Preparation of Azolopyridazinecarboxylic Acids [1]

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Oxidation reactions of various methyl substituted azolopyridazines **2a-d**, **3a-h**, **4a,b** were investigated in order to gain access to the title compounds. This procedure was found to be of limited scope affording only the carboxylic acids **5**, **7** and **9**. A variety of novel azolopyridazinecarboxylic acid methyl esters bearing one or two methoxycarbonyl groups at the pyridazine core **17**, **18** and **12**, **14**, **16**, **20**, respectively, however, could be prepared by means of a regioselective radical substitution process.

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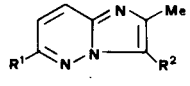
The chemistry of azolo- and azinopyridazines has been of major interest of many research groups and there are numerous derivatives with substituents attached either to the five- or to the six-membered ring described in the literature [2]. However, carboxy substituted compounds and their derivatives are rare. They have been mostly synthesized by cyclization of appropriate starting materials to which a carboxy group (or a derivative thereof) already has been attached. In this manner, 6-chloro-3-ethoxycarbonyl-2-methylimidazo[1,2-*b*]pyridazine (**1a**) [3], 6-chloro-3-carboxy-2-methylimidazo[1,2-*b*]pyridazine (**1b**) [3] and 3-ethoxycarbonyl-6-methoxy-2-methylimidazo[1,2-*b*]pyridazine (**1c**) as well as other functional carboxylic acid derivatives [4] have been prepared previously. On the other hand, oxidation of the methyl group in 6-chloro-2-methylimidazo-[1,2-*b*]pyridazine (**1d**) using potassium permanganate or chromium trioxide has been reported to afford the corresponding carboxylic acid which readily decarboxylates [3].

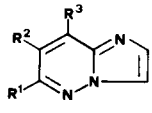
In an attempt to prepare azolopyridazinecarboxylic acid derivatives by oxidation of appropriately substituted precursors, the following methyl substituted derivatives of the bicyclic systems with a bridgehead nitrogen atom were selected: imidazo[1,2-*b*]pyridazines **2a-d** [5], *s*-triazolo[4,3-*b*]-pyridazines **3a-h** [6,7,8,9,10] and tetrazolo[1,5-*b*]pyridazines **4a,b** [10]. These compounds were treated with potassium permanganate in aqueous solution during heating on a water bath for 6-7 hours.

Scheme 1



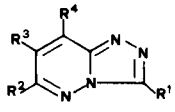
1a-d

a: R^1=Cl, R^2=COOEt
b: R^1=Cl, R^2=COOH
c: R^1=OMe, R^2=COOEt
d: R^1=Cl, R^4=H



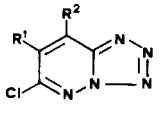
2a-d

a: R^1=Cl, R^2=Me, R^3=H
b: R^1=Cl, R^2=H, R^3=Me
c: R^1=R^3=H, R^2=Me
d: R^1=R^2=H, R^3=Me



3a-h

a: R^1=R^3=R^4=H, R^2=Me
b: R^1=R^2=R^4=H, R^3=Me
c: R^1=R^3=H, R^2=R^4=Me
d: R^1=Me, R^2=Cl, R^3=R^4=H
e: R^1=R^3=R^4=Me, R^2=Cl
f: R^1=R^4=H, R^2=Cl, R^3=Me
g: R^1=R^3=H, R^2=Cl, R^4=Me
h: R^1=R^4=Me, R^2=R^3=H



