A Novel Approach to the Pyrido[4,3-*c*]pyridazine Ring. Synthesis of Pyrido[4,3-*c*]pyridazin-5(6*H*)-one from 3,4-Disubstituted Pyridazines

Jean-Pierre Vors

Rhône-Poulenc Agrochimie, Centre de Recherches de la Dargoire, 14-20 rue Pierre Baizet, B. P. 9143, 69263 Lyon cedex 09, France

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The synthesis of new pyrido[4,3-*c*]pyridazin-5(6*H*)-one from ethyl 3-methyl-4-pyridazinecarboxylate using an enamination/ring closure sequence is described. The starting material is easily available from a hetero Diels-Alder reaction between a 1,2-diaza-1,3-diene and ethyl vinyl ether and oxidation of the resulting 1,4,5,6-tetrahydropyridazine.

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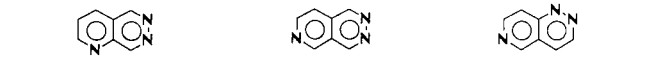
Amongst the 6 possible pyridopyridazines, the pyrido[2,3-*d*]pyridazine **A** and the pyrido[3,4-*d*]pyridazine **B** are the most described due to their easy accessibility [1].

However, only a few references exist in the literature about the pyrido[4,3-*c*]pyridazine ring **C** [2-5] (Scheme 1).

Scheme 1



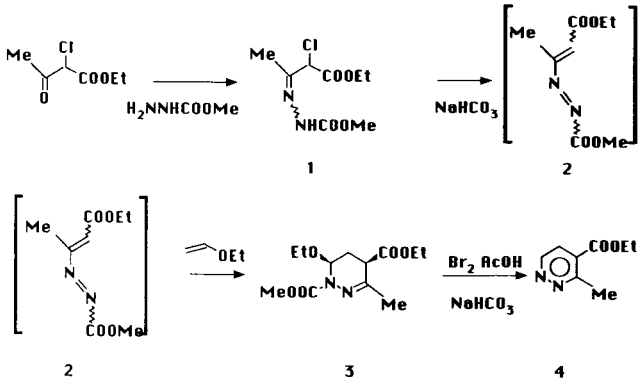
Although the fully unsaturated pyrido[4,3-*c*]pyridazine ring is not described to date [2], some publications deal with the partially saturated system [3-5]. Their synthesis involves cycloaddition of azodicarboxylic esters to vinylpyridines [3] or a reaction between a 4-oxopiperidine derivative and hydrazine [4] or a hydrazone [5].

We wish to report here a novel approach to the pyrido[4,3-*c*]pyridazine ring from ethyl 3-methyl-4-pyridazinecarboxylate.

In connection with our synthesis program on biologically active compounds, we prepared pyridazine-3,4-dicarboxylic acid by an hetero Diels-Alder reaction followed by the aromatization of the intermediate [6]. Starting from the readily available compound **1** [7], the same approach leads to ethyl 3-methyl-4-pyridazinecarboxylate **4** (Scheme 2). After the previously described [8] hetero Diels-Alder reaction between the unstable 1,2-diaza-1,3-diene **2** generated *in situ* by basic treatment of **1** and ethyl vinyl ether, the resulting 1,4,5,6-tetrahydropyridazine **3** was oxidized without further purification with bromine in acetic acid according to our method [6] in good overall yield (56%). This sequence constitutes a practical method to obtain quantities of ethyl 3-methyl-4-pyridazinecarboxylate **4** compared to the radical ethoxycarbonylation of pyridazines [9].

The pyridine ring of the title compounds can be synthesized by enamination of the methyl group of the crude **4** using Bredereck's reagent (*t*-Butoxybis(dimethylamino)-

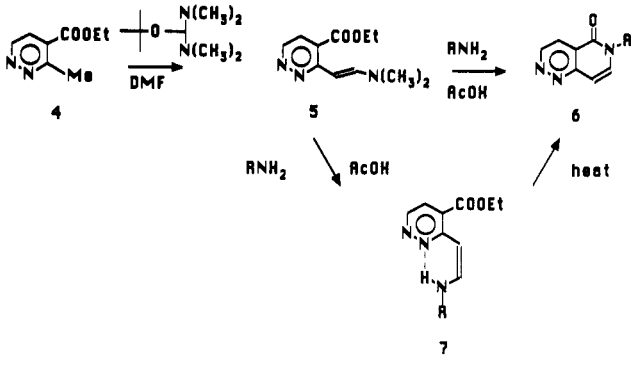
Scheme 2



methane) followed by ring closure either with ammonia or with an aniline of the crude enamine **5** to give directly the compounds **6**. In two cases, **7b** and **7c**, the intermediate enamine without obvious reason could be isolated although not pure enough to give correct elemental analysis. Only one isomer of these enamines is observed. Its configuration according to their nmr spectra is likely *Z*. The value of the coupling constant (9 Hz for the vinyl protons) is identical with that of an analogous *Z* enamine in the pyridine series [10b]. This configuration is favoured due to an hydrogen bond between the 2 nitrogen of the pyridazine ring and the hydrogen of the NH enamine.

