Synthesis and Reactions of 2(5)-[Benzyl or Cyanomethyl]-1,3,4-oxadiazoles

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A series of five membered heterocycles, namely 5-(benzyl or cyanomethyl)-3-acetyl-2,2-disubstituted-1,3,4-oxadiazolines (**3a-e**), 2,5-disubstituted-1,3,4-oxadiazoles (**4a, b**), 2-hydroxy-5-(benzyl or cyanomethyl)-1,3,4-oxadiazoles (**5a, b**), 1,2,5-trisubstituted-1,3,4-triazoles (**6a, b**), and 2-(benzyl or cyanomethyl)-1,3,4-oxadiazole-5-thiols (**10a, b**), were synthesized. Also 5-chloro-2-benzyl-1,3,4-oxadiazole **7** was prepared. Reaction of amines, hydrazines, and sodium azide with **7** gave the corresponding 2-arylamino (**8a, b**), 5-hydrazino or phenylhydrazino (**8c, d**) and 2-azido derivatives **9**, respectively. Mannich bases (**11a, b**) were prepared by the reaction of sec. amines with **9a**. 5-Carboxymethylthio-1,3,4-oxadiazoles (**12a, b**) and their ethyl esters (**13a, b**) were also prepared. The ester **13a** reacted with amines and hydrazines to give the corresponding amides (**14a-d**).

Synthese und Reaktionen von 2(5)-[Benzyl- oder Cyanomethyl]-1,3,4-oxadiazolen

Eine Serie fünfgliedriger Heterocylen, nämlich 5-(Benzyl- oder Cyanomethyl)-3-acetyl-2,2-disubstituierte-1,3,4-oxadiazoline (**3a-e**), 2,5-disubstituierte 1,3,4-Oxadiazole (**4a, b**), 2-Hydroxy-5-(benzyl- oder cyanomethyl)-1,3,4-oxadiazole (**5a, b**), 1,2,5-trisubstituierte 1,3,4-Triazole (**6a, b**) und 2-(Benzyl- oder Cyanomethyl)-1,3,4-oxadiazol-5-thiole (**10a, b**) wurden synthetisiert. Auch 5-Chlor-2-benzyl-1,3,4-oxadiazol (**7**) wurde hergestellt. Reaktionen von Aminen, Hydrazinen und Natriumazid mit **7** führten zu den entspr. 2-Arylamino-(**8a, b**), 5-Hydrazino- oder Phenylhydrazino (**8c, d**) und 2-Azido-Derivaten (**9**). Sek. Amine reagieren mit **9a** zu den Mannich-Basen **11a, b**. Auch die 5-Carboxymethylthio-1,3,4-oxadiazole (**12a, b**) wurden hergestellt, desgleichen die entspr. Ethylester **13a, b**. Der Ester **13a** reagierte mit Aminen und Hydrazinen zu den entspr. Amiden **14a-d**.

A considerable number of 1,3,4-oxadiazole derivatives were found to have bactericidal, analgesic, muscle relaxant and tranquilizing properties[1-5]. 5-Aryl-2-thiono-1,3,4-oxadiazoles have analgesic, antipyretic, antiphlogistic properties[6,7] and show antitubercular activity[8]. This manuscript describes the synthesis and reactions of some 1,3,4-oxadiazoles.

Thus, 2-cyano (or phenyl) ethanoic acid hydrazides **1a, b** were condensed with selected carbonyl compounds to give the hydrazones **2a, f**, which upon treatment with acetic anhydride afforded the corresponding 5-benzyl- (or cyanomethyl)-3-acetyl-2,2-disubstituted-1,3,4-oxadizolines **3a, e**.

Interaction of the hydrazide **1a** or **b** with aliphatic or aromatic acid chlorides in pyridine yielded the corresponding N,N'-diacylhydrazines as unisolated intermediates, which upon reflux with $POCl_3$[9] or acetic anhydride gave the expected 2,5-disubstituted-1,3,4-oxadiazoles **4a, b**. Prolonged heating of **4a** with the appropriate aliphatic primary amine in xylene yielded the corresponding triazole derivatives **6a, b**.

