Facile synthesis of 3-(4-oxo-4H-pyrido[1,2-a]pyrimidin-3-yl)-1-phenyl-1H-pyrazole-4-carbaldehyde and its condensation with various active methylene groups

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Vilsmeier-Haack formylation of 3-acetyl-4H-pyrid[1,2-a]pyrimidin-4-one 5a-b gives the pyrazole aldehyde i.e., 3-(4-oxo-4H-pyrido[1,2-a]pyrimidin-3-yl)-1-phenyl-1H-pyrazole-4-carbaldehyde 6a-b which on condensation with various active methylene group containing compounds 7-10 gives the corresponding Knoevenagel products i.e., 11a,b-14a,b respectively. Structures of all the Knoevenagel products are assigned based on spectral and analytical data.

Keywords: Phenylhydrazine, 3-methyl-1H-pyrazole-5(4H)-one, 3-methyl-1-phenyl-pyrazole-5(4H)-one, Meldrum’s acid, barbituric acid

Pyrido[1,2-a]pyrimidin-4-one is a well known class of aza-bridged fused heterocyclic compounds which has a variety of biological activities such as anti-bacterial, anti-psychotic, anti-cytotoxic, etc. Therefore, it was considered worthwhile to synthesise pyrido[1,2-a]pyrimidin-4-ones as potential biologically active compounds and as new chemical entities.

Vanelle et al. reported that the preparation of 3-aryl(alkyl)-1-phenyl-1H-pyrazole-4-carbaldehyde via the Vilsmeier-Haack formylation of the appropriate phenylhydrazones derived from the reaction of aryl methyl ketones with phenylhydrazine. Kumar et al. reported the reaction of acetylphenone with phenyl hydrazine in methanol containing a catalytic amount of glacial acetic acid at reflux temperature to yield the corresponding phenyl hydrazine which upon Vilsmeier-Haack formylation led to the phenylpyrazolaldehyde. The latter, on condensation with thiazolidinedione, resulted in the corresponding pyrazolothiazolidinediones. Brehme et al. reported that 2-phenylglyoxal hydrazones underwent Vilsmeier-Haack formylation of benzaldehyde followed by hydrolysis in aq. NaHCO₃ giving N,N-dimethylhydrazones. Damljanovic et al. reported that the condensation of acetyl ferrocene with phenyl hydrazine followed by intramolecular cyclization of the intermediate hydrazone under Vilsmeier-Haack conditions formed 1H-3-ferrocenyl-1-phenylpyrazole-4-carboxaldehyde. Rajput et al. reported that the condensation of 4-chlorophenyl carboxylic acid hydrazide with different acetoophenones and acetaldehydes afforded the corresponding acetoophenones/acetaldehyde 4-chlorophenyl carbonyl hydrazones which on Vilsmeier-Haack reaction gave the formylated the compounds 1-(3-aryl/alkyl-4-formyl pyrazole-1-carbonyl)-4-chlorobenzenes.

Results and Discussion

Commercially available 2-aminopyridine 1a (i.e., 1, X=H) was condensed with ethyl ethoxymethylene acetoacetate (2) in ethanol under refluxing conditions for 4 h giving a product which has been characterized as ethyl 3-oxo-2-((pyridin-2-ylamino)methylene)butanoate 3a (i.e., 3, X=H) on the basis of its spectral data. Similar reaction of 1b (i.e., 1, X=Br) with 2 resulted in the formation of 3b (i.e., 3, X=Br) whose structure was assigned based on its spectral data.

On thermal cyclization in diphenyl ether for 30 min at 255°C, 3a gave a product which has been characterized as 3-acetyl-4H-pyrido[1,2-a]pyrimidin-4-one 4a (i.e., 4, X=H) on the basis of its spectral data. Similar reaction of 3b (i.e., 3, X=Br) gave the product 4b (i.e., 4, X=Br) whose structure was assigned based on its spectral data.

Compound 4a (i.e., 4, X=H) with phenylhydrazine in ethanol containing a catalytic amount of acetic acid at RT for 6 h gave the corresponding phenyl-
Condensation of $6$ with 3-methyl-1H-pyrazol-5(4H)-one, $7$

Condensation of $6a$ (i.e., $6, X = H$), with 3-methyl-1H-pyrazol-5(4H)-one ($7$) in DMF containing a few drops of piperidine at RT for 2 h gave 3-(4-(3-methyl-5-oxo-1H-pyrazol-4(5H)-ylidene)methyl)-1-phenyl-1H-pyrazole-3-yl)-4H-pyrido[1,2-a]pyrimidin-4-one $11a$ (i.e., $11, X = H$) as the product whose structure was assigned on the basis of its spectral data. Similar condensation of $6b$ (i.e., $6, X = Br$) with $7$ gave $11b$ (i.e., $11, X = Br$) whose structure was assigned based on its spectral data.