The same sequence enamination/ring closure was used as this work was in progress for the synthesis of the

Scheme 3



isomeric 8-phenylpyrido[3,4-*d*]pyridazin-5(6*H*)-one [10a] and for the synthesis of substituted 1,6-naphthridin-5(6*H*)-ones [10b].

In summary, the synthesis of several pyrido[4,3-*c*]pyridazin-5(6*H*)-one was achieved in five to six steps from the commercially available ethyl 2-chloro-4-oxobutanoate in good yield.

This sequence, therefore, constitutes a facile route to the pyrido[4,3-*c*]pyridazine ring.

An attempt to obtain the novel unsubstituted fully unsaturated pyrido[4,3-*c*]pyridazine in two steps from **6a** by treatment with phosphorus oxychloride and subsequent reduction of the 5-chloropyrido[4,3-*c*]pyridazine as described for the isomeric 8-phenylpyrido[3,4-*d*]pyridazine [10a] failed at the first step. The reaction mixture was fully water soluble and no organic material could be extracted by common organic solvents even after careful neutralization of the aqueous phase.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage apparatus or on a Mettler FP61 and are uncorrected. The nmr spectra were recorded on a Bruker WP100 and Bruker AC 250 spectrometers. Chemical shifts are expressed in parts per million to TMS (^{1}H nmr) or using deuteriochloroform or dimethyl sulfoxide-d_6 as the internal reference (^{13}C nmr). The ir spectra and the mass spectra were recorded on a VG 70E/11250.

Ethyl 2-Chloro-3-(methoxycarbonylhydrazinylidene)butanoate (**1**).

This compound was prepared (94%) according to the literature [7]. The ir, ^{1}H nmr and the mp (mp 102°) are identical with those described; ms: (70 eV, electron impact) m/e 236 (molecular ion), 191 (M-OC_2H_5)$^+$, 163 (M-$COOC_2H_5$)$^+$; ^{13}C nmr (deuteriochloroform): 166.7 (two CO), 146.0 (C=N), 62.8 (CH_2CH_3), 61.0 (C-Cl), 53.3 (OCH_3), 14.0 (CH_2CH_3), 11.6 (CH_3C=N).

Ethyl 3-Methylpyridazine-4-carboxylic Acid (**3**).

This compound was prepared according to our method [6].

a) 6-Ethoxy-4-ethoxycarbonyl-1-methoxycarbonyl-3-methyl-1,4,5,-6-tetrahydropyridine (**2**).

To 677 g (2.86 moles) of **1** in suspension into 3 l of diisopropyl ether was added in one portion 254 g (3.02 moles) of sodium bicarbonate in 1.6 l of water. The temperature rose from 17° to 20°. After 2 hours the red organic phase was decanted and dried over magnesium sulfate. To this solution was added streamwise in 12 minutes 478 g (6.64 moles) of ethyl vinyl ether. The temperature rose from 20° to 37° within 6 hours. After 4 days at room temperature, the reaction mixture was concentrated *in vacuo* to give 658.4 g (84%) of **3** as a crude yellow oil which was used without further purification. The chemical shifts and the coupling constants are very similar with those of the previously reported *cis*-6-ethoxy-4-methoxycarbonyl-1-methoxycarbonyl-3-methyl-1,4,5,6-tetrahydropyridine [8c].

b) Ethyl 3-Methylpyridazine-4-carboxylic Acid (**4**).

