Transformations of the Pyrido[1,2-*a*]pyrazine Ring System into Imidazo[1,2-*a*]pyridines, Imidazo[1,2-*a*]pyrimidines and 2-Oxa-6a,10c-diazaaceanthrylenes

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Transformations of methyl 3-dimethylamino-2-(1-methoxycarbonyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrazin-3-yl)acrylate with some cyanomethylenecarbonyl group containing compounds or cyanamide into imidazo-[1,2-*a*]pyridines, imidazo[1,2-*a*]pyrimidines and 2-oxa-6a,10c-diazaaceanthrylenes are described.

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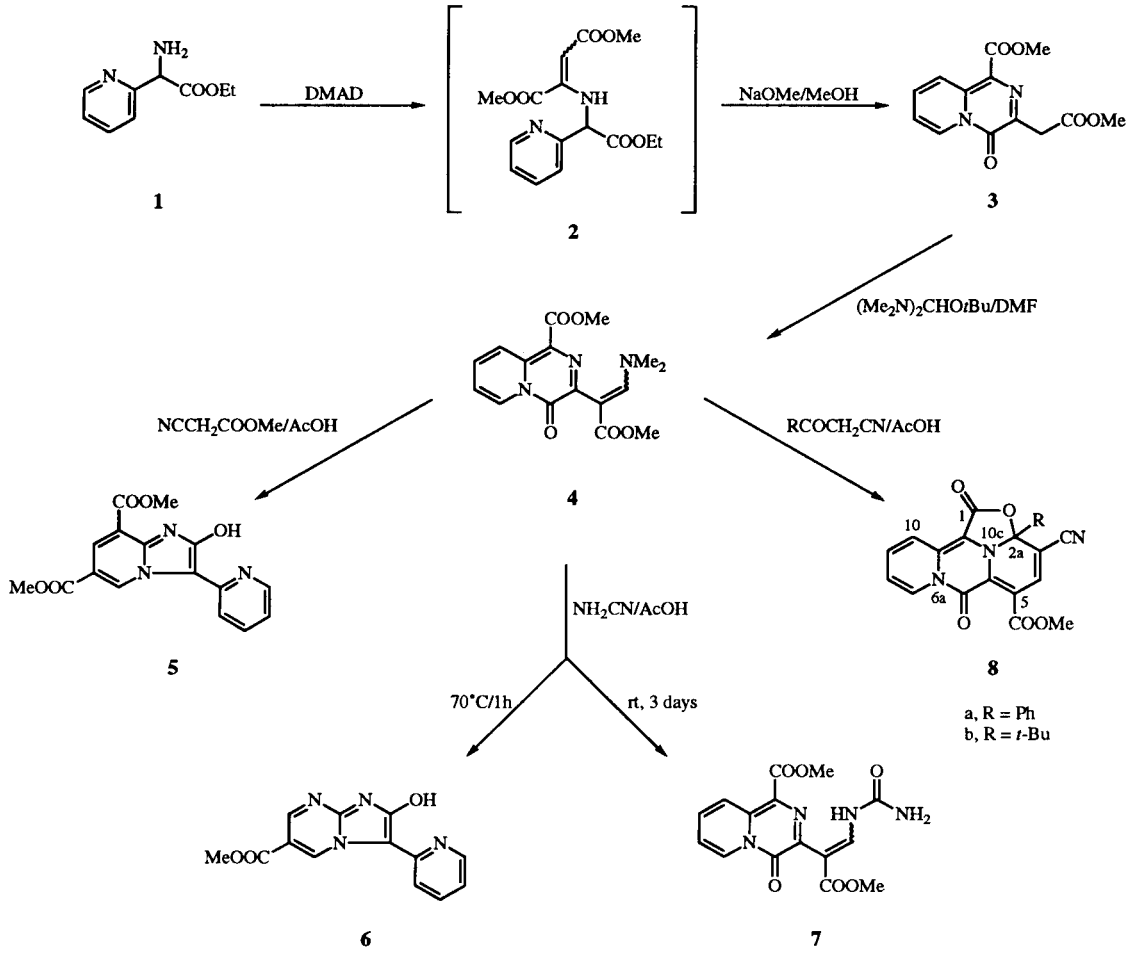
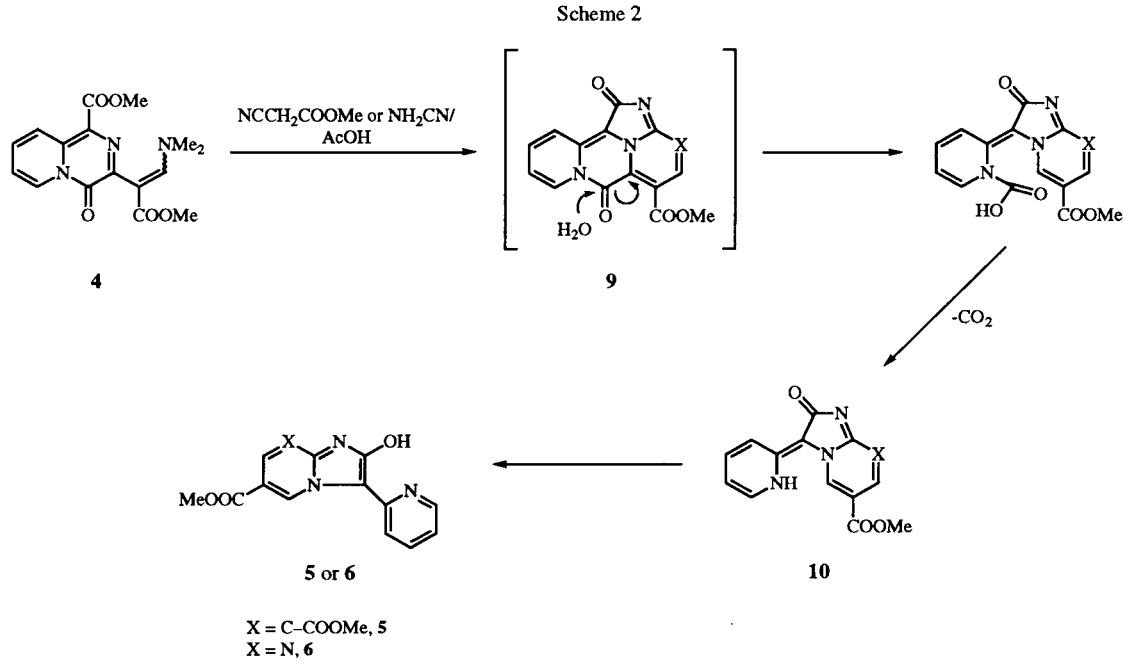
Amino acids are important synthons for many natural products and various heterocyclic systems [1]. We have recently developed several new approaches towards different heterocyclic systems starting from heterocyclic amino acid derivatives [2-8]. A new synthesis was also developed for the bicyclic pyrido[1,2-*a*]pyrazine system [2] for which only a few synthetic approaches have been described so far [9].

