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A NEW CLASS OF PYRIDOPYRIMIDINE DERIVATIVES: FURO[2,3-d]PYRIDO[1,2-a]PYRIMIDINES

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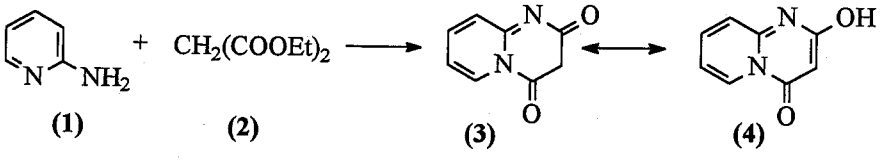
ABSTRACT

Novel pyrido[1,2-a]pyrimidine derivatives; 2,3-dihydro-4H-furo[2,3-d]pyrido[1,2-a]pyridimidine-4-ones were prepared by acidic cyclisation of 3-(2-methyl prop-1-enyl)-2-hydroxy-4H-pyrido[1,2-a] pyrimidin-4-ones, which were obtained from condensation reaction of 2-aminopyridines with diethyl alkylmethylene malonates.

INTRODUCTION

Pyrido[1,2-a]pyrimidines are nitrogen-bridged heterocyclic compounds and can be formed by the condensation reaction of 2-aminopyridines with a suitable 1,3-dicarbonyl compound. The first example of these compounds was made by Chichibabin[1] by the thermal condensation of 2-aminopyridine with diethyl malonate and described as a dioxo compound (**3**). Later, the structure of this compound was assigned as 4H-pyrido[1,2-a]primidine-2-hydroxy-4-one (**4**)[2-3].



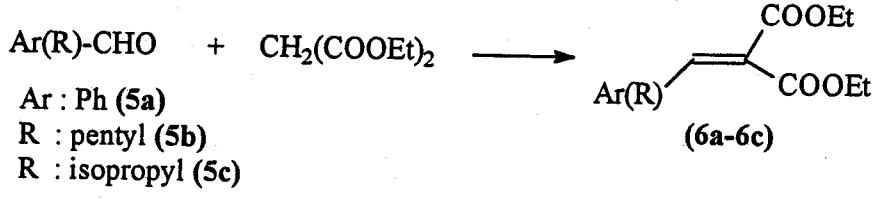
(1) (2) (3) (4)

Several different examples of this type bridged compounds have been made[4] and most of them were found to be biologically active in a wide range; such as antiallergy agents, anti-ulcer agents, central nervous system stimulants (CNS) and antiinflammatory agents[5-8]. The biological activities of these pyrimidine bases were found to be greatly affected by the presence of different functional groups on the pyridine or pyrimidine ring. Therefore, there has been an increasing interest on the synthesis of new substituted pyrido[1,2-a]pyrimidine derivatives.

On our earlier attempts, direct functionalisation at the pyridine ring of 3-alkyl-2-hydroxy-4H-pyrido[1,2-a]pyrimidin-4-ones was studied by anodic oxidation[9]. Nevertheless, a substitution at the ring could no be achieved, but unexpected dimerisation products were obtained by a radical-radical coupling at the C-3 and O-4 positions[10]. The enolic form of these compounds was assumed to be the reason for the dimerisation reaction. In order to achieve the desired functionalisation and improve the reactivity of these compounds towards electrochemical reactions, new methods were proposed. One of the alternative approach is to make new 4H-pyrido [1,2-a]pyrimidine derivatives having a 2,4-dioxo structure, where enolisation is avoided.

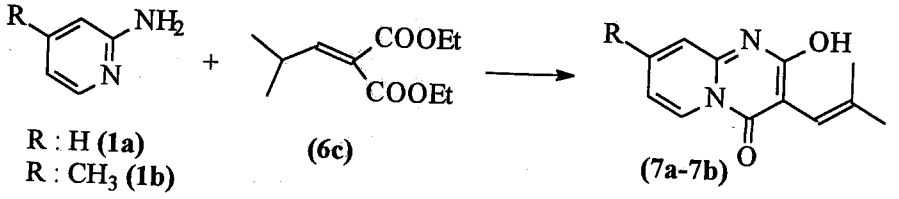
RESULTS AND DISCUSSION

The aim of this work was to explore the synthesis of new pyrido[1,2-] pyrimidines which would not have a reactive oxidisable enolic group under anodic oxidation conditions. The simplest solution is the use of an alkyl or aryl substituted methylenemalonate ester in the condensation reaction with 2-amino pyridine so that it would be expected to provide a 3-arylmethylene or 3-alkylmethylene-4H-pyrido [1,2-a]pyrimidine-2,4-dione. The aforementioned malonate esters are easily accessible by Knoevenagel condensation[11] and three different examples of them were made in good yields by the reaction of corresponding aldehydes with diethyl malonate.