Refluxing of equimolar amounts of **1a** or **b** and $ClCOOC_2H_5$ produced 2-hydroxy-5-(benzyl or cyanomethyl)-1,3,4-oxadiazoles **5a, b**. **5a** reacted with $SOCl_2$[10] to give 5-chloro-2-benzyl-1,3,4-oxadiazole (**7**).

When N-nucleophiles[10] such as aniline, p-toluidene, hydrazine hydrate, and phenylhydrazine were reacted with **7**, 2-arylamino, hydrazino, or phenylhydrazino-5-benzyl-1,3,4-oxadiazoles **8a-d** were readily obtained. On the other hand when **7** was reacted with NaN_3 in boiling acetic acid, the 2-azido derivative **9** was obtained.

Condensation of hydrazide **1a** or **b** with KOH and CS_2 in ethanol[11] gave the corresponding 2-(benzyl or cyanomethyl)-1,3,4-oxadiazol-5-thiols **10a, b**. Evidently[12], these compounds exist as thiol-thione equilibrium:

Thus, compound **10a** reacted with piperidine or morpholine in the presence of formaldehyde to give the expected *Mannich* bases[13] **11a, b**. On the other hand 2-(benzyl or cyanomethyl)-5-carboxymethylthio-1,3,4-oxadiazoles **12a, b** and their esters **13a, b** were obtained by condensation of **10a** and **b** with chloroacetic acid in alkaline medium or with ethyl bromoacetate in the presence of NaOH[14], respectively.

The ester **13a** reacted readily with prim. aromatic amines and hydrazines, namely: aniline, p-toluidene, hydrazine hydrate, and phenylhydrazine giving the corresponding amides, hydrazide, and phenylhydrazide derivatives **14a-d**, respectively.

Experimental Part

Melting points: uncorrected. - IR spectra (KBr): Pye-Unicam SP 1000 ($\bar{\nu}$ in cm-1). - 1H-NMR-spectra (CDCl3): Varian EM-390-90 MHz, TMS as internal reference (chemical shift d in ppm).

N-Arylidene-N'-(cyanoacetyl or phenylacetyl)-hydrazine **2a-f**

The appropriate carbonyl compound (0.01 mol) was added to a hot solution of **1a** or **b** (0.01 mol) in 50 ml ethanol and the mixture was refluxed for 1 h. The solid which separated on cooling was washed with ethanol and recrystallized from the proper solvent (Table 1).