In this communication we would like to report on an unusual transformation of the last mentioned heterocyclic system into imidazo[1,2-*a*]pyridines and imidazo-[1,2-*a*]pyrimidines. 2-Aminopyridines were usually employed as a starting material for the preparation of imidazo[1,2-*a*]pyridines and only a few examples are known when this bicyclic system was prepared starting from substituted imidazoles [10-12]. In a similar manner,

Scheme 1



Scheme 2



2-aminopyrimidines were commonly used for the synthesis of imidazo[1,2-*a*]pyrimidines, whereas the alternative approaches involve various cyclization reactions starting from 2-aminoimidazoles [13-16]. Many derivatives of both mentioned imidazo[1,2-*a*]azines have been found to possess interesting biological activities such as antibacterial [17], antiulcer [18,19], inotropic [20], calcium channel blocking and local anesthetic activity [21].

The starting methyl (pyrido[1,2-*a*]pyrazin-3-yl)acetate **3** was prepared in a two-step reaction sequence from ethyl 2-(2'-pyridyl)glycinate **1** and dimethyl acetylenedicarboxylate (DMAD). The primarily formed enamine **2** cyclized in methanolic sodium methoxide solution at room temperature to give **3** in 75% yield [22]. During this transformation also a simultaneous transesterification of the ethoxycarbonyl group into the methoxycarbonyl group took place. After treatment of **3** with *t*-butoxybis(dimethylamino)methane in anhydrous *N,N*-dimethylformamide at 40-50° for 3 hours the dimethylaminomethylene derivative **4** was obtained in good yield.

When compound **4** reacted with methyl cyanoacetate in 95% acetic acid at 70° after 2 hours the imidazo[1,2-*a*]pyridine derivative **5** was obtained in 55% yield. Under similar reaction conditions **4** reacted with cyanamide and formed the imidazo[1,2-*a*]pyrimidine **6**. If in the last case the reaction mixture was allowed to react at the room temperature for 3 days, only the ureido derivative **7** was obtained. Surprisingly, when **4** reacted in 95% acetic acid at 70° with either benzoylacetonitrile or 4,4-dimethyl-3-oxopentanenitrile not the corresponding imidazo[1,2-*a*]pyridines were formed but the reaction resulted in the formation of the 2a-phenyl substituted or 2a-*t*-butyl substituted 1*H*-2-oxa-6a,10c-diazaaceanthrylene-1,6(2a*H*)-diones **8a** and **8b**, derivatives of a new tetracyclic heterocyclic system (Scheme 1).

The transformation of the pyrido[1,2-*a*]pyrazine **4** into the corresponding imidazo[1,2-*a*]pyridine **5** and imidazo[1,2-*a*]pyrimidine **6** can be explained in terms of the formation of a tetracyclic intermediate **9**, which is transformed into compounds **5** or **6** after acid-catalyzed hydrolytic cleavage of the pyrazinone ring followed by decarboxylation and tautomerization of the intermediate **10**, as indicated in Scheme 2, although we have no firm proof for such a reaction sequence.

It is evident from the ^{1}H nmr spectra that the reaction product formed from the pyrido[1,2-*a*]pyrazine **4** and cyanamide after heating in 95% acetic acid to 70° exists in dimethyl sulfoxide solution in only one tautomeric form. The coupling constants observed between the protons on the pyridyl ring are in agreement with those expected for the fully aromatized pyridine ring therefore suggesting the presence of the structure **6** and not of its tautomer **10** (or its geometrical isomer).

The above described transformation of the pyrido-[1,2-*a*]pyrazine ring system into imidazo[1,2-*a*]pyridine **5** and imidazo[1,2-*a*]pyrimidine **6** represents a new approach towards these heterocyclic systems.

EXPERIMENTAL

Melting points were determined on a Büchi 535 capillary apparatus and are uncorrected. The ^{1}H and ^{13}C nmr spectra were

recorded on a JEOL JFX400 spectrometer (^{1}H - 400 MHz, ^{13}C - 100 MHz) with TMS as an internal standard. Infrared spectra were recorded on a Perkin-Elmer 1310 spectrometer. Mass spectra were recorded on a VG Analytical Autospec Q spectrometer by electron impact ionization at 70 eV. Microanalyses (C, H, N) were obtained on a Perkin-Elmer 2400 elemental analyzer.

Reaction progress was monitored by tlc on Fluka silicagel 60778 plates using ethyl acetate or a mixture of chloroform and methanol (8:2) as a mobile phase. Ethyl 2-(2'-pyridyl)glycinate was prepared according to the procedure described in the literature [23].

Methyl (1-Methoxycarbonyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrazin-3-yl)acetate (**3**).

