Synthesis of 3-Amino-6-dimethylamino-4-oxopyrazolo[3,4-*d*][1,3]oxazine Derivatives

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Dedicated to may dear colleague Herbert Stricker, Heidelberg, with best wishes on the occasion of his 60th birthday

3-Amino-1-aryl-6-dimethylamino-4-oxo-1,4-dihydropyrazolo[3,4-*d*][1,3]oxazines **4a–7a** and 3-amino-2-aryl-6-dimethylamino-4-oxo-2,4-dihydropyrazolo[3,4-*d*][1,3]oxazines **4b–6b** were synthesized from 4-chloro-5-cyano-2-dimethylamino-6-oxo-6*H*-1,3-oxazine **2** and arylhydrazines in good yields. The substituent effect of the arylhydrazines on the yields of products was clearly observed.

Alkyl dicyanoacetates[1-9] have proved to be useful building blocks for the synthesis of heterocyclic and related compounds.[10-17] One of the interesting heterocyclic compounds we have obtained from the reactions of alkyl dicyanoacetates with *N*-(dichloromethylene)dimethylammonium chloride is 4-chloro-5-cyano-2-dimethylamino-6-oxo-6*H*-1,3-oxazine (**2**) in which the chloro atom at position 4 can be substituted easily by nucleophilic reagents such as alcohols and amines.[10] Therefore, it was of interest to investigate reactions of **2** with binucleophiles like arylhydrazines.

We have found that **2** reacts in dichloromethane at room temperature with phenylhydrazine **1A** to yield the fused heterocyclic compounds 3-amino-6-dimethylamino-1-phenyl-4-oxo-1,4-dihydropyrazolo[3,4-*d*][1,3]oxazine (**4a**) and 3-amino-6-dimethylamino-2-phenyl-4-oxo-2,4-dihydropyrazolo[3,4-*d*][1,3]oxazine, (**4b**) (Scheme **1**) which were separated by column chromatography. The chloro atom at position 4 of **2** must be first substituted by one of the nitrogen atoms of phenylhydrazine followed by nucleophilic addition of the other nitrogen atom to the cyano group at position 5 of the 1,3-oxazine intermediates **3a** and **3b**. Intermediates **4α** and **4β** are then tautomerized to **4a** and **4b**. The structures of **4a** and **4b** can be distinguished from each other by means of NMR methods since the amino group of **4b** at position 5 gave NOE with the protons of the phenyl group and that of **4a** did not.

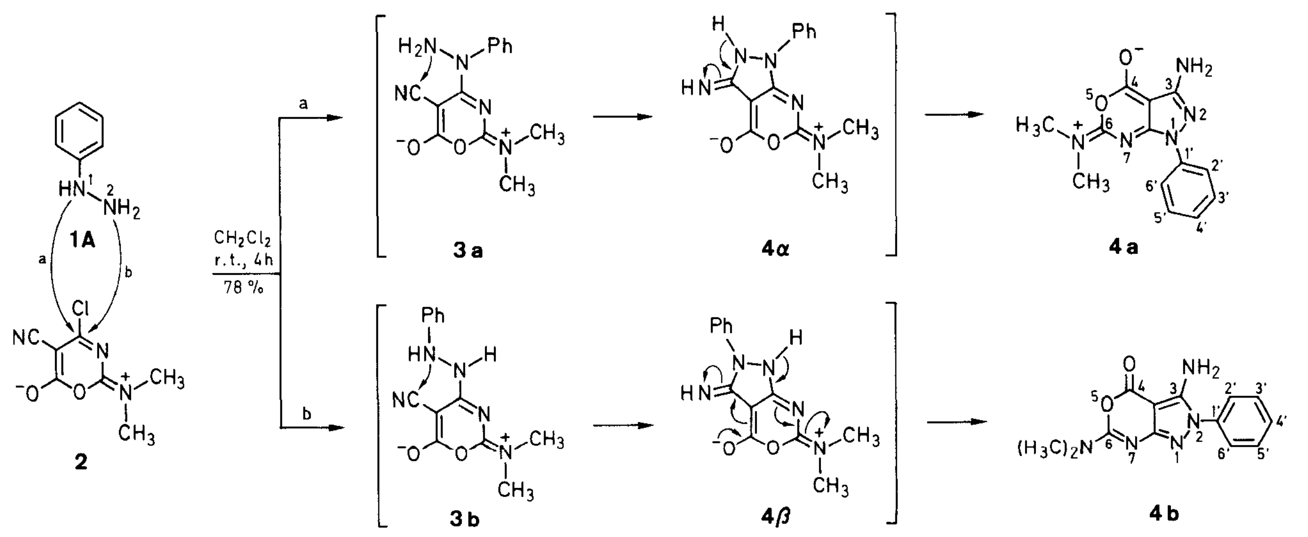
Similarly, the reaction of the hydrochloride salts of arylhydrazines **1B–1D** with **2** in dichloromethane at room temperature followed by reflux in the presence of triethylamine afforded the corresponding 4-oxo-pyrazolo[3,4-*d*][1,3]oxazine derivatives **5–7** in good yield (Scheme **2**). The mechanism of this reaction should be the same as shown in Scheme **1**.