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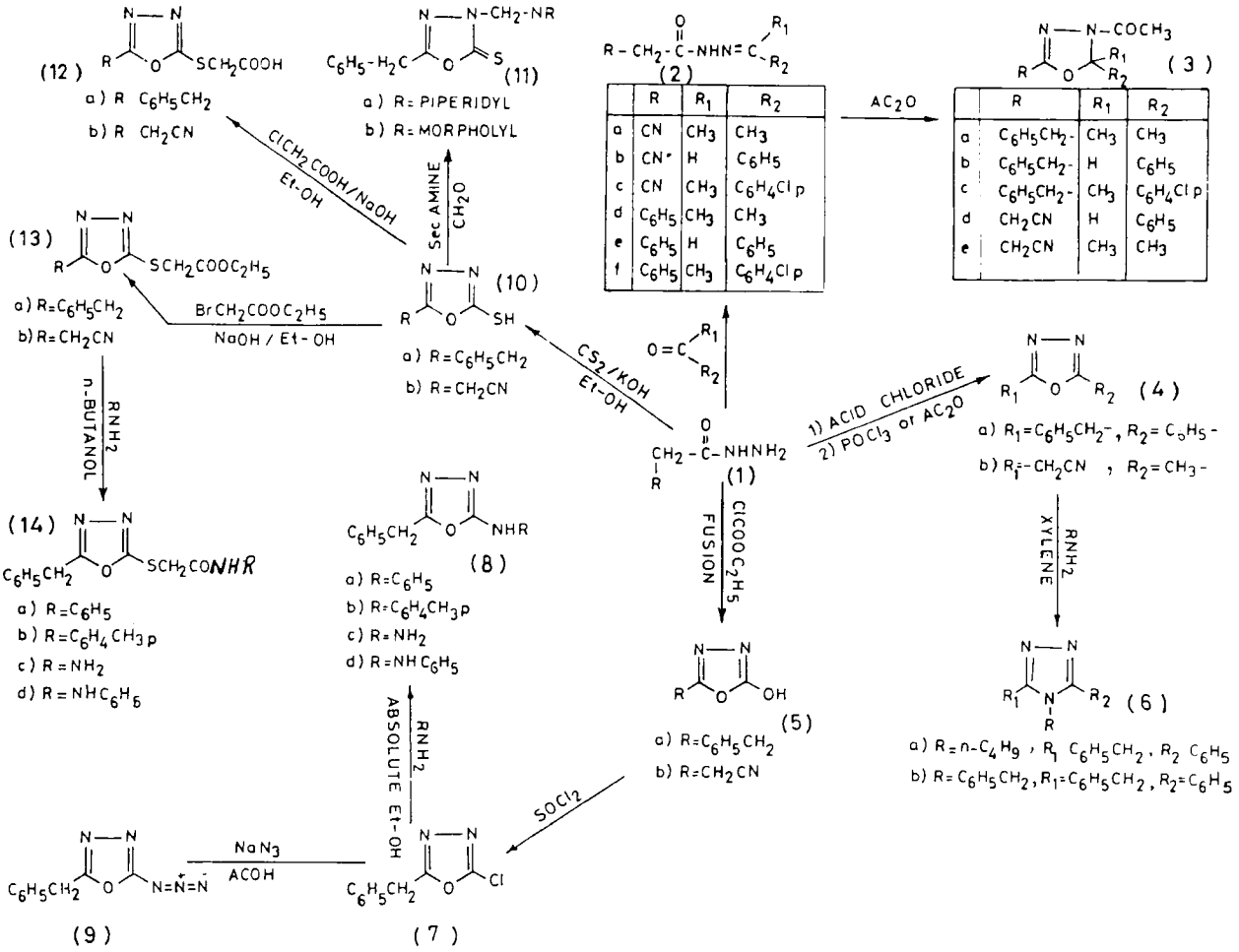

	R	R_1	R_2
a	CN	CH_3	CH_3
b	CN	H	C_6H_5
c	CN	CH_3	C_6H_4Cl p
d	C_6H_5	CH_3	CH_3
e	C_6H_5	H	C_6H_5
f	C_6H_5	CH_3	C_6H_4Cl p

	R	R_1	R_2
a	$C_6H_5CH_2$-	CH_3	CH_3
b	$C_6H_5CH_2$-	H	C_6H_5
c	$C_6H_5CH_2$-	CH_3	C_6H_4Cl p
d	CH_2CN	H	C_6H_5
e	CH_2CN	CH_3	CH_3

5-(Benzyl or cyanomethyl)-3-acetyl-2,2-disubstituted-1,3,4-oxadiazolines **3a-e**

The appropriate hydrazine **2a-f** (2g) was heated under reflux with acetic anhydride (10 ml) for 30 min. After cooling, the mixture was poured onto 100 g crushed ice and stirred for 20 min. The separated solid was washed with water and recrystallized from the suitable solvent (Table 1). The solid was washed with water and recrystallized from the suitable solvent (Table 1). The IR-spectrum of **3a** exhibited bands at 1700 (C=O), 1610 (C=N), and 1250 (C-O-C). The ^{1}H-NMR spectrum of **3d** displayed signals at 8.2-7.4 (m, 6H; oxadiazoline-H and arom-H), 2.8 (s, 2H, CH_2-CN) and 2.3 (s, 3H; $COCH_3$).

2,5-Disubstituted-1,3,4-oxadiazoles **4a, b**

Preparation of N,N'-diacylhydrazines

To a solution of **1a** or **b** (0.01 mol) in 50 ml pyridine, the appropriate acid chloride (0.01 mol) was added dropwise and the mixture was heated under reflux for 20 min. On cooling, the mixture was poured onto 100 ml dil. HCl and the separated solid was washed and dried.

Cyclization of N,N'-diacylhydrazines: Formation of **4a, b**

A mixture of the appropriate N,N'-diacylhydrazine (the solid separated as described above) (0.01 mol) and 10 ml of $POCl_3$ or acetic anhydride was refluxed for 6 h. The mixture was distilled under reduced pressure and the solid which separated was crystallized from the proper solvent (Table 1).

