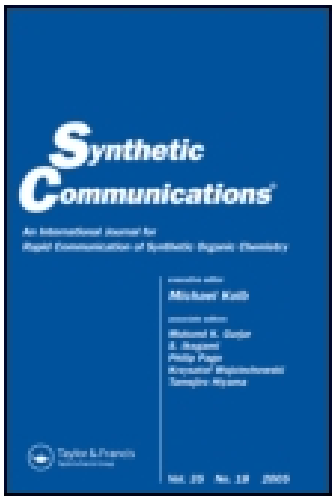

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AN UNEQUIVOCAL SYNTHESIS OF 4-METHYL-2-OXO-(2H)-PYRIDO- [1,2-a]PYRIMIDINES*

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AN UNEQUIVOCAL SYNTHESIS OF 4-METHYL-2-OXO-(2H)-PYRIDO-[1,2-a]PYRIMIDINES*

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ABSTRACT

An unequivocal high yielding synthesis of 4-methyl-2-oxo-(2H)-pyrido[1,2-a]pyrimidines from *N*-(1,3-dioxobutyl)-2-amino pyridines/picolines/quinoline, is being reported.

Recently, we have observed that aryl and hetaryl amines get aceto-acetylated on microwave assisted interaction with ethyl acetoacetate.[1] The *N*-(1,3-dioxobutyl)-2-aminopyridines/quinoline have been subjected to PPA catalysed cyclization to get 2-oxo-(2H)-pyrido[1,2-a]pyrimidines in appreciable yields. This constitutes first report about unequivocal synthesis of 4-methyl-2-oxo-(2H)-pyrido[1,2-a]pyrimidines by interaction of β-oxoester and 2-amino pyridines/picolines/quinoline. Earlier reported syntheses of title compounds are poor yielding and in some cases the synthesized compounds were later reassessed to be 4-oxo-(4H)-isomers.[2]

In one of the reports,[3] it was claimed that 2-oxo-(2H)-pyrido[1,2-a]-pyrimidines are produced by interaction of 2-amino-4-methyl pyridines

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and ethyl ethoxymethylenecyanoacetate; however, the products were later determined to be 4-oxo-isomers. Another poor yielding synthesis of 2-oxo-(2H)-pyrido[1,2-a]pyrimidines involved interaction of 2-aminopyrimidines and an acid chloride.[4] The therapeutic potential of 2-oxo-(2H)-pyrido[1,2-a]-pyrimidines has not been explored vis-a-vis 4-oxo-(4H)-isomers, some of which viz., pemirolast, pirenperone, metrenperone, risperidone, are already in clinical use, in all probability, due to lack of sound synthetic procedures.

In the present communication 4-methyl-2-oxo-(2H)-pyrido[1,2-a]-pyrimidines have been synthesised via *N*-acetoacetylated products obtained by microwave assisted condensation of 2-aminopyridines/picolines/quinoline. The synthetics have been characterised by ^{1}H-NMR, ^{13}C-NMR (CPD, HOMOCOR and HETCOR), MS, IR spectroscopy and elemental analytical data.

An important observation recorded on examination of HOMOCOR & HETCOR spectra of the compounds was the effect of C-4 methyl on chemical shifts of C-6 and its α-proton. In all the endproducts, C6-H, as expected, was the most deshielded one and the C-6 possessed lower chemical shift in comparison to C-8 except in compound 2, where C-6 is of quaternary character. The abnormal shielding of C-6, in spite of being attached to nitrogen, can be easily attributed to peri-effect of C-4 methyl group.

EXPERIMENTAL

Melting points were determined in open capillaries, and are uncorrected. Mass spectra were recorded on JEOL JMS D-300 mass spectrometer at 70 eV and IR spectra on Hitachi 270-30 spectrophotometer. NMR spectra were recorded on Bruker DPX-200 spectrometer. Elemental analytical data have been determined on Carlo Erba, Model 1106, elemental analyzer.

General Procedure

Phosphorous pentoxide and orthophosphoric acid in the ratio of w/v (3.5 g : 1.3 ml) were taken in a round bottomed flask fitted with a reflux condenser and a guard tube. The mixture was heated for 4 h on a steam bath with frequent shaking. The resulting PPA was used for the cyclization reactions.

