NH), 1750 and 1680 (C=O), 1180 cm^{-1} (CF_3); nmr (DMSO-d_6): δ 2.85 (s, 6, $(CH_3)_2N$), 7.4 (m, 4, C_6H_4) and 8.2 ppm (s, 1, NH).

2-*t*-Butyl-4-(3-trifluoromethyl)phenyl-Δ^2-1,3,4-oxadiazolin-5-one (**3l**).

A mixture of **1b**, 12.35 g. (0.05 mole), and pivalic anhydride, 25 ml., was briefly (5 minutes) heated to 150°. Tlc revealed that two substances had been formed. The reaction mixture was cooled and diluted with hexane. This gave a white solid which was filtered, washed with hexane and dried to give 12.1 g. (83.5%) of **3l**, m.p. 110-111°; ir: 1790 (C=O), 1360 and 1600 (C=); nmr (deuteriochloroform): δ 1.4 (s, 9, $(CH_3)_3C$) and 7.8-8.5 ppm (m, 4, C_6H_4).

The mother liquor was concentrated under reduced pressure and treated with aqueous potassium hydroxide in dioxane (4 days, ambient temperature). Extraction with ether gave 2.5 g. (20%) of a dark yellow liquid which was identified as dimethylpivalamide; nmr (deuteriochloroform): δ 1.3 (9, $(CH_3)_3C$) and 3.0 ppm (6, $(CH_3)_2N$); ms: (70 eV) 129 (M^+), 114 (M^+-CH_3), 87, 86 ($(CH_3)_3CCOH_2$)(H-transfer), 74, 73, 72 (base peak)($(CH_3)_2NCO^+$), 69, 57 ($(CH_3)_3C^+$), 44 ($(CH_3)_2N^+$), 41 ($(CH_3)_2C^+$).

REFERENCES AND NOTES

(1) J. H. Boyer, "Heterocyclic Compounds", R. C. Elderfield, Ed., Vol. 7, Wiley, New York, N. Y., 1961, p. 525.

(2) L. C. Behr, "The Chemistry of Heterocyclic Compounds", A. Weissberger, Ed., Vol. 7, Interscience Publ., New York, N. Y., 1962, Ch. 10.

(3) M. Freund and F. Kuh, *Ber.*, 23, 2821 (1890).

(4) A. Dornow and K. Brunken, *Chem. Ber.*, 82, 121 (1949).

(5) R. Boesch and J. Metivier, Belgian patent 675,562; *Chem. Abstr.*, 63, 1796 (1965).

(6) K. H. G. Pilgram, German patent 2,342,688; *Chem. Abstr.*, 80, 145845r (1974).

(7) Solvent No. 3 (by volume): Hexane (66), ethyl acetate (30), tetrahydrofuran (4).