An electron-withdrawing group such as a chloro atom at the phenyl ring decreases the electron density at N-1 of the arylhydrazine, consequently the yield of **5a** is lower than that of **5b**. The methoxy group increases the electron density at N-1 now **7a** was formed predominantely and **7b** could not be observed (Table 1).

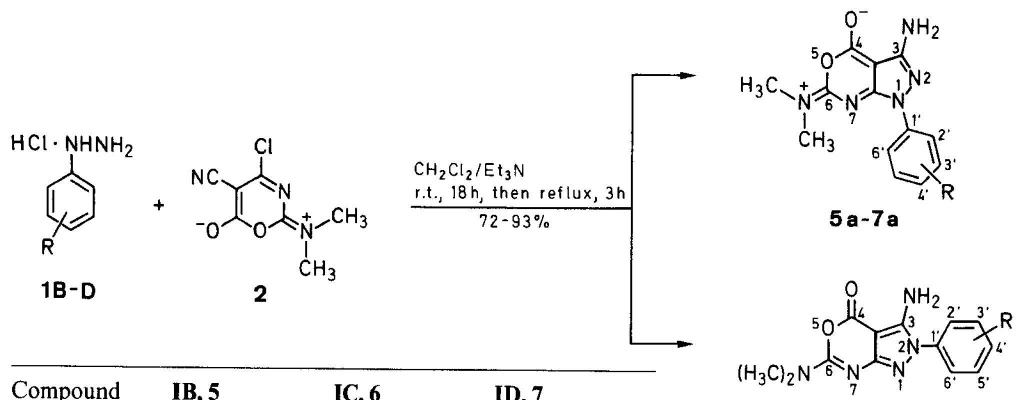
Table 1. 4-Oxopyrazolo[3,4-*d*][1,3]oxazines **4–7** Prepared

Product	R	Yield (%)[a]	Yield **a+b**	R_f	Molecular[b] Formula	mp (°C)
4a	H	48	78	0.45	$C_{13}H_{13}N_5O_2$ (271.3)	207–208
4b	H	30		0.26	$C_{13}H_{13}N_5O_2$ (271.3)	209–211
5a	3-Cl	28	80	0.50	$C_{13}H_{12}ClN_5O_2$ (305.7)	179–180
5b	3-Cl	52		0.33	$C_{13}H_{12}ClN_5O_2$ (305.7)	201–202
6a	4-Me	72	72	0.53	$C_{14}H_{15}N_5O_2$ (285.3)	211–214
6b	4-Me	trace		0.31		–
7a	4-MeO	93	93	0.47	$C_{14}H_{15}N_5O_2$ (285.3)	204–206
7b	4-MeO	–		–		–

[a] Yields of pure products.
[b] Satisfactory microanalysis obtained: C ±0.25, H ±0.19, N ±0.30.