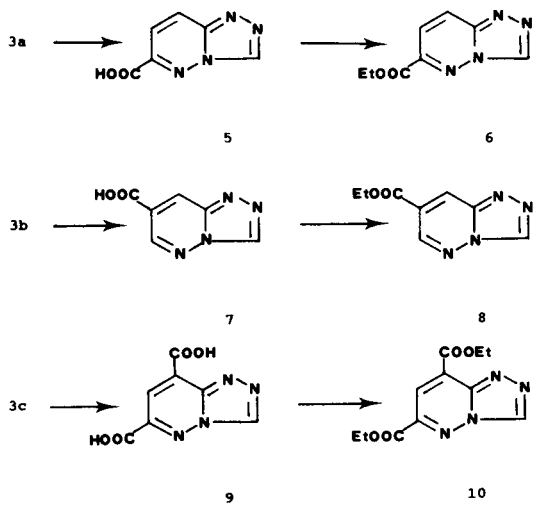
4a,b

a: R^1=Me, R^2=H
b: R^1=H, R^2=Me

Only from the reactions of 6-methyl-, 7-methyl- and 6,8-dimethyl-*s*-triazolo[4,3-*b*]pyridazine **3a**, **3b** and **3c** the corresponding carboxylic acids **5**,**7** and **9** could be isolated albeit in moderate yields. They were further transformed into their ethyl esters **6**, **8** and **10** according to the standard procedure (Scheme 2). However, methyl substituted 6-chloro-*s*-triazolo[4,3-*b*]pyridazines **3d-g** and 6-chloroimidazo[1,2-*b*]pyridazines **2a,b** were decomposed under the reaction conditions. Most probably in alkaline solution the chlorine at position 6 is hydrolysed into a hydroxy group and the pyridazine ring is further decomposed [11]. The same observation applies to the methyl substituted 6-chlorotetrazolo[1,5-*b*]pyridazines **4a,b**. On the other hand, the low yields obtained upon oxidation of methyl substituted azolopyridazines bearing no substituent at position 6 can be explained by abstraction of a proton from C-6 in alkaline solution followed by N-4/N-5 bond cleavage and further oxidation of the intermediate [13].

These problems encountered in the attempted preparation of azolopyridazinecarboxylic acids *via* the oxidative route discussed above prompted us to develope an alterna-

Scheme 2

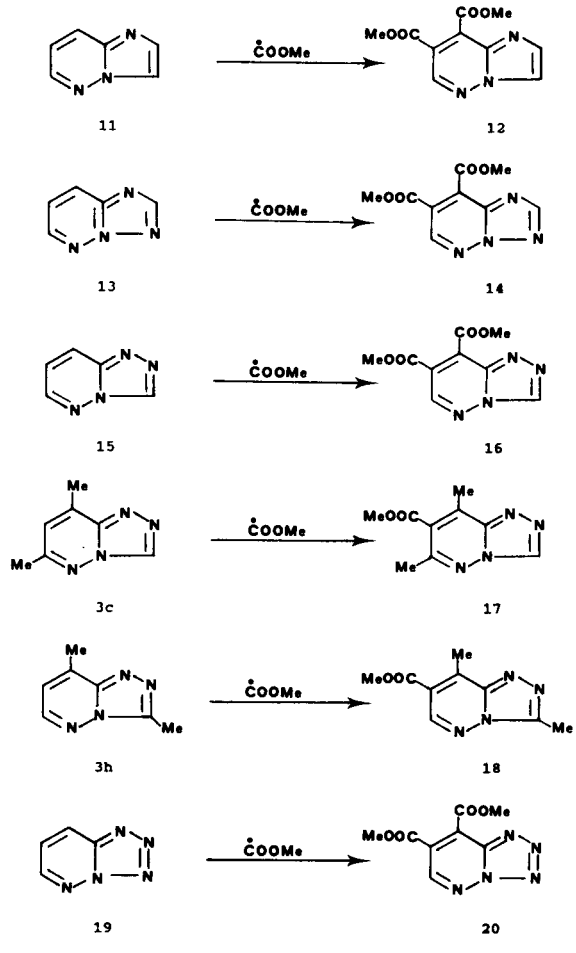


tive approach characterized by the direct introduction of carboxylic functionalities into the heterocyclic system. Thus, reactions of imidazo[1,2-*b*]pyridazine (**11**) [14], *s*-triazolo[1,5-*b*]pyridazine (**13**) [15], *s*-triazolo[4,3-*b*]pyridazine (**15**) [16], the dimethyl derivatives **3c** [8] and **3h** [7] of the latter and tetrazolo[1,5-*b*]pyridazine (**19**) [16] with methoxycarbonyl radicals generated according to ref [17] were investigated.