Dimethyl acetylenedicarboxylate (DMAD) (1.42 g, 10 mmoles) was added dropwise to a solution of ethyl 2-(2'-pyridyl)glycinate (1.80 g, 10 mmoles) in methanol (8 ml) on ice bath with stirring during 5 minutes and thereafter the stirring was continued for one hour. The solvent was evaporated *in vacuo* and the residual orange-red oil was dissolved in methanol (25 ml). To this solution a freshly prepared solution of sodium methoxide (prepared from 0.23 g of sodium and 7 ml of methanol) was added dropwise with stirring at room temperature. Stirring was continued for 24 hours, water (20 ml) was added and the reaction mixture was acidified with 10% acetic acid (25 ml). The crude product was filtered and crystallized from absolute ethanol to give golden-yellow crystals of **3**, mp 168-172° (2.07 g, 75%); ir (potassium bromide): ν 1735 (COOMe), 1660 (CO), 1620 (C=C) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.74 (s, 3H, COOMe), 4.00 (s, 3H, COOMe), 4.07 (s, 2H, CH_2), 7.35 (ddd, 1H, H_7), 7.76 (ddd, 1H, H_8), 9.12 (dt, 1H, H_6), 9.27 (dt, 1H, H_9), $J_{6,7}$ = 7.3, $J_{6,8}$ = $J_{6,9}$ = $J_{7,9}$ = 1.2, $J_{7,8}$ = 6.8, $J_{8,9}$ = 9.3 Hz; ^{13}C nmr (deuteriochloroform): δ 39.9 (t), 52.1 (q), 52.6 (q), 117.5 (s), 118.5 (s), 124.0 (d), 127.0 (d), 134.1 (d), 136.9 (s), 139.7 (s), 150.9 (s), 165.1 (s), 170.3 (s); high resolution ms: m/z = 276.0746 (M$^+$, 53%); Calcd. 276.0750.

Anal. Calcd. for $C_{13}H_{12}N_2O_5$: C, 56.52; H, 4.38; N, 10.14. Found: C, 56.47; H, 4.39; N, 10.06.

Methyl 3-Dimethylamino-2-(1-methoxycarbonyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrazin-3-yl)acrylate (**4**).

To an ice-cold solution of **3** (2.76 g, 10 mmoles) in anhydrous *N,N*-dimethylformamide (55 ml) *t*-butoxybis(dimethylamino)methane (4.35 g, 25 mmoles) was added dropwise with stirring. The reaction mixture was heated at 40-50° for 3 hours. The solvent was evaporated *in vacuo* and the solid residue was purified either by crystallization from a mixture of ethyl acetate and *n*-hexane or by flash chromatography on silica gel, using ethyl acetate as a mobile phase; mp 189-192° (2.65 g, 80%); ir (potassium bromide): ν 1700, 1670, 1660 (C=O), 1620 (C=C) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.85 (broad s, 6H, NMe_2), 3.63 (s, 3H, COOMe), 3.97 (s, 3H, COOMe), 7.26 (ddd, 1H, H_7), 7.67 (ddd, 1H, H_8), 7.72 (s, 1H, C=CH), 9.10 (d, 1H, H_6), 9.21 (d, 1H, H_9), $J_{6,7}$ = 7.2, $J_{6,8}$ = $J_{7,9}$ = 1.3, $J_{7,8}$ = 6.6, $J_{8,9}$ = 9.3 Hz; ^{13}C nmr (deuteriochloroform): δ 43.5 (q), 50.9 (q), (s), 151.9 (d), 165.3 (s), 168.8 (s); high resolution ms: m/z = 331.1173 (M$^+$, 76%); Calcd. 331.1168.

Anal. Calcd. for $C_{16}H_{17}N_3O_5$: C, 58.00; H, 5.17; N, 12.68. Found: C, 57.73; H, 4.95; N, 12.41.

General Procedure for the Reaction of Acrylate **4** with Cyanomethylenecarbonyl Compounds and Cyanamide.

A mixture of acrylate **4** (331 mg, 1 mmole) and the corresponding cyanomethylenecarbonyl compound (methyl cyanoacetate, 4,4-dimethyl-3-oxopentanenitrile, benzoylacetonitrile) or cyanamide (1.2 mmoles) was heated and stirred at 70° in 95% acetic acid (5 ml) for the time indicated for each particular compound. Upon cooling, the separated product was filtered, washed with saturated solution of sodium hydrogencarbonate and thereafter with water, dried and crystallized from the appropriate solvent. (Compounds **6** and **7** were precipitated as analyticaly pure products from the reaction mixture.)

