A Mild and Convenient Synthesis of Ethyl 2-Phenyl- and 2-(3-Pyridazine)-diazenecarboxylates (Azocarboxylates)

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Oxidation of aromatic hydrazinecarboxylates can be performed with a variety of strong oxidants including chromium trioxide[1], potassium permanganate[2], lead(IV) acetate[2], mercury(II) oxide[2], nitric acid[3], and chlorine[4]. Air, widely used for the oxidation of various hydrazo compounds[5,6], has not been thus far employed in the preparation of aromatic diazenecarboxylates.

We now report a new oxidative procedure for preparing ethyl 2-aryldiazenecarboxylates **2** which involves bubbling air into a toluene solution of ethyl 2-arylhydrazinecarboxylates **1** at room temperature in the presence of 10% palladium on charcoal (Table). Platinum oxide (Adams catalyst) freshly reduced may be used as well. The reaction conditions and yields are the same as those obtained with palladium, but the latter is cheaper.

$$\underset{\textbf{1a-g}}{Ar{-}NH{-}NH{-}COOC_2H_5} \xrightarrow{air/Pd-C} \underset{\textbf{2a-g}}{Ar{-}N{=}N{-}COOC_2H_5}$$

Whenever the hydrazinecarboxylates **1** are not sufficiently soluble in toluene, dioxan can be employed as solvent. In this case, before evaporation in vacuo, a suitable treatment is advised in order to destroy the possibly present peroxy compounds [e.g. by passing the solution through a column of alumina][7]. If ethanol, rather than toluene, is employed as the solvent, partial decomposition of the final products might take place, especially in the case of low rate oxidations (e.g. **2f**). This is indicated by the heterolysis of the diazenecarboxylates to unstable diazene intermediates which, in turn, afford a mixture of products[2]. This behaviour may account for the decomposition of cadralazine (**1d**) in aqueous solution[8].

The oxidation of ethyl 2-(6-chloro-3-pyridazine)-hydrazinecarboxylate (**1f**) gives the diazenecarboxylate **2f** in very low yield, probably because of the electron with-drawing effect of the chlorine substituent. The same deactivating effect by the newly formed diazenecarboxylate group may also explain the selective oxidation of the bis-hydrazinecarboxylate **1e** to **2e**. In contrast, oxidation of **1e** with concentrated nitric acid is reported[3] to afford diethyl 2,2-(pyridazin-3,6-diyl)-bis[diazenecarboxylate].

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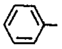
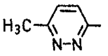
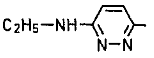
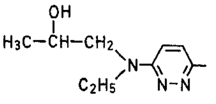
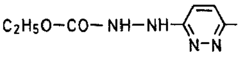
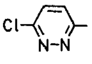
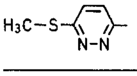
Table. Ethyl 2-Phenyl- and 2-(3-Pyradizine)-diazenecarboxylates **2a-g** prepared

Ar in **1**	Product[a]	Yield [%]	Solvent/ reaction time	m.p. [°C] or b.p. [°C]/torr	Molecular formula[b] or Lit. b.p. [°C]/torr	U.V. (CH_3OH) λ_{max} [nm] (ε)
	**2a**	98	toluene[c]/4 h	110°/0.5	108°/0.5	286 (5471)
	**2b**	40[d]	dioxan/48 h	74-76° (i-C_3H_7OH)	$C_8H_{10}N_4O_2$ (194.2)	258 (7527); 420 (75)
	**2c**	98	dioxan/4 h	170-172° (toluene/hexane)	$C_9H_{13}N_5O_2$ (223.2)	225 (6029); 360 (14512)
	**2d**	95 95 48	toluene/4 h dioxan/4 h ethanol[c]/5 h	79-80° (toluene/hexane)	$C_{12}H_{19}N_5O_3$ (281.3)	230 (8625); 378 (17418)
	**2e**	85	dioxan/14 h	102-105° (dec, toluene)	$C_{10}H_{14}N_6O_4$ (282.3)	333 (9750)
	**2f**	10	dioxan[e]/48 h	64-65° [i-C_3H_7OH/(i-C_3H_7)$_2$O]	$C_7H_7ClN_4O_2$ (214.6)	256 (8125)
	**2g**	30[d]	dioxan/48 h	75-76° (toluene/hexane)	$C_8H_{10}N_4O_2S$ (226.2)	232 (6530); 334 (12244)

[a] Purity of products checked by T.L.C. on silica gel using 9 : 1 chloroform/methanol. I.R. and ^{1}H-N.M.R. spectra are in accord with the assigned structures.

[b] Satisfactory microanalyses obtained: C ±0.40, H ±0.20, N ±0.30.

[c] When ethanol is used as solvent, **2a** is obtained in a form difficult to purify.

[d] After purification by column chromatography on Florisil®, eluting with 80 : 20 ethyl acetate/hexane.

[e] Oxidation in ethanol affords a mixture of products which is separated by column chromatography on Florisil®, eluting with 99.5 : 0.5 chloroform/methanol.