It is well documented in the literature that the protonated pyridazine system in general is attacked by nucleophilic carbon-centered radicals with pronounced regioselectivity at the ring positions 4 and 5 [18]. On the other hand, it has been shown that in homolytic alkoxycarbonylation reactions of the 1,2-diazine system also considerable amounts of side products are formed under standard reaction conditions [19]. These side products mainly result from additional attack of the radical at the carbon atoms 3 and 6; moreover, also *N*-alkoxycarbonylated compounds have been isolated recently from these reaction mixtures [19,20]. With the parent pyridazine system this problem can be overcome only by performing the radical substitution process in the presence of an appropriate organic layer [19] which permits the rapid extraction of the initially formed dialkyl 4,5-pyridazinedicarboxylate from the aqueous reaction medium.

In the azolopyridazine series, glc/ms investigations indicated that attack of methoxycarbonyl radicals exclusively occurs at the β-carbon atoms of the pyridazine nucleus, even if the reactions were performed in the absence of dichloromethane. Thus, by reacting the azolopyridazines **11**, **13** and **15** (applying a base:peroxide ratio of 1:3) the dimethyl azolopyridazine-7,8-dicarboxylates **12**, **14** and **16**, respectively, could be prepared in a simple one-step procedure. Similarly, the dimethyl tetrazolo[1,5-*b*]pyridazine-7,8-dicarboxylate **20** was obtained in reasonable yield from the parent system **19** (base:peroxide = 1:10). The dimethyl-*s*-triazolo[4,3-*b*]pyridazine derivatives **3c** and **3h**, characterized by only one free β-position in the pyridazine core, finally afforded the methyl monocarboxylates **17** and **18** in satisfactory yields.

Scheme 3



With all the new compounds prepared, the ring positions into which carboxylic acid ester groups have been introduced could be established simply by ^{1}H-nmr spectroscopy (Table 1).

EXPERIMENTAL

Melting points were taken on a Kofler hot stage microscope and are uncorrected. The ir spectra were recorded on a Jasco IRA-1 or a Perkin-Elmer 727 spectrometer. The ^{1}H-nmr spectra were obtained on a JOEL FX 90 Q spectrometer or a Varian EM 390 (90 MHz) instrument. Glc/ms analyses were carried out with a Hewlett Packard 5890A/5970B-MSD, using a 12 m HP1-FS-WCOT column. The microanalyses for C, H, and N were taken on a Perkin-Elmer Analyser 240 C. For analytical tlc, DC-Alufolien, Kieselgel 60 F_{254} (Merck) were used, column chromatography was performed on Kieselgel 60 (70-230 mesh, Merck).

Oxidation of Methyl Substituted *s*-Triazolo[4,3-*b*]pyridazines **3a-c** into Carboxy Substituted *s*-Triazolo[4,3-*b*]pyridazines **5**,**7** and **9**.

General Procedure.

To a suspension of methyl substituted *s*-triazolo[4,3-*b*]pyridazine (0.02 mole) in water (100 ml) heated on a steam bath in a

Table 1

Analytical and Spectroscopic Data of Azolopyridazinecarboxylic Acid Derivatives **5-10, 12, 14, 16-18, 20**