To 14 g (0.051 mole) of crude **3** in 0.1 l of acetic acid cooled to 17°, 3 ml (0.059 mole) of bromine was added in 17 minutes. The color changed from yellow to brown, and there was evolution of gas. To the reaction mixture was added after 24 hours, 150 ml of diisopropyl ether. The precipitate was filtered, rinsed with 2 portions of 20 ml of diisopropyl ether and dried *in vacuo* to give 10.5 g of a brown solid. This solid was dissolved in 50 ml of water and the light insoluble was filtered. This aqueous solution was neutralized with 6.5 g of sodium bicarbonate and extracted with 3 portions of 50 ml of diisopropyl ether after 100 g of sodium chloride were added. The combined organic phases were dried over magnesium sulfate and concentrated *in vacuo* to give 6 g (71%) of **4** as a light brown solid, mp 60° in which the ^{1}H nmr was identical which that previously described [9]; ir (Nujol): 1732 (C=O) cm^{-1}; ^{13}C nmr (deuteriochloroform): 164.9 (C=O), 150.8 (C-3), 150.3 (C-6), 128.1 (C-4), 126.1 (C-5), 62.2 (CH_2CH_3), 22.1 (C-3-$CH3$), 14.1 (CH_2CH_3); ms: (70 eV, electron impact) m/e 166 (molecular ion), 138 (M-C_2H_4)$^{+\cdot}$, 121 (M-OC_2H_5)$^+$, 93 (M-$COOC_2H_5$)$^+$.

Anal. Calcd. for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.73; H, 6.11. N, 16.90.

Ethyl 3-(2-Dimethylaminoethenyl)methylpyridazine-4-carboxylic Acid (**5**).

To a solution of 5 g (0.03 mole) of **4** in 21 ml of dimethylformamide was added 7.5 g (0.043 mole) of *t*-butoxybis(dimethylamino)methane, and the mixture was heated 9 hours to 110° under and atmosphere of nitrogen. The volatile components were recovered in a Dean-Stark trap. After cooling, the dark reaction mixture was poured into water and extracted with 3 portions of 30 ml of methylene chloride. The organic phase was washed with 3 portions of 30 ml of water, dried over magnesium sulfate and concentrated *in vacuo* to give 4.7 g (71%) of a dark yellow solid containing *ca.* 80 molar percent of **5** according to nmr which can be used without further purification. By extraction of an aliquot of the crude material with hot diisopropyl ether followed by concentration of the solvent, we were able to isolate some yellow crystals, mp 64°; ir (Nujol): 1715 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): 8.76 (d, H-6, J = 5 Hz), 8.22 (d, C*H*-CH-N(CH_3)$_2$, J = 15 Hz), 7.58 (d, H-5, J = 5 Hz), 6.04 (d, CH = C*H*-N(CH_3)$_2$, J = 15 Hz), 4.37 (q, CH_2CH_3, J = 7.3 Hz), 3.00 (s, N(CH_3)$_2$, 6H), 1.4 (t, CH_2CH_3, J = 7.3 Hz); ^{13}C nmr (deuteriochloroform): 166.0 (C=O), 158.5 (C-3), 148.0 (C-6), 145.2 (*C*-N(CH_3)$_2$), 126.3 (C-5), 120.4 (C-4), 89.7 (*C*=CH-N(CH_3)$_2$), 61.5 (CH_2CH_3), 40.8 (N(CH_3)$_2$), 14.2 (CH_2CH_3); ms: (70 eV, electron impact) m/e 221 (molecular ion), 192 (M-C_2H_5)$^+$, 176 (M-OC_2H_5)$^+$, 148 (M-$COOC_2H_5$)$^+$.

Anal. Calcd. for $C_{11}H_{15}N_3O_2$: C, 59.71; H, 6.83; N, 18.99. Found: C, 59.47; H, 6.932; N, 19.00.

Pyrido[4,3-*c*]pyridazin-5(6*H*)-one (**6a**).

A heterogeneous mixture of 12.5 g (56 mmoles) of **5** and 43.5 g of ammonium acetate (564 mmoles) in 200 ml of ethanol was heated 2 days under reflux. After cooling, the precipitate was collected and rinsed thoroughly with ether and with water, and dried to afford 6.85 g of **6a** (83%) as a grey solid mp, 260-270°; ir (Nujol): 1693 (C=O) cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): 11.8 (br, NH, 1H), 9.43 (d, H-3, J = 5.5 Hz), 8.21 (d, H-4, J = 5.5 Hz), 7.54 (d, H-7, J = 7.5 Hz), 6.92 (d, H-8, J = 7.5 Hz); ^{13}C nmr (dimethyl sulfoxide-d_6): 161.5 (C=O), 154.5 (C-8a), 148.8 (C-3), 134.6 (C-7), 122.8 (C-4), 121.9 (C-4a), 103.4 (C-8); ms: (70 eV, electron impact) m/e 147 (molecular ion), 119 (M-CO)$^{+\cdot}$.