The IR-spectrum of **4b** shows bands at 2250 (C≡N), 1630 (C=N), and 1210 cm^{-1} (C-O-C).- ^{1}H-NMR Spectrum of **4a** reveales signals at 8.6-7.8 (m, 10H; arom. H) and 2.9 (s, 2H; benzylic-H).

1,2,5-Trisubstituted-1,3,4-triazoles **6a, b**

To a solution of **4a** (0.01 mol) in 40 ml xylene, the appropriate primary aliphatic amine (0.02 mol) was added and the mixture was refluxed for 12 h. On cooling a solid precipitated which was washed with xylene and crystallized from the proper solvent (Table 1).

The IR-spectrum of **6b** shows bands at 1650 (C=N) and at 1000 cm^{-1} (C-N). - The ^{1}H-NMR spectrum of the same compound displays signals at 7.9-7.3 (m, 15H; arom. H), and 2.7 (s, 4H; benzylic-H).

2-Hydroxy-5-(benzyl or cyanomethyl)-1,3,4-oxadiazoles **5a, b**

After refluxing **1a** or **b** (0.01 mol) with ethyl chloroformate (0.01 mol) in an oilbath for 3 h the separated solid was recrystallized from the suitable solvent, forming **5a, b.**

The IR-spectrum of **5a** shows bands at 1700 (C=O), and 3250 cm^{-1} (N-H) (these bands confirm the assumption that **5a** exits as the keto tautomer), and 1620 cm^{-1} (C=N). - The ^{1}H-NMR spectrum of **5b** exhibits signals at 2.6 (s, 2H; CH_2-CN) and 2.2 (broad, s, 1H; O-H or N-H).

5-Chloro-2-benzyl-1,3,4-oxadiazole (**7**)

$SOCl_2$ (10 ml) was added dropwise to **5a** (0.01 mol), the mixture was warmed on a water bath for 7 h, cooled and then poured onto 100 ml

Table 1: Analytical data of compounds **2** - **14**.

Comp. No.	M.P. °C Solvent	Yield %	Molecular-Formula (Mol. Wt)	Analysis Calcd/Found C	H	N
2a	149-150	85	$C_6H_9N_3O$	51.8	6.52	30.2
	Et-OH		(139-2)	51.6	6.44	30.1
2b	183	82	$C_{10}H_9N_3O$	64.2	4.85	22.
	Et-OH		(187.2)	64.1	4.72	22.5
2c	190	75	$C_{11}H_{10}N_3ClO$	56.1	4.28	17.8
	Et-OH		(235.7)	55.9	4.15	17.7
2d	109-111	80	$C_{11}H_{14}N_2O$	69.5	7.42	14.7
	Et-OH		(190.3)	69.3	7.29	14.6
2e	146-148	87	$C_{15}H_{14}N_2O$	75.6	5.92	11.8
	n-Pr-OH		(238.3)	75.5	5.90	11.6
2f	164-166	79	$C_{16}H_{15}N_2ClO$	67.0	5.27	9.8
	n-Pr-OH		(286.8)	66.8	5.10	9.7
3a	160	48	$C_{12}H_{16}N_2O_2$	67.2	6.94	12.1
	n-Pr-OH		(232.3)	67.0	6.84	12.0
3b	220	52	$C_{17}H_{16}N_2O_2$	72.8	5.75	10.0
	Me-OH		(280.3)	72.6	5.66	9.8
3c	213-215	45	$C_{18}H_{17}N_2ClO_2$	65.8	5.21	8.5
	Me-OH		(328.8)	65.5	5.20	8.4
3d	150 dil ACOH	55	$C_{12}H_{11}N_3O_2$ (229.2)	62.9 62.6	4.84 4.7	18.3 18.2
3e	>280 dil ACOH	43	$C_9H_{11}N_3O_2$ (181.2)	53.0 52.9	6.12 6.1	23.2 22.9
4a	104-105	65	$C_{15}H_{12}N_2O$	76.3	5.12	11.9
	Et-OH		(236.3)	76.1	4.8	11.6
4b	85.86	54	$C_5H_5N_3O$	48.8	4.09	34.1
	Et-OH		(123.1)	48.5	3.8	34.1
5a	225	68	$C_9H_8N_2O_2$	61.4	4.58	15.9
	Dioxane		(176.2)	61.2	4.4	15.6
5b	203	60	$C_4H_3N_3O_2$	38.4	2.42	33.6
	Dioxane		(125.1)	38.3	2.3	33.4
6a	144	38	$C_{19}H_{21}N_3$	78.3	7.26	14.4
	Benzene		(291.4)	78.1	7.2	14.3
6b	162	32	$C_{22}H_{19}N_3$	81.2	5.89	12.9
	Et-OH		(325.4)	80.9	5.6	12.7
7	140	75	$C_9H_7N_2ClO$	55.5	3.63	14.4
	Me-OH		(194.6)	55.3	3.4	14.1