Compound	Yield (%)	M.P. (°C)	IR $\nu_{C=O}$ (cm^{-1})	^{1}H-NMR δ (ppm), TMS internal standard	MS (m/z, %)	Molecular Formula		Analysis C	H	N
5	23	294-295	1720	9.79 (s, 1H, H-3), 8.46 (d, 1H, H-8) 7.78 (d, 1H, H-7), 5.76 (br s, 1H, COOH), $J_{H-7,H-8}$ = 9.8 Hz	-	$C_6H_4N_4O_2$ (164.1)	Calcd.	43.91	2.46	34.14
							Found	44.07	2.57	34.23
6	89	182-185	1730	9.90 (d, 1H, H-3), 8.53 (dd, 1H, H-8) 7.79 (d, 1H, H-7), 4.46 (q, 2H, CH_2CH_3), 1.39(t, 3H, CH_2CH_3), $J_{H-7,H-8}$ = 9.8 Hz, $J_{H-3,H-8}$ = 0.7 Hz, $J_{CH_2CH_3}$= 7.2 Hz	-	$C_8H_8N_4O_2$ (192.2)	Calcd.	49.99	4.20	29.16
							Found	50.11	4.42	29.09
7	31	325-326	1710	9.87 (d, 1H, H-3), 8.92 (d, 1H, H-6), 8.80 (dd, 1H, H-8), 5.97 (br s, 1H, COOH), $J_{H-6,H-8}$ = 1.7 Hz, $J_{H-3,H-8}$ = 0.8 Hz	-	$C_6H_4N_4O_2$ (164.1)	Calcd.	43.91	2.46	34.14
							Found	43.87	2.61	34.23
8	78	128-130	1720	9.87 (d, 1H, H-3), 8.97 (d, 1H, H-6), 8.90 (dd, 1H, H-8), 4.42 (q, 2H, CH_2CH_3), 1.38 (t, 3H, CH_2CH_3), $J_{H-6,H-8}$ = 1.9 Hz, $J_{CH_2CH_3}$ = 7.2 Hz, $J_{H-3,H-8}$ = 0.8 Hz	-	$C_8H_8N_4O_2$ (192.2)	Calcd.	49.99	4.20	29.16
							Found	49.81	4.34	29.31
9	42	288-289	1700 1710	9.89 (s, 1H, H-3), 8.08 (s, 1H, H-7), 5.68 (br s, 2H, COOH)	-	$C_7H_4N_4O_4$ (208.1)	Calcd.	40.39	1.94	26.92
							Found	40.21	2.03	27.02
10	82	232-234	1720 1730	9.94 (s, 1H, H-3), 8.11 (s, 1H, H-7), 4.55 (q, 2H, CH_2CH_3), 4.35 (q, 2H, CH_2CH_3), 1.22 (t, 6H, CH_2CH_3), $J_{CH_2CH_3}$= 7.2 Hz	-	$C_{11}H_{12}N_4O_4$ (264.2)	Calcd.	50.00	4.58	21.20
							Found	50.23	4.67	21.06
12	37	97-101	1710	8.88 (s, 1H, H-6), 8.14, 7.99 (2d, 1H each, H-3, H-2), 4.11, 3.98 (2s, 3H each, 2 x $COOCH_3$), $J_{H-2,H-3}$ = 0.8 Hz	235 (M^+, 64) 119 (100)	$C_{10}H_9N_3O_4$ (235.2)	Calcd.	51.01	3.86	17.87
							Found	51.12	3.96	17.49
14	37	84-90	1720 1740	9.07, 8.63 (2s, 1H each, H-6, H-2) 4.12, 4.03 (2s, 3H each, 2 x $COOCH_3$)	236 (M^+, 42) 205 (100)	$C_9H_8N_4O_4$ (236.2)	Calcd.	45.77	3.41	23.72
							Found	45.38	3.45	23.33
16	18	159-162	1710 1730	9.30, 8.95 (2s, 1H each, H-6, H-3) 4.15, 4.00 (2s, 3H each, 2 x $COOCH_3$)	236 (M^+, 30) 120 (100)	$C_9H_8N_4O_4$ (236.2)	Calcd.	45.77	3.41	23.72
							Found	45.62	3.50	23.58
17	49	109-111	1720	9.10 (s, 1H, H-3), 4.00 (s, 3H, $COOCH_3$) 2.75, 2.60 (2s, 3H each, 2 x CH_3)	206 (M^+, 100)	$C_9H_{10}N_4O_2$ (206.2)	Calcd.	52.42	4.89	27.17
							Found	52.33	4.91	26.96
18	35	105-112	1705	8.80 (s, 1H, H-6), 4.00 (s, 3H, $COOCH_3$) 3.05, 2.80 (2s, 3H each, 2 x CH_3)	206 (M^+, 100)	$C_9H_{10}N_4O_2$ (206.2)	Calcd.	52.42	4.89	27.17
							Found	52.30	4.94	26.99
20	34	98-104	1730	9.17 (s, 1H, H-6), 4.14, 4.07 (2s, 3H each, 2 x $COOCH_3$)	181 (100) [a]	$C_8H_7N_5O_4$ (237.2)	Calcd.	40.51	2.98	29.53
							Found	40.41	2.99	29.34

[a] M^+ not observed.