Anal. Calcd. for $C_7H_5N_3O_1$: C, 57.14; H, 3.43; N, 28.56. Found: C, 56.90; H, 3.72; N, 28.46.

General Procedure for the Preparation of the Intermediate Enamines **7b**, **7c** and the 6-Arylpyrido[4,3-*c*]pyridazin-5(6*H*)-one **6d**, **6e**.

To a solution of 10 mmoles of the enamine **5** in 10 ml of methylene chloride and 1 ml of glacial acetic acid was added 10 mmoles of the aniline and the mixture was stirred overnight at room temperature. The mixture diluted with 90 ml of methylene chloride was washed with saturated sodium bicarbonate, then with water. The organic phase was dried upon sodium sulfate and the solvents concentrated *in vacuo*. The solid was recrystallized in a suitable solvent.

6-(2,4-Dichlorophenyl)pyrido[4,3-*c*]pyridazin-5(6*H*)-one (**6b**).

3-[2-(2,4-Dichlorophenylamino)ethenyl]-4-ethoxycarbonylpyridazine (**7b**).

Compound **6b** was obtained in 82% yield as a green-yellow solid mp, 146°; ir (Nujol): 1724 (C=O), 1649 (C=C) cm^{-1}; ^1H nmr (deuteriochloroform): 12.08 (d, NH, J = 11 Hz), 9.00 (d, H-4, J = Hz), 7.78 (d, H-5, J = 5 Hz), 7.40 (d, H-3', J = 1 Hz), 7.30 (dd, = C*H*NH, J = 11 Hz, =CHNH, J = 9 Hz, CH=CH), 7.23 (d, H-5', J = 1 Hz), 7.12 (d, H-6', J = 8 Hz), 6.42 (d, C*H*=CHNH, J = 9 Hz), 4.43 (q, CH_2, J = 7 Hz), 1.44 (t, CH_3, J = 7 Hz); ms: (70 eV, electron impact) m/e 291 (molecular ion), 256 $(M-Cl)^+$.

6-(2,4-Dichlorophenyl)pyrido[4,3-*c*]pyridazin-5(6*H*)-one (**6b**).

The crude enamine **7b** obtained as described above was heated in NMP for 3 hours under reflux. The solvent was then distilled off. The residue was chromatographed (ethyl acetate/cyclohexane - 30/70) to give **6b** (83%) as a yellow solid mp, 260-270° (ethano/2-propanol 10/1); ir (Nujol): 1670 (C=O) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): 9.54 (d, H-3, J = 5.3 Hz), 8.33 (d, H-4, J = 5.3 Hz), 7.95 (d, H-3', J = 1.8 Hz), 7.79 (d, H-7, J = 7.6 Hz), 7.73-7.60 (m, 2H, H-5', H-6'), 7.16 (d, H-8, J = 7.6 Hz); ^{13}C nmr (dimethyl sulfoxide-d_6): 160.0 (C=O), 153.4 (C-8a), 149.3 (C-3), 137.9 (C-7), 136.1 (C-1'), 134.4 (C-4'), 132.0 (C-2'), 131.1, 129.4, 128.5 (C-4, C-3', C-5'), 123.1 (C-6'), 121.4 (C-4a), 104.4 (C-8); ms: (70 eV, electron impact) m/e 291 (molecular ion), 256 $(M-Cl)^+$.

Anal. Calcd. for $C_{13}H_7Cl_2N_3O_1$: C, 53.44; H, 2.41; N, 14.38; Cl, 24.27. Found: C, 53.71; H, 2.37; N, 14.35; Cl, 24.62.

6-(3,4-Dimethoxyphenyl)pyrido[4,3-*c*]pyridazin-5(6*H*)-one (**6c**).

3-[2-(3,4-Dimethoxyphenylamino)ethenyl]-4-ethoxycarbonylpyridazine (**7c**).

Compound **7c** was chromatographed (11%) ethyl acetate/heptane, 30/70) and obtained as a bordeaux solid mp, 93°; ir (Nujol): 1718 (C=O), 1634 (C=C) cm^{-1}; ^1H nmr (deuteriochloroform): 12.20 (d, NH, J = 11.3 Hz), 8.86 (d, H-6, J = 5.2 Hz), 7.70 (d, H-5, J = 5.2 Hz), 7.24 (dd, =C*H*NH, J = 12.2 Hz, =CHNH, J = 8.85 Hz, CH=CH), 6.85 (d, H-5', J = 8.5 Hz), 6.64-6.61 (m, 2H, H-2', H-2', H-6'), 6.15 (d, C*H*=CHNH, J = 8.85 Hz), 4.42 (q, $COOCH_2$, J = 7 Hz), 4.11 (q, OCH_2, J = 7 Hz), 4.06 (q, OCH_2, J = 7 Hz), 1.47 (t, $COOCH_2CH_3$, J = 7 Hz), 1.42 (6H, OCH_2CH_3, J = 7 Hz).