In this manner the following compounds were prepared.

6,8-Di(methoxycarbonyl)-2-hydroxy-3-(2-pyridyl)imidazo-[1,2-*a*]pyridine (**5**).

This compound was prepared from methyl cyanoacetate; reaction time was 2 hours, yield 55%, mp 272° dec (from ethanol); ir (potassium bromide): ν 1725, 1720 (C=O), 1640, 1630 (C=C), 1590 (C=N) cm^{-1}; high resolution ms: m/z = 327.0860 (M$^+$, 100%); Calcd. 327.0855 [24].

Anal. Calcd. for $C_{16}H_{13}N_3O_5$: C, 58.71; H, 4.00; N, 12.84. Found: C, 58.60, H, 3.97, N, 12.50.

2-Hydroxy-6-methoxycarbonyl-3-(2-pyridyl)imidazo-[1,2-*a*]pyrimidine (**6**).

This compound was prepared from cyanamide, reaction time was 1 hour, yield 35%, mp >320°; ir (potassium bromide): ν 1720 (C=O), 1640 (C=C), 1590 (C=N); ^{1}H nmr (DMSO-d_6): δ 3.88 (s, 3H, COOMe), 6.88 (dt, 1H, $H_{5'}$), 7.59 (dt, 1H, $H_{4'}$), 8.49 (d, 1H, $H_{6'}$), 8.51 (d, 1H, H_7), 8.71 (d, 1H, $H_{3'}$), 10.61 (d, 1H, H_5), $J_{5,7}$ = 2.3, $J_{3',4'}$ = 8.3, $J_{3',5'}$ = 1.0, $J_{4',5'}$ = $J_{5',6'}$ = 6.1 Hz; ^{13}C nmr (DMSO-d_6): δ 51.9 (q), 100.1 (s), 108.7 (s), 116.5 (d), 118.7 (d), 131.7 (s), 135.1 (d), 147.5 (s and d), 152.6 (s), 165.1 (d), 170.6 (s); high resolution ms: m/z = 270.0763 (M$^+$, 100%); Calcd. 270.0753.

Anal. Calcd. for $C_{13}H_{10}N_4O_3$: C, 57.77; H, 3.73; N, 20.73. Found: C, 57.67; H, 3.75; N, 20.55.

Methyl 2-(1-Methoxycarbonyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrazin-3-yl)-3-ureidoacrylate (**7**).

This compound was prepared from cyanamide by stirring the reaction mixture at room temperature for 3 days and was obtained as a 2:1 mixture of both geometrical isomers, yield 65%, mp 235-237°; ir (potassium bromide): ν 3430, 3300, 3200 (NH, NH_2), 1730, 1710 (C=O), 1670 (CO-N), 1630, 1610 (C=C); ^{1}H nmr (DMSO-d_6): δ 3.64 and 3.65 (two s, 3H, COOMe), 3.89 and 3.90 (two s, 3H, COOMe), 6.42 and 6.80 (two s, 2H, NH_2), 7.50 and 7.59 (two dt, 1H, H_7), 7.73 and 8.11 (d, 1H, NHC*H*), 7.91 and 8.02 (two ddd, 1H, H_8), 8.89 and 9.91 (d, 1H, N*H*CH), 9.02 and 9.09 (d, 1H, H_9), $J_{6,7}$ = 7.3, $J_{6,8}$ = 1.5, $J_{7,8}$ = 6.6, $J_{7,9}$ = 1.1, J_{CH-NH} = 12.2 Hz; ^{13}C nmr (DMSO-d_6) [25]: δ 51.3 (q), 52.0 (q), 103.9 (s), 117.2 (s), 119.7 (d), 123.0 (d), 127.7 (d), 133.9 (s), 136.1 (s), 137.4 (d), 138.9 (s), 149.6 (s), 153.7 (d), 164.9 (s), 166.9 (s); high resolution ms: m/z = 346.0914 (M$^+$, 93%); Calcd. 346.0913.