First attempts to make a 2,4-dioxo derivative by thermal condensation (at 190^{0}C) of diethyl benzylidenemalonate (**6a**) or diethyl hexylidenemalonate (**6b**) with 2-aminopyridine did not produce any 3-substituted 4H-pyrido[1,2-a]pyrimidine-2,4-dione (**3**). On the other hand, under similar conditions diethyl isopropyl

methylenemalonate (**5c**) with 2-amino pyridine gave a 4H-pyrido[1,2-a]pyrimidine derivative successfully. However isomerisation of the methylene double bond (α, β) to the more stable $\beta, \gamma-$ position precluded formation of a 2,4-diketo derivative, but gave instead a novel 2-hydroxy-4H-pyrido[1,2-a]pyrimidin-4-one derivative with an olefinic side group. Spectral data for this compound were found to be sufficient enough to explain the structure. Attempts to avoid isomerisation did not result in formation of any 2,4-diketo compound.

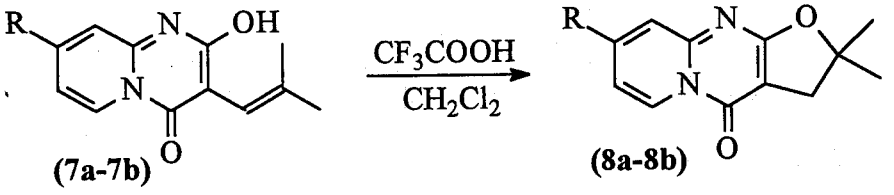


R : H (**1a**)
R : CH_3 (**1b**)

(**6c**)

(**7a-7b**)

These new compounds were found to give an unexpected cyclisation in acidic media, surprisingly and resulted in formation of a new class of pyrido[1,2-a] pyrimidine derivatives, 2,3-dihydro-4H-furo[2,3-d]pyrido[1,2-a]pyrimidine-4-ones.



(**7a-7b**)

(**8a-8b**)

Cyclisation reaction took place smoothly in trifluoroacetic acid/ dichloromethane solution at room temperature with almost quantitative yield. Optimisation experiments showed that a strong acid, such as trifluoroacetic acid was required for cyclisation, and that no reaction took place in acetic acid. The effect of inorganic acids, like H_2SO_4, HCI, HBr etc. has not been studied yet, but results already obtained from trifluoroacetic acid were found to be satisfactory. The required ratio of trifluoroacetic acid in dichloromethane should be 1:1 (v/v) to obtain high cyclic product yield. Ring closure easily took place at room temperature at longer reaction periods (>12hrs). Heating to reflux increased the reaction speed, but also increased the formation of the ring cleavage porducts.

It can be concluded that the synthesis of proposed 2,4-dioxo derivatives of 4H-pyrido[1,2-a]pyrimidines could not be realised, but instead novel 3-(2-methyl prop-1-enyl)-2-hydroxy-4H-pyrido[1,2-a]pyrimidine-4-ones and 2,3-dihydro-4H-furo

[2,3-d]pyrido[1,2-a]pyrimidine-4-ones were successfully prepared by a simple route using diethyl alkylidenemalonates and 2-aminopyridines. On the other hand, diethyl benzylidenemalonate and diethly hexylidenemalonate did not produce similar cyclic products, indicating that the presence of branching at γ-position of diethyl alkylidenemalonates is essential. The reaction and its mechanism is under detailed study for further improvements and wider application of the method.

EXPERIMENTAL PART

^{1}H-nmr spectra were recorded on a Bruker WP 80 nmr spectrometer. Tetramethylsilane (TMS) was used as internal reference and all shifts are expressed as δ(ppm) values. The coupling constants (J) are given in Hz. The following abbreviations are used to describe the multiplicity of signals: (s) singlet, (d) doublet, (t) triplet, (q) quartet, (m) multiplet, (br) broad. Ir absorption spectra were obtained by Perkin Elmer 1600 series FTIR with polystyrene film calibration. The spectra were taken as a liquid film for liquid samples and as a potassium bromide (KBr) disc for solid samples. Only major or important peaks are reported in cm^{-1}, together with their assignments when possible. Mass spectra were obtained by a Kratos MS 50 RF instrument in conjunction with a Kratos DS 90 Data Requisition system. All commercially supplied chemicals were purified by an appropriate method.