A mixture of *N*-acetoacetylated product obtained by microwave assisted condensation of 2-amino pyridines/picolines/quinoline and PPA in the ratio of 1 : 10 w/w was taken in a round bottomed flask fitted with

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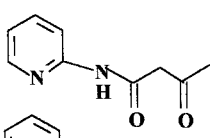
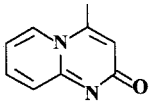
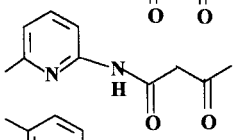
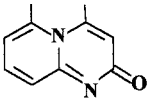
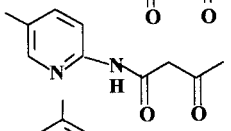
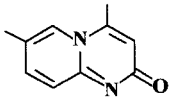
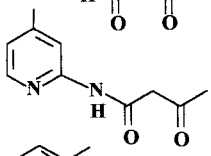
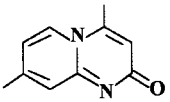
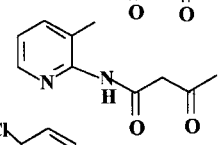
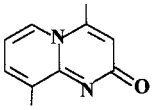
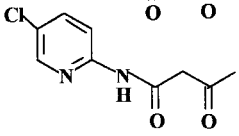
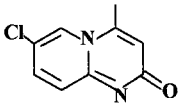
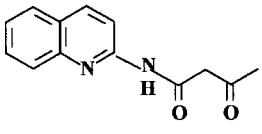
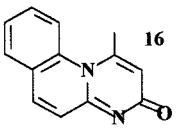
a reflux condenser and a guard tube. The reaction mixture was heated on steam bath with frequent shaking. The progress of the reaction was monitored on TLC. After completion of the reaction, the reaction mixture was diluted with distilled H_2O (20 ml), basified with ammonia solution and then extracted with $CHCl_3$ (5×50 ml). $CHCl_3$ extract was dried over anhy. Na_2SO_4 and concentrated under reduced pressure. The products were purified by filtration through a small silica gel column, using chloro-

Table. PPA Catalysed Cyclization of *N*-(1,3-Dioxobutyl)-2 Amino Pyridines/Picolines/Quinoline

Entry	Substrate	Product	Time (hrs)	Yield* (%)	mp ^0C
1.			8	70	117-118
2.			10	58	98
3.			9	69	126-127
4.			10	64	130
5.			10	72	123-24
6.			12	61	162-163
7.			16	52	129-30

*Yields refer to pure isolated products

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form : methanol (99 : 1) as eluant. TLC homogeneous fractions were crystallised from pet. ether (60–80°) in 52–72% yield (Table).

Spectral Data of Cyclised Products

4-Methyl-2-oxo-(2H)-pyrido[1,2-a]pyrimidine

IR (KBr): 1700 (CO), 1630 (C=N); ^{1}H NMR ($CDCl_3$): δ 2.47 (s, 3H, CH_3), 6.35 (s, 1H, H-3), 7.13 (dt, 1H, $J = 7.12$ and 1.28 Hz, H-7), 7.60 (bd, 1H, $J = 7.12$ Hz, H-9), 7.74 (dt, 1H, $J = 7.12$ and 1.28 Hz, H-8), 9.03 (bd, 1H, $J = 7.12$ Hz, H-6); MS (m/z) M^+: 160, calcd for $C_9H_8N_2O$; C, 67.50; H, 5.00; N, 17.50; found: C, 67.45; H, 5.09; N, 17.42%; ^{13}C NMR: δ 25.00 (CH_3), 103.63 (C-3), 115.39 (C-7), 126.14 (C-9), 127.56 (C-6), 136.61 (C-8), 151.06 (C-4), 158.18 (C-10), 165.62 (C-2).

4,6-Dimethyl-2-oxo-(2H)-pyrido[1,2-a]pyrimidine

IR (KBr): 1692 (CO), 1636 (C=N); ^{1}H NMR ($CDCl_3$): δ 2.35 (s, 3H, C4-CH_3), 3.03 (s, 3H, C6-CH_3), 6.14 (s, 1H, H-3), 6.62 (dd, 1H, $J = 6.58$ and 1.26 Hz, H-9), 7.32 (dd, 1H, $J = 6.58$ and 1.26 Hz, H-7), 7.42 (dd, 1H, $J = 6.58$ Hz, H-8); MS (m/z) M^+: 174, calcd for $C_{10}H_{10}N_2O$; C, 68.96; H, 5.74; N, 16.09; found: C, 68.92; H, 5.77; N, 15.96%; ^{13}C NMR: δ 24.16 (C4-CH_3), 25.09 (C6-CH_3), 105.99 (C-3), 118.26 (C-9), 125.08 (C-7), 135.54 (C-8), 144.29 (C-6), 153.61 (C-4), 162.43 (C-10), 163.75 (C-2).