Scheme 1



Compound	IB, 5	IC, 6	ID, 7
R	3-Cl	4-Me	4-MeO

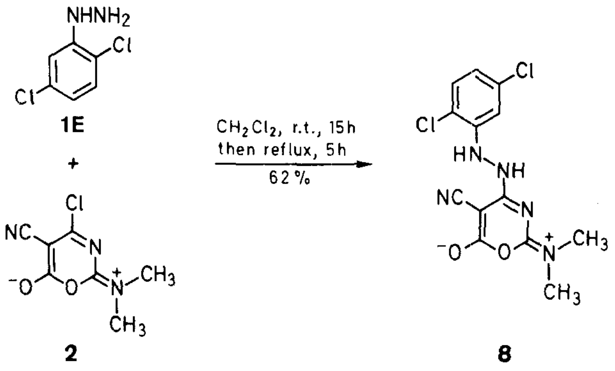
Scheme 2

Table 2. Compounds 4–7 Prepared

Prod-uct	UV (MeCN) λ_{max} (nm) (log ε)	IR (KBr) ν (cm^{-1})	^{1}H-NMR ($CDCl_3/CD_2Cl_2$)[a] δ	^{13}C-NMR ($CDCl_3/CD_2Cl_2$)[a] δ	MS (80 eV) m/z (%)
4a	232 (4.322), 260 (4.284), 310 (3.988)	3410(w), 3370(w), 1760(s), 1615(s)	3.21 (s, 6H, =$N(CH_3)_2$), 4.55 (brs, 2H, NH_2), 7.19–7.25 (m, 1H, 4′-H), 7.42 (t, 2H, 3′-, 5′-H), 7.94 (dd, 2H, 2′-, 6′-H)	36.8 (q, =$N(CH_3)_2$), 37.6 (q, =$N(CH_3)_2$), 84.3 (s, C-3a), 120.5 (d, C-2′, C-6′), 125.5 (d, C-4′), 128.8 (d, C-3′, C-5′), 138.9 (s, C-1′), 152.0 (s, C-3), 153.8 (s, C-6), 155.2 (s, C-4), 158.6 (s, C-7a)	271 (M^+, 68), 227 (M^+-$N(CH_3)_2$, 100)
4b	250 (4.617)	3430(w), 3330(w), 1760(s), 1635(s)	3.16 (s, 6H, $N(CH_3)_2$), 5.15 (s, 2H, NH_2), 7.35–7.50 (m, 1H, 4′-H), 7.57 (t, 2H, 3′-, 5′-H), 7.59 (d, 2H, 6′-H)	37.2 (q, =$N(CH_3)_2$), 83.0 (s, C-3a), 123.6 (d, C-2′, C-6′), 128.0 (d, C-4′), 129.8 (d, C-3′, C-5′), 137.4 (s, C-1′), 145.9 (s, C-3), 156.8 (s, C-6), 157.3 (s, C-4), 158.4 (s, C-7a)	271 (M^+, 63), 227 (M^+-$N(CH_3)_2$, 100)
5a	225 (4.396), 260 (4.304), 310 (4.043)	3410(w), 3360(w), 1760(s), 1620(s)	3.19 (s, 6H, =$N(CH_3)_2$), 4.57 (brs, 2H, NH_2), 7.18 (td, 1H, 6′-H), 7.35 (t, 1H, 5′-H), 8.00 (td, 1H, 4′-H), 8.15 (t, 1H, 2′-H)	37.0 (−, =$N(CH_3)_2$), 37.9 (−, =$N(CH_3)_2$), 84.8 (+, C-3a), 118.3 (−, C-6′), 120.4 (−, C-2′), 125.2 (−, C-4′), 130.3 (−, C-5′), 134.7 (+, C-3′), 140.6 (+, C-1′), 152.4 (+, C-3), 155.2 (+, C-4), 159.2 (+, C-7a)	307 (M^+ + 2, 30), 305 (M^+, 91), 261 (M^+-$N(CH_3)_2$, 100)
5b	250 (4.614)	3430(w), 3320(w), 1760(s), 1640(s)	3.16 (s, 6H, $N(CH_3)_2$), 5.30 (s, 2H, NH_2), 7.33–7.50 (m, 3H, 4′-, 5′-, 6′-H), 7.61 (s, 1H, 2′-H)	37.3 (−, $N(CH_3)_2$), 83.5 (+, C-3a), 122.7 (−, C-6′), 124.0 (−, C-2′), 128.2 (−, C-4′), 131.2 (−, C-5′), 135.7 (+, C-3′), 19.2 (+, C-1′), 146.8 (+, C-3), 156.8 (+, C-6), 157.7 (+, C-4), 158.8 (+, C-7a)	307 (M^+ + 2, 30), 305 (M^+, 91), 261 (M^+-$N(CH_3)_2$, 100)
6a	230 (4.572), 260 (4.328), 305 (4.002)	3430(w), 3320(w), 1760(s), 1640(s)	2.36 (s, 3H, $PhCH_3$), 3.19 (s, 6H, =$N(CH_3)_2$), 4.55 (brs, 2H, NH_2), 7.21 (d, 2H, 2′-, 6′-H), 7.85 (t, 1H, 3′-, 5′-H)	21.0 (q, $C_6H_4CH_3$), 36.8 (q, =$N(CH_3)_2$), 37.5 (q, =$N(CH_3)_2$), 84.1 (s, C-3a), 120.6 (d, C-2′, C-6′), 129.4 (d, C-3′, C-5′), 135.3 (s, C-4′), 136.4 (s, C-1′), 151.9 (s, C-3), 153.5 (s, C-6), 155.3 (s, C-4), 158.5 (s, C-7a)	285 (M^+, 76), 241 (M^+-$N(CH_3)_2$, 100)
7a	230 (4.300), 260 (4.255), 295 (3.986)	3460(w), 3380(w), 1760(s), 1610(s)	3.18 (s, 6H, =$N(CH_3)_2$), 3.83 (s, 3H, OCH_3), 4.56 (brs, 2H, NH_2), 6.94 (d, 2H, 3′-, 5′-H), 7.86 (t, 1H, 2′-, 6′-H)	36.7 (−, =$N(CH_3)_2$), 37.6 (−, =$N(CH_3)_2$), 55.5 (−, OCH_3), 83.9 (+, C-3a), 114.0 (−, C-3′, C-5′), 122.1 (−, C-2′, C-6′), 132.2 (+, C-1′), 151.9/153.1/155.3/157.4/158.5 (5+, C-3/C-6/C-4/C-4′/C-7a)	301 (M^+, 95), 261 (M^+-$N(CH_3)_2$, 100)

[a] $CDCl_3$ for **4a**, **4b**, **6a**, **7a**; CD_2Cl_2 for **5a**, **5b**; ^{13}C-NMR: spin-echo for **5a**, **5b**, **7a**.