Syntheses of diethyl alkylmethylenemalonates

In a 250 ml flask, acetic acid (0.005 mol, 0.25g) and piperidine (0.015 mol, 1.28 g) were mixed to make piperidinium acetate. Diethyl malonate (0.1 mol, 16g, redistilled), aldehyde (0.1 mol, contains 1%-5% impurity i.e. the corresponding carboxylic acid) and dried xylene (100 ml) were placed into the flask, which was fitted with a Dean-Stark trap, and a reflux condenser. The mixture was refluxed at 140^{0}C until no more water was collected. This operation requires 6-16 hours. After the mixture had been cooled, the solution was washed with water, dilute hydrochloric acid, and saturated sodium bicarbonate respectively. The organic layer was then dried (Na_2SO_4). Xylene was removed under pressure on a rotary evaporator. The residue was prified by vacuum distillation.

***Diethyl benzylidenemalonate* (6a);**

(23g,93%), b.p. 120-24^{0}C/0.2mmHg; ν_{max} (liq.)/cm^{-1} 3060, 2984, 2857, 1730-1712 (C=0 ester), 1649, 1642, 1462, 1445, 1377, 1255, 1200, 1062, 1020, 770, 695; δ_H (80 MHz; $CDCl_3$; Me_4Si) 1.1-1.4 (6H, t, 2Me), 4.0-4.4 (4H, 2q, $2CH_2$ of esters), 7.3 (5H, br, Ph), 7.7 (1H, s, -CH=); m/z 248.103 (M^+, 56.7%, $C_{14}H_{16}O_4$ requires 248.105), 203.1 (62.7), 173.0 (7.3), 158.0 (35.5), 130.0 (28.9), 102.0 (52.2), 84.0 (38.0).

***Diethyl pentylmethylenemalonate* (6b);**

(19.1g, 75%), b.p. 84-6^{0}C/0.5mmHg; ν_{max}(liq.)/cm^{-1} 2932,2858, 1732-1715 (C=0 ester), 1646, 1458, 1375, 1253, 1216, 1059, 860; δ_H (80 MHz; $CDCl_3$; Me_4Si) 0.8-1.0 (3H, t, Me), 1.2-1.4 (6H, dt, 2Me), 1.3-2.5 (8H, br, CH_2), 4.0-4.5 (4H, dq, $2CH_2$ of esters), 7.05 (1H, t, J=9.0Hz, -CH=); *m/z* 242.152 (M^+, 23.0%, $C_{13}H_{22}O_4$ requires 242.152), 197.1 (55.4), 169.1 (33.7), 150.1 (50.6), 127.0 (27.5) 95.1 (25.2), 85.0 (15.7).

***Diethyl isopropylmethylenemalonate* (6c);**

(17g, 80%), b.p. 100^{0}C/4.5mmHg; ν_{max} (liq.)/cm^{-1} 2989, 2856, 1722 (C=0 ester), 1644, 1468, 1446, 1372, 1323, 1252, 1215, 1149, 1055, 960, 867; δ_H (80 MHz; $CDCl_3$; Me_4Si) 1.1 (6H, d, 2Me of isopropyl), 1.35 (6H, dt, 2Me of ester), 2.7 (1H, br, CH), 4.25 (4H, dq, $2CH_2$ of esters), 6.78 (1H, d, J=10.5Hz,-CH=); m/z 214.120 (M^+, 2.5%, $C_{11}H_{18}O_4$ requires 214.120), 169.1 (24.9), 123.0 (31.4), 122.0 (100), 94.0 (4.8).

Syntheses of 3-(2-methylprop-1-enyl)-2-hydroxy-4H-pyrido[1,2-a]pyrimidine-4-ones

Finely mixed diethyl alkylmethylenemalonate (0.005 mol) and 2-amino pyridine (0.006 mol) were dissolved in 5 ml ethanol and heated on a silicon-oil bath at 160-170^{0}C. Ethanol was removed from system continually by distillation. Thirty minutes later a yellow solid started to precipitate, and after two or three hours heating the reaction was complete. The flask contents were dissolved in hot ethanol and product was crystallised by cooling. It was filtered-off and dried under vacuum.

***2-Hydroxy-3-(2-methyl prop-1-enyl)-4H-pyrido[1,2-a]pyridimidine-4-one* (7a);**

(73%), m.p. 232-35^{0}C. ν_{max} (KBr)/cm^{-1} 3107, 3072, 2966, 2895, 2813-2200 br (O-H enolic), 1672 (C=0 amide), 1649 (C=0 amide), 1613, 1528, 1478, 1410, 1278, 1255, 1049, 1026, 916, 890, 773, 750; δ_H (80 MHz; $CDCl_3$; Me_4Si) 1.7 (3H, s, CH_3), 2.0 (3H, s, CH_3), 6.05 (1H, s, -CH=), 7.25 (1H, t, J=7Hz, 7-/ or 8-H), 7.65 (1H, d, J=7Hz, 9-H), 8.0 (1H, t, J=7Hz, 7-/ or 8-H), 9.2 (1H, d, J=7Hz, 6-H); (Found : C, 66.67, H, 5.43, N, 13.04. $C_{12}H_{12}N_2O_2$ requires C, 66.67, H, 5.56, N, 12.96); *m/z* 216.090 (M^+, 91.5%, $C_{12}H_{12}N_2O_2$ requires 216.090), 187.1 (10.6), 147.1 (6.0), 121.0 (100), 94.1 (32.4), 78.0 (77.1).