petrolum ether (60-80°C). The precipitate was crystallized from the suitable solvent (Table 1).

2-Arylamino-5-benzyl-1,3,4-oxadiazoles **8a, b**

To a solution of **7** (0.01 mol) in 30 ml ethanol, the appropriate amine (0.01 mol) was added and the reaction mixture was refluxed for 4 h. The mixture was concentrated and the precipitate was recrystallized from the proper solvent. The IR-spectrum of 8a shows bands at 3340 (N-H). 1630 (C=N), and 1240 cm^{-1} (C-O-C). -The ^{1}H-NMR spectrum of the same compound displays signals at 8.2-7.7 (m, 10H; arom-H), 2.7 (s, 2H; benzylic-H), and 2.1 (broad s, 1H; N-H).

5-Hydrazino or phenylhydrazino-2-benzyl-1,3,4-oxadiazoles **8c, d**

To a solution of **7** (0.005 mol) in 50 ml ethanol, hydrazine hydrate (1 ml; 100%) or phenylhydrazine hydrochloride (0.005 mol), and 5 ml KOH (10%) were added. The mixture was left over night. The products which were obtained were recrystallized from the suitable solvent (Table 1).

2-Azido-5-benzyl-1,3,4-oxadiazole **(9)**

A mixture of **7** (0.01 mol), NaN_3 (0.01 mol), acetic acid (30 ml), and water (5 ml) was refluxed for 5 h. The product obtained after concentration was crystallized from the suitable solvent. The IR-spectrum of **9** reveals bands at 2150 (azide) and 1640 (C=N).

2-(Benzyl or cyanomethyl)-1,3,4-oxadiazole-5-thiols **10a, b**

A mixture of **1a** or **b** (0.1 mol), KOH (0.1 mol), and 20 ml CS_2 in 50 ml ethanol was heated under reflux and stirring on a water bath until the evolution of H_2S ceased (about 6 h). The excess solvent was removed by distillation and the residue was stirred with cold water, filtered and the filtrate was acidified with dil. HCl. The precipitated solid was washed with water and crystallized from the proper solvent (Table 1). The IR-Spectrum of **9a** shows bands at 3370 (N-H), 1220 (C-O-C), and 1280-1290 (C=S), the latter band conferms the assumption that the compound exists as the thione tautomer.

Table 1: Cont.