If the electron density at N-1 was further decreased, e.g. R = 2,5-*dichloro, the only* product obtained was the ring opening compound **8** which was formed by substitution of the chloro atom of **2** by N-2 of 2,5-dichlorophenylhydrazine **1E** (Scheme 3).



Scheme 3

Melting points were determined on a Reichert hot stage microscope and are uncorrected. Microanalyses were performed on a Heraeus automatical analyser. UV spectra were recorded on a Carl Zeiss DMR 10 spectrophotometer and IR spectra on a Perkin-Elmer 325 spectrophotometer. NMR spectra were recorded on a Bruker WM-250 spectrometer (for ^{1}H-NMR at 250.13 MHz, for ^{13}C-NMR at 62.89 MHz). Mass spectra were obtained on a Varian MAT 311A instrument.

3-Amino-6-dimethylamino-1-phenyl-4-oxo-1,4-dihydropyrazolo[3,4-*d*][1,3]oxazine (4a) and 3-Amino-6-dimethylamino-2-phenyl-4-oxo-2,4-dihydropyrazolo[3,4-*d*][1,3]oxazine (4b):

A solution of 4-chloro-5-cyano-2-dimethylamino-6-oxo-6*H*-1,3-oxazine (**2**) (199.6 mg, 1 mmol) and phenylhydrazine (**1A**) (0.5 mL) in abs. CH_2Cl_2 (30 mL) is stirred at r.t. for 4 h and then washed with dil. H_2SO_4 (2 mL) and water (10 mL). The organic phase is dried ($MgSO_4$). After filtration the solvent is removed and the residue is chromatographed on silica gel with EtOAc as eluent. For yields and physical data see Tables 1 and 2.

3-Amino-1-(3'-chlorophenyl)-6-dimethylamino-4-oxo-1,4-dihydropyrazolo[3,4-*d*][1,3]oxazine (5a) and 5-Amino-2-(3'-chlorophenyl)-6-dimethylamino-4-oxo-2,4-dihydropyrazolo[3,4-*d*][1,3]oxazine (5b); Typical Procedure:

Et_3N (0.3 mL) is added to a suspension of 3-chlorophenylhydrazine hydrochloride (**1B**) (179 mg, 1 mmol) and 4-chloro-5-cyano-2-dimethylamino-6-oxo-6*H*-1,3-oxazine (**2**) (199.6 mg, 1 mmol) in abs. CH_2Cl_2 (7 mL). The suspension is stirred at r.t. for 18 h and then refluxed for 3 h. After filtration the solvent is removed and the residue is then isolated by column chromatography (silica gel, EtOAc). For yields and physical data see Tables 1 and 2.

5-Cyano-4-(2',5'-dichlorophenylhydrazino)-2-dimethylamino-6-oxo-6*H*-1,3-oxazine (8):

A solution of 4-chloro-5-cyano-2-dimethylamino-6-oxo-6*H*-1,3-oxazine (**2**) (199.6 mg, 1 mmol) and 2,5-dichlorophenylhydrazine (**1E**) (177 mg, 1 mmol) in abs. CH_2Cl_2 (10 mL) is stirred at r.t. for 15 h and then refluxed for 5 h. The solution is washed with water (10 mL) and dried ($MgSO_4$). After filtration the solvent is removed and the residue is purified by column chromatography (silica gel, EtOAc) to give white crystals; yield: 210 mg (62%), mp 208–210 °C.

		C	H	Cl	N
$C_{13}H_{11}ClN_5O_2$	calc.	45.90	3.26	20.84	20.59
(340.18)	found	45.94	3.32	20.93	20.46

IR (KBr): ν = 3340, 3100, 2220, 1735, 1635 cm^{-1}.

UV (MeCN): λ_{max} (log ε) = 210 (4.538), 225 (4.475), 240 (4.348), 290 nm (4.239).

^{1}H-NMR ($CDCl_3$/TMS): δ = 3.02–3.14 (s, 6 H, $N(CH_3)_2$), 6.69 (d, 1 H, NH), 6.86 (dd, 1 H, 4'-H), 691 (s, 1 H, 6'-H), 7.22 (d, 1 H, 3'-H), 7.45 (s, 1 H, NH).

MS (80 eV, 100 °C): *m/z* (%) = 341 (M^+ + 2, 4), 339 (M^+, 7), 304 (M^+ − Cl), 72 (C_3H_6NO, 100).

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