4,7-Dimethyl-2-oxo-(2H)-pyrido[1,2-a]pyrimidine

IR (KBr): 1686 (CO), 1638 (C=N); ^{1}H NMR ($CDCl_3$): δ 2.42 (s, 3H, C4-CH_3), 2.45 (s, 3H, C7-CH_3), 6.32 (s, 1H, H-3), 7.52 (d, 1H, $J = 9.04$ Hz, H-9), 7.60 (dd, 1H, $J = 9.04$ and 1.25 Hz, H-8), 8.85 (bs, 1H, H-6); MS (m/z) M^+: 174, calcd for $C_{10}H_{10}N_2O$; C, 68.96; H, 5.74; N, 16.09; found; C, 68.84; H, 5.79; N, 16.01%; ^{13}C NMR: δ 18.66 (C7-CH_3), 24.98 (C4-CH_3), 103.45 (C-3), 116.96 (C-7), 125.06 (C-6), 125.65 (C-9), 139.54 (C-8), 150.07 (C-4), 158.16 (C-10), 165.12 (C-2).

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4,8-Dimethyl-2-oxo-(2H)-pyrido[1,2-a]pyrimidine

IR (KBr): 1706 (CO), 1642 (C=N); ^{1}H NMR ($CDCl_3$): δ 2.45 (s, 3H, C4-CH_3), 2.48 (s, 3H, C8-CH_3), 6.27 (s, 1H, H-3), 6.95 (dd, 1H, $J = 7.27$ and 1.29 Hz, H-7), 7.38 (bs, 1H, H-9), 8.92 (d, 1H, $J = 7.27$ Hz, H-6); MS (m/z) M^+: 174, calcd for $C_{10}H_{10}N_2O$; C, 68.96; H, 5.74; N, 16.09; found: C, 68.86; H, 5.80; N, 16.13%; ^{13}C NMR: δ 21.81 (C8-CH_3), 25.05 (C4-CH_3), 102.82 (C-3), 118.13 (C-7), 124.23 (C-9), 126.93 (C-6), 148.81 (C-8), 151.15 (C-4), 158.34 (C-10), 165.91 (C-2).

4,9-Dimethyl-2-oxo-(2H)-pyrido[1,2-a]pyrimidine

IR (KBr): 1688 (CO), 1628 (C=N); ^{1}H NMR ($CDCl_3$): δ 2.47 (s, 3H, C4-CH_3), 2.57 (s, 3H, C9-CH_3), 6.33 (s, 1H, H-3), 6.99 (dd, 1H, $J = 7.12$ Hz, H-7), 7.55 (bd, 1H, $J = 7.12$ Hz, H-8), 8.92 (bd, 1H, $J = 7.12$ Hz, H-6); MS (m/z) M^+: 174, calcd for $C_{10}H_{10}N_2O$; C, 68.96; H, 5.74; N, 16.09; found: C, 68.83; H, 5.81; N, 16.01%; ^{13}C NMR: δ 18.65 (C9-CH_3), 25.27 (C4-CH_3), 103.49 (C-3), 114.78 (C-7), 125.71 (C-6), 134.84 (C-9), 135.15 (C-8), 150.68 (C-4), 158.84 (C-10), 164.86 (C-2).

7-Chloro-4-methyl-2-oxo-(2H)-pyrido[1,2-a]pyrimidine

IR (KBr): 1680 (CO), 1624 (C=N); ^{1}H NMR ($CDCl_3$): δ 2.47 (s, 3H, CH_3), 6.36 (s, 1H, H-3), 7.55 (d, 1H, $J = 9.44$ Hz, H-9), 7.66 (dd, 1H, $J = 9.44$ and 2.17 Hz, H-8), 9.05 (d, 1H, $J = 2.17$ Hz, H-6); MS (m/z) M^+: 194, calcd for $C_9H_7N_2OCl$; C, 55.67; H, 3.60; N, 14.43; found: C, 55.59; H, 3.53; N, 14.49%; ^{13}C NMR: δ 23.62 (CH_3), 102.78 (C-3), 122.59 (C-7), 123.99 (C-6), 125.84 (C-9), 136.35 (C-8), 148.03 (C-4), 155.75 (C-10), 164.17 (C-2).

4-Methyl-benzo[f]-2-oxo-(2H)-pyrido[1,2-a]pyrimidine

IR (KBr): 1664 (CO), 1630 (C=N); ^{1}H NMR ($CDCl_3$): δ 2.39 (s, 3H, CH_3), 6.39 (s, 1H, H-3), 7.24 (d, 1H, $J = 8.64$ Hz, H-11), 7.61 (m, 4H, H-6, H-7, H-8 and H-9), 8.64 (d, 1H, $J = 8.64$ Hz, H-10); MS (m/z) M^+: 210, calcd for $C_{13}H_{10}N_2O$; C, 74.28; H, 4.76; N, 13.33; found: C, 74.21; H, 4.71; N, 13.38%; ^{13}C NMR: δ 23.85 (CH_3), 109.61 (C-3), 122.70 (C-10), 124.68 (C-11), 125.20 (C-9a), 127.19 (C-6), 128.45 (C-8), 130.05 (C-7), 135.84, (C-4), 136.90 (C-9), 151.47 (C-5a), 162.19 (C-11a), 163.67 (C=O).

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