6-(3.4-Dimethoxyphenyl)pyrido[4,3-*c*]pyridazin-5(6*H*)-one (**6c**).

The crude enamine **7c** obtained as described above was heated in dioxane 1 hour under reflux in the presence of a catalytic amount of sodium hydride. The solvent was distilled off and the residue was chromatographed (ethyl acetate) to give **6c** (37%) as a green-yellow solid mp, 126°; ir (Nujol): 1670 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): 9.47 (d, H-3, J = 4.4 Hz), 8.35 (d, H-4, J = 4.4 Hz), 7.50 (d, H-7, J = 7.7 Hz), 7.16 (d, H-8, J = 7.7 Hz), 6.85-7.00 (m, 3H, H-5', H-6', H-2'), 4.20-4.07 (6H, OCH_2, J = 7 Hz), 1.70-1.44 (6H, OCH_2CH_3, J = 7 Hz); ^{13}C nmr (deuteriochloroform): 161.4 (C=O), 153.9, (C-8a), 149.2 (C-4', C-3', C-3), 137.9 (C-7), 132.9 (C-1'), 123.5 (C-4), 122.5 (C-4a), 118.5 (C-6'), 113.3 (C-5'), 111.8 (C-2'), 105.4 (C-8), 64.8 (CH_2), 14.8 (CH_3); ms: (70 eV, electron impact) m/e 311 (molecular ion), 283 $(M-CO)^{+\cdot}$.

Anal. Calcd. for $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5.50; N, 13.50. Found: C, 65.33; H, 5.54; N, 13.42.

6-(3-Chloro-4-methoxyphenyl)pyrido[4,3-*c*]pyridazin-5(6*H*)-one (**6d**).

Compound **6d** was obtained in 94% yield as a yellow solid, mp 260°; ir (Nujol): 1670 (C=O) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): 9.51 (d, H-3, J = 5.5 Hz), 8.30 (dd, H-4, J = 5.5 Hz, H-4-H-3, J = 0.6 Hz, H-4-H-8), 7.82 (d, H-7, J = 7.6 Hz), 7.67 (d, H-2', J = 2.8 Hz, H-2'-H-5'), 7.47 (dd, H-6', J = 8.8 Hz, H-6'-H-5', J = 2.8 Hz, H-6'-H-2'), 7.31 (d, H-5', J = 8.8 Hz, H-5'-H-6'), 7.07 (dd, H-8, J = 7.6 Hz, H-8-H-7, J = 0.6 Hz, H-8-H-4); ms: (70 eV, electron impact) m/e 287 (molecular ion), 272 $(M-CH_3)^+$.

Anal. Calcd. for $C_{14}H_{10}ClN_3O_2$: C, 58.45; H, 3.50; N, 14.61; Cl, 12.32. Found: C, 58.35; H, 3.48; N, 14.58; Cl, 12.45.

6-(2,4-Difluorophenyl)pyrido[4,3-*c*]pyridazin-5(6*H*)-one (**6e**).

Compound **6e** was obtained in 43% yield, as a grey solid mp, 183° (ethanol); ir (Nujol): 1682 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): 9.50 (d, H-3, J = 5.5 Hz), 8.35 (d, H-4, J = 5.5 Hz), 7.36 (d, H-7 J = 7.6 Hz), 7.19 (d, H-8, J = 7.6 Hz), 7.50-6.90 (m, 3H, H-3', H-5', H-6'); ^{13}C nmr (deuteriochloroform): 160.8 (C=O), 162.8, 157.5 (C-2', C-4'), 153.8 (C-8a), 149.4 (C-3), 136.9 (C-7), 129.7 (C-6'), 123.5 (C-4), 122.4 (C-4a), 112.4 (C-5'), 106.2 (C-8), 105.6 (C-3'); ms: (70 eV, electron impact) m/e 259 (molecular ion), 240 $(M-F)^+$.

Anal. Calcd. for $C_{13}H_7F_2N_3O_1$: C, 60.24; H, 2.72; N, 16.21; F, 14.66. Found: C, 59.91; H, 2.67; N, 16.16; F, 14.31.

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