250 ml three-necked flask, equipped with a condenser and stirrer, potassium permanganate (6.32 g, 0.04 mole for each methyl group) was added in small portions and the heating was continued until the color of permanganate disappeared (6-7 hours). The hot reaction mixture was filtered and the precipitated manganese oxide was washed with hot water (4 times, 50 ml each time). The combined filtrates were acidified with concentrated hydrochloric acid to $pH=2$ and evaporated *in vacuo*. The dry residue was extracted in a Soxhlet apparatus with anhydrous ethanol (3 hours). The extract was then evaporated and the dry residue recrystallized twice from a mixture of water and ethanol. The spectroscopic and analytical details are summarized in Table 1.

Preparation of Ethoxycarbonyl Substituted *s*-Triazolo[4,3-*b*]-pyridazines **6**, **8** and **10**.

General Procedure.

A mixture of carboxy substituted *s*-triazolo[4,3-*b*]pyridazine (0.01 mole) anhydrous ethanol (20 ml) and concentrated sulphuric acid (1 ml) was heated under reflux (3 hours). The solution was evaporated *in vacuo*, the oily residue was poured onto crushed ice (20 g) and the mixture was neutralized with solid sodium carbonate. The precipitated ester was collected by filtration and recrystallized from a mixture of ethanol and water. The spectroscopic and analytical data are summarized in Table 1.

Reaction of Azolopyridazine Derivatives **3c**, **3h**, **11**, **13**, **15**, and **19** with Methoxycarbonyl Radicals.

General Procedure.

Under stirring and cooling (−10°-0°) a 30% aqueous solution of hydrogen peroxide (0.03 mole; for **19**, 0.1 mole) was added dropwise to methyl pyruvate (0.045 mole; for **19**, 0.15 mole). This solution was then added dropwise at −5°-0° to a stirred mixture of the heteroaromatic base (0.01 mole), ferrous sulfate heptahydrate (0.03 mole; for **19**, 0.1 mole), concentrated sulfuric acid (0.03 mole; for **19**, 0.1 mole) and water (4 ml). Stirring was continued for another 15 minutes, then the reaction mixture was poured into ice water and extracted with dichloromethane. The organic layer was washed with water and dried over anhydrous sodium sulfate. The solvent and excess methyl pyruvate was removed *in vacuo*, the remaining residue was separate by column chromatography or preparative tlc. The spectroscopic and analytical data are summarized in Table 1.

Dimethyl Imidazo[1,2-*b*]pyridazine-7,8-dicarboxylate (**12**).

Compound **12** was separated by column chromatography (dichloromethane/methanol 9/1). The analytical sample was prepared by recrystallisation from isopropyl ether.

Dimethyl *s*-Triazolo[1,5-*b*]pyridazine-7,8-dicarboxylate (**14**).

This compound was separated by column chromatography (dichloromethane/methanol 9/1) and the analytical sample was prepared by recrystallisation from cyclohexane.

Dimethyl *s*-Triazolo[4,3-*b*]pyridazine-7,8-dicarboxylate (**16**).

This compound was separated by column chromatography (dichloromethane/methanol 9/1). The analytical sample was prepared by recrystallisation from isopropyl ether.

Methyl 6,8-Dimethyl-*s*-triazolo[4,3-*b*]pyridazine-7-carboxylate (**17**).

Compound **17** was separated by column chromatography (acetone/petroleum benzine (50°-70°) 3/2) and the analytical sample was obtained by recrystallisation from isopropyl ether.

Methyl 3,8-Dimethyl-*s*-triazolo[4,3-*b*]pyridazine-7-carboxylate (**18**).

This compound was separated by column chromatography (dichloromethane/methanol 9/1). The analytical sample was prepared by recrystallisation from isopropyl ether.

Dimethyl Tetrazolo[1,5-*b*]pyridazine-7,8-dicarboxylate (**20**).

Separation of **20** by preparative tlc was accomplished on Kieselgel 60 F_{254}/2 mm (dichloromethane/ethyl acetate 5/1). The analytical sample was obtained by recrystallisation from diethyl ether.

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