Comp. No.	M.P. °C Solvent	Yield %	Molecular-Formula (Mol. Wt)	Analysis Calcd/Found C	H	N
8a	179-180	71	$C_{15}H_{13}N_3O$	71.7	5.22	16.7
	Me-OH		(251.3)	71.6	5.12	16.6
8b	186	79	$C_{16}H_{15}N_3O$	72.4	5.70	15.8
	Me-OH		(265.3)	72.3	5.63	15.6
8c	201-202	62	$C_9H_{10}N_4O$	56.8	5.30	29.5
	Dioxane		(190.2)	56.6	5.25	29.3
8d	162	75	$C_{15}H_{14}N_4O$	67.7	5.30	21.0
	Me-OH		(266.3)	67.5	5.14	21.0
9	>280	55	$C_9H_7N_5O$	53.7	3.51	34.8
	D.M.F		(201.2)	53.6	3.45	34.7
10a	125	83	$C_9H_8N_2OS$	56.2	4.20	14.6
	Et-OH		(192.3)	56.1	4.10	14.4
10b	158-160	52	$C_4H_3N_2OS$	37.	2.38	22.0
	Et-OH		(127.2)	37.6	2.21	21.9
11a	139	43	$C_{15}H_{19}N_3OS$	62.3	6.62	14.5
	Me-OH		(289.4)	62.1	6.53	14.3
11b	150-151	60	$C_{14}H_{17}N_3O_2S$	57.7	5.88	14.4
	Me-OH		(291.4)	57.5	5.71	14.2
12a	112 dil	47	$C_{11}H_{10}N_2O_3S$	52.8	4.03	11.9
	Me-OH		(250.3)	52.5	3.8	11.7
12b	144 dil	42	$C_6H_5N_3O_3S$	36.2	2.53	21.1
	Et-OH		(199.2)	36.1	2.4	20.8
13a	98	63	$C_{13}H_{14}N_2O_3S$	56.1	5.07	10.1
	Benzene		(278.3)	55.9	4.8	10.1
13b	110	58	$C_8H_9N_3O_3S$	42.3	3.99	18.
	Benzene		(227.3)	42.1	3.7	18.2
14a	180-181	63	$C_{17}H_{15}N_3O_2S$	62.8	4.65	12.9
	Et-OH		(325.4)	62.4	4.5	12.8
14b	200-202	72	$C_{18}H_{17}N_3O_2S$	63.7	5.05	12.4
	Et-OH		(339.4)	63.6	4.9	12.2
14c	223	57	$C_{11}H_{12}N_4O_2S$	50.0	4.58	21.2
	Et-OH		(264.3)	49.7	4.4	21.1
14d	193	65	$C_{17}H_{16}N_4O_2S$	60.0	4.74	16.5
	Benzene		(340.4)	59.8	4.6	16.2

Mannich bases **11a, b**

Formaldehyd (10 ml, 40%) was added to **10a** (0.01 mol) and the mixture was heated gently untill the solution became clear. The appropriate amine (0.01 mol) in ethanol was added and the mixture was stirred at room temp. for 3 h. The mixture was evaporated gently to dryness and the residue was recrystallized from the proper solvent. The IR-spectrum of **11a** shows bands at 1640 (C=N), 1250-1270 (C=S), and 1210 (C-O-C).

2-(Benzyl or cyanomethyl)-5-carboxymethylthio-1,3,4-oxadiazoles **12a, b**

To a solution of **10a** or **b** (0.01 mol) in aqueous NaOH (30 ml, 8%), chloroacetic acid (0.94 g, 0.01 mol) was added portionwise at room temp. with vigorous shaking. The mixture was then stirred for 4 h. The clear solution was acidified with dil. HCl and the separated product was washed with water and recrystallized from the suitable solvent (Table 1). The IR-spetrum of **12b** shows bands 3400-2600 (carboxylic-OH), 2230 (C≡N), 1710 (C=O), and 1630 (C=N). - The ^{1}H-NMR-spectrum of the same compound displays signals at 11.3 (s, 1H; -COOH), 3.8 (s, 2H; -S-CH_2-COOH), and 2.4 (s, 2H; -CH_2CN).

2-(Benzyl or cyanomethyl)-5-carbethoxymethylthio-1,3,4-oxadiazoles **13a, b**

A solution of **10a** or **b** (0.01 mol) in 50 ml alcoholic NaOH was treated with ethyl bromoacetate (0.015 mol). The mixture was then heated on a water bath for 1 h. The separated solid was recrystallized from the suitable solvent (Table 1). The IR-spectrum of **13a** shows bands at 1730 (C=O), 1640 (C=N), and 1300 (C-O-C).

Amides, hydrazide and phenylhydrazide derivatives **14a-d**

A mixture of the ester **13a** (0.01 mol) and the appropriate amine or hydrazine (0.01 mol) in 50 ml n-butanol was refluxed for 6 h. The separated solid after cooling was crystallized from the proper solvent (Table 1). The IR-spectrum of **14a** shows bands at 3400 (N-H), 1670 (C=O), and 1620 cm^{-1} (C=N). Also the IR-spectrum of **14c** shows absorptions at 3350 (N-H), 1660 (C=O), and 1630 cm^{-1} (C=N).

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