Finally, this mild method is applicable to substrates which are sensitive to the commonly used oxidizing agents. For example, reaction of cadralazine (**1d**) with pyridinium chlorochromate in dry dichloromethane results in degradation of the alkylamino side chain. Oxidation of ethyl 2-(1-phthalazine)-hydrazinecarboxylate (binazine) under the described conditions gives rise to a mixture of decomposition products, probably resulting from the high instability of the hydrazine derivative. Use of stronger oxidants such as potassium permanganate or chromium trioxide leads to destruction of the heterocyclic ring. The present method is also applicable to the oxidation of acylhydrazine derivatives, e.g. oxidation of N-phenyl-N'-benzoylhydrazine in toluene affords the corresponding azo compound in 98% yield (see Ref.[2]).

I.R. spectra were measured on a Perkin-Elmer Model 157 spectrophotometer. ^{1}H-N.M.R. spectra were recorded on a Perkin-Elmer R-12B spectrometer using TMS as internal standard and U.V. spectra on a Beckman DB-GT spectrophotometer fitted with a W-W recorder.

Ethyl 2-(6-Methyl-3-pyridazine)-hydrazinecarboxylate (1b):

The compound is prepared by the reaction of 3-chloro-6-methylpyridazine[9] and ethyl hydrazinecarboxylate in boiling ethanol for 48 h. After cooling, the solvent is removed in vacuo, the residue is taken up with chloroform, washed with water, and dried with sodium sulfate. Evaporation of the solvent gives **1b**; yield: 60%; m.p. 142-143 °C (from isopropanol).

$C_8H_{12}N_4O_2$	calc.	C 48.97	H 6.16	N 28.55
(196.2)	found	49.05	6.11	28.50

I.R. (oil mull): ν = 1760 cm^{-1} (C=O).

Ethyl 2-(6-Ethylamino-3-pyridazine)-hydrazinecarboxylate (1c):

Similarly prepared from 3-chloro-6-ethylaminopyridazine[10] in boiling isopentyl alcohol; yield: 60%; m.p. 219-220 °C.

$C_9H_{15}N_5O_2$	calc.	C 47.99	H 6.71	N 31.09
(225.2)	found	47.80	6.60	30.96

I.R. (oil mull): ν = 1725 cm^{-1} (C=O).

Ethyl 2-(6-Chloro-3-pyridazine)-hydrazinecarboxylate (1f):

Prepared similarly from 3,6-dichloropyridazine in boiling ethanol; yield: 70%; m.p. 154-156 °C.

$C_7H_9ClN_4O_2$	calc.	C 38.81	H 4.19	Cl 16.37	N 25.86
(216.6)	found	38.75	4.21	16.24	25.66

I.R. (oil mull): ν = 1715 cm^{-1} (C=O).

Ethyl 2-(6-Methylthio-3-pyridazine)-hydrazinecarboxylate (1g):

Prepared similarly from 3-chloro-6-methylthiopyridazine[11] in boiling isopentyl alcohol; yield: 88%; m.p. 65-68 °C.

$C_8H_{12}N_4O_2S$	calc.	C 42.09	H 5.30	N 24.54
(228.3)	found	42.19	5.25	24.46

I.R. (oil mull): ν = 1740 cm^{-1} (C=O).

The other hydrazinecarboxylates **1a**[2], **1d**[12], and **1e**[3] were prepared as described in the literature.

Ethyl 2-{6-[(2-hydroxypropyl)-ethylamino]-3-pyridazine}-diazenecarboxylate (2d); Typical Procedure:

A two-necked reaction flask equipped with magnetic stirrer is charged with ethyl 2-{6-[(2-hydroxypropyl)ethylamino]-3-pyridazine}-hydrazinecarboxylate[12] (**1d**; 2.83 g, 0.01 mol), toluene (150 ml), and 10% palladium on charcoal (0.3 g). One neck of the flask is connected with an aspirator and the other neck is open to the atmosphere through a concentrated sulfuric acid bubbler. The mixture is stirred at room temperature for 4 h while air is bubbled through the solution. The catalyst is filtered and the solvent removed under reduced pressure. The red oily residue solidifies when taken up with isopropyl ether. After filtration, the solid is crystallized from toluene/hexane to give **2d**; yield: 2.67 g (95%); m.p. 79-80 °C.

$C_{12}H_{19}N_5O_3$	calc.	C 51.24	H 6.81	N 24.90
(281.3)	found	51.35	6.92	25.09

I.R. (oil mull): ν = 1750 cm^{-1} (C=O).

^{1}H-N.M.R. (CDCl$_3$): δ = 1.17 (t, 3 H, J = 6.6 Hz); 1.23 (d, 3 H, J = 5.5 Hz); 1.41 (t, 3 H, J = 6.6 Hz); 3.4-3.9 (m, 4 H); 4.1-4.5 (m, 1 H); 4.44 (s, 1 H); 4.45 (q, 2 H, J = 6.6 Hz); 7.00, 7.60 ppm (AB q, 2 H, J = 9.7 Hz).

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