Anal. Calcd. for $C_{15}H_{14}N_4O_6$: C, 52.02; H, 4.08; N, 16.18. Found: C, 52.17; H, 3.90; N, 16.08.

3-Cyano-5-methoxycarbonyl-2a-phenyl-1*H*-2-oxa-6a,10c-diazaaceanthrylene-1,6(2a*H*)-dione (**8a**).

This compound was prepared from benzoylacetonitrile, reaction time was 1 hour, yield 59%, mp 300-305° (from acetic acid); ir (potassium bromide): ν 2240 (C≡N), 1750 (lactone

C=O), 1700 (COOMe), 1620 (C=C); ^{1}H nmr (deuteriochloroform): δ 4.03 (s, 3H, COOMe), 7.52 (dt, 1H, H_8), 7.56-7.66 (m, 3H, *m*- and *p*-H of Ph), 7.94 (ddd, 1H, H_9), 8.09 (s, 1H, H_4), 8.10-8.15 (m, 2H, *o*-H of Ph), 9.33 (dt, 1H, H_7), 9.41 (dt, 1H, H_{10}), $J_{7,8}$ = 7.2, $J_{7,9}$ = $J_{7,10}$ = $J_{8,10}$ = 1.1, $J_{8,9}$ = 6.9, $J_{9,10}$ = 9.3 Hz; ^{13}C nmr (deuteriochloroform): δ 52.8 (q), 90.5 (s), 115.9 (s), 118.8 (s), 119.6 (d), 123.3 (s), 124.5 (d), 128.3 (three d), 129.2 (two d), 129.4 (s), 131.1 (s), 133.2 (d), 136.0 (d), 138.6 (s), 143.6 (d), 149.3 (s), 156.7 (s), 164.8 (s), 168.6 (s); high resolution ms: m/z = 399.0860 (M^+, 100%); Calcd. 399.0855.

Anal. Calcd. for $C_{22}H_{13}N_3O_5$: C, 66.16; H, 3.28; N, 10.52. Found: C, 66.10; H, 3.26; N, 10.20.

2a-*t*-Butyl-3-cyano-5-methoxycarbonyl-1*H*-2-oxa-6a,10c-diazaaceanthrylene-1,6(2a*H*)-dione (**8b**).

This compound was prepared from 4,4-dimethyl-3-oxopentanenitrile, reaction time was 10 hours, yield 40%, mp 257-259° (from 1-propanol); ir (potassium bromide): ν 2200 (C≡N), 1750 (lactone C=O), 1690 (COOMe), 1670 (N-C=O), 1620 (C=C); ^{1}H nmr (deuteriochloroform): δ 1.54 (s, 9H, *t*-Bu), 4.02 (s, 3H, COOMe), 7.51 (dt, 1H, H_8), 7.90 (s, 1H, H_4), 7.93 (ddd, 1H, H_9), 9.31 (dt, 1H, H_7), 9.39 (ddd, 1H, H_{10}), $J_{7,8}$ = 7.1, $J_{7,9}$ = 1.2, $J_{7,10}$ = 0.9, $J_{8,9}$ = 6.8, $J_{8,10}$ = 1.3, $J_{9,10}$ = 9.2 Hz; ^{13}C nmr (deuteriochloroform): δ 28.2 (three q), 39.1 (s), 52.8 (q), 90.4 (s), 115.5 (s), 118.7 (s), 119.6 (d), 122.6 (s), 124.4 (d), 128.2 (d), 131.3 (s), 135.9 (d), 138.5 (s), 144.4 (d), 149.3 (s), 156.8 (s), 164.7 (s), 182.1 (s); high resolution ms: m/z = 379.1179 (M^+, 100%); Calcd. 379.1168.

Anal. Calcd. for $C_{20}H_{17}N_3O_5$: C, 63.32; H, 4.52; N, 11.08. Found: C, 63.20; H, 4.46; N, 10.80.

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[24] ^{1}H and ^{13}C nmr spectra could not be recorded because of the insolubility of this compound in common nmr solvents.

[25] Only the chemical shifts for the predominanting geometrical isomer are given.