***2-Hydroxy-3-(2-methylprop-1-enyl)-8-methyl-4H-pyrido[1,2-a]pyrimidine-4-one* (7b);**

(81%), m.p. 280-85^{0}C. ν_{max} (KBr)/cm^{-1} 3130, 2954, 2867, 2790-2250 br (O-H enolic), 1689 (C=0 amide), 1654 (C=0 amide), 1613, 1610, 1578, 1507, 1472, 1361, 1270, 757; δ_H (80 MHz; $CDCl_3$; Me_4Si) 1.7 (3H, s, CH_3), 2.0 (3H, s, CH_3), 2.6 (3H, s, 8-Me), 6.1 (1H, s, - CH=), 7.1 (1H, d, J=7Hz, 7-H), 7.45 (1H, s, 9-H), 9.1 (1H, d, J=7Hz, 6-H); (Found : C, 67.80, H, 5.98, N, 12.18, $C_{13}H_{14}N_2O_2$ requires C, 67.82, H, 6.08, N, 12.18); *m/z* 230.108 (M^+, 19.7%, $C_{13}H_{14}N_2O_2$ requires 230.106), 215.1 (45.2), 189.0 (19.6), 135.1 (100), 108.1 (32.0), 92.1 (53).

Syntheses of 2,3-dihydro-4H-furo[2,3-d]pyrido[1,2-a]pyrimidine-4-ones

A solution of 3-(2-methylprop-1-enyl) derivative (**7a,7b**) (1g) in trifluoroacetic acid/dichloromethane mixture (10ml) was stirred at room temperature for 4-6 hours.Then, the solution was concentrated under reduced pressure to an oily residue, which was treated with 50ml of ice-water mixture and neutralised with saturated sodium carbonate to pH 7-8. Organic materials precipitated were extracted with dichloromethane, washed with water, and dried ($MgSO_4$). Products were purifed by passing the dichloromethane solution through silica gel. (Unreacted starting materials could be recovered afterwards by washing the silica gel with methanol). Evaporation of dichloromethane gave the pure cyclic compound.

***2,2-Dimethyl-2,3-dihydro-4H-furo[2,3-d]pyrido[1,2-a]pyrimidine-4-one* (8a);**

(0.92g, 92%), m.p. 132-34^{0}C. ν_{max} (KBr)/cm^{-1} 3147, 3067, 2973, 2927, 2855, 1707 (C=0 amide) 1586, 1520, 1485, 1453, 1335, 1285, 1269, 1178, 1092, 962, 923, 850, 760, 736, 698; δ_H (80 MHz; $CDCl_3$; Me_4Si) 1.55 (6H, s, 2Me), 3.0 (2H, s, 3-CH_2), 7.0 (1H, t, 7-H), 7.5 (1H, d, 9-H), 7.6 (1H, t, 8-H), 9.1 (1H, d, 6-H), (Found : C, 66.78, H, 5.70, N, 12.99, $C_{12}H_{12}N_2O_2$ requires C, 66.67, H, 5.56, N, 12.96); *m/z* 216.091 (M^+, 100%, $C_{12}H_{12}N_2O_2$ requires 216.090), 201.1 (24.0), 175.1 (17.7), 130.1 (33.6), 121.0 (50.8), 105.0 (8.8), 96.1 (15.6), 78.0 (59.4).

***2,2,8-Trimethyl-2,3-dihydro-4H-furo[2,3-d]pyrido[1,2-a]pyrimidine-4-one* (8b);**

(0.87g, 87%), m.p. 135-36^{0}C. ν_{max} (KBr)/cm^{-1} 2966, 2924, 2855, 1702 (C=0 amide) 1585, 1487, 1342, 1373, 1099, 862, 761, 701; δ_H (80 MHz; $CDCl_3$; Me_4Si) 1.55 (6H, 2Me), 2.5 (3H, s, 8-Me), 3.0 (2H, s, 3-CH_2), 6.95 (1H, d, 7-H), 7.35 (1H, s, 9-H), 9.0 (1H, d, 6-H), (Found : C, 67.92, H, 6.16, N, 12.04, $C_{13}H_{14}N_2O_2$ requires C,

67.82, H, 6.08, N, 12.18); *m/z* 230.106 (M^+, 100%, $C_{13}H_{14}N_2O_2$ requires 230.106), 189.1 (21.4), 172.1 (20.6), 144.1 (26.1), 135.1 (42.5), 113.0 (18.1), 92.1 (46.4).

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