Condensation of $6$ with 3-methyl-1-phenyl-pyrazol-5(4H)-one, $8$

Compound $6a$ on treatment with 3-methyl-1-phenyl-pyrazol-5(4H)-one ($8$) in DMF containing a catalytic amount of piperidine at RT for 2 h gave 3-(4-(3-methyl-5-oxo-1-phenyl-pyrazol-4(5H)-ylidene)methyl)-1-phenyl-1H-pyrazole-3-yl)-4H-pyrido[1,2-a]pyrimidin-4-one $12a$ (i.e., $12, X = H$) as the product whose structure was assigned on the basis of its spectral data. Similar condensation of $6b$ (i.e., $6, X = Br$) with $8$ gave $12b$ (i.e., $12, X = Br$) whose structure was assigned based on its spectral data.

Condensation of $6$ with Meldrum’s acid, $9$

Compound $6a$ on treatment with Meldrum’s acid in DMF containing a catalytic amount of piperidine at RT for 2 h gave 2,2-dimethyl-5-((3-4-oxo-4H-pyrido[1,2-a]pyrimidin-3-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)-1,3-dioxane-4,6-dione. ($13a$ i.e., $13, X = H$) as the product whose structure was assigned on the basis of its spectral data. Similar condensation of $6b$ (i.e., $6, X = Br$) with $9$ gave $13b$ (i.e., $13, X = Br$) whose structure was assigned based on its spectral data.

Condensation of $6$ with barbituric acid, $10$

Compound $6a$ on treatment with barbituric acid in DMF containing a catalytic amount of few drops of piperidine at RT for 2 h gave 2,2-dimethyl-5-((3-(4-oxo-4H-pyrido[1,2-a]pyrimidin-3-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)dihydropyrimidine-4,6(1H,5H)-dione. ($14a$ i.e., $14, X = H$) as the product whose structure was assigned on the basis of its spectral data. Similar condensation of $6b$ (i.e., $6, X = Br$) with $9$
gave 14b (i.e., 14, X = Br) whose structure was assigned based on its spectral data (Scheme II).

**Experimental Section**

All the reagents used in this work were obtained from commercial suppliers, except ethyl ethoxy methylene acetoacetate (2). The latter was prepared in the laboratory using a reported procedure\textsuperscript{13}. Melting points are uncorrected and were determined using open capillary tubes in sulfuric acid bath. TLC analyses were done on plastic sheets coated with silica gel G and spotting was done using Iodine/UV lamp. IR spectra were recorded on a Perkin-Elmer model 1000 instrument in KBr pellet. \textsuperscript{1}H NMR spectra were recorded in CDCl\textsubscript{3} or in DMSO-\textit{d}\textsubscript{6} using 400 MHz Varian Gemini spectrometer and TMS as a reference standard. Mass spectra were recorded on an Agilent-LCMS and Agilent HR-MS instrument.

**Preparation of ethyl-3-oxo-2-((pyridin-2-ylamino)methylene)butanoate, 3**

A mixture of 1 (10 mmol), 2 (10 mmol) and ethanol (30 mL) was refluxed for 4 h on a hot-water bath. The reaction was monitored by TLC. After completion of the reaction, as indicated by disappearance of 1, the mixture was poured into ice-cold water (50 mL) and stirred for 5 min. The separated solid was filtered, washed with water (2x30 mL) and dried. The product was recrystallized from a suitable solvent to obtain pure 3.

**Ethyl-3-oxo-2-((pyridin-2-ylamino)methylene)butanoate, 3a:** Yield 79\%. m.p. 82-85°C (methanol). IR (KBr): 3119-3070 (medium, broad, NH), 1724 and 1700 cm\textsuperscript{−1} (strong, sharp, two C=O groups); \textsuperscript{1}H NMR (DMSO-\textit{d}\textsubscript{6}/TMS): δ 1.3 (s, 3H, CH\textsubscript{3}), 4.2 (q, 2H, CH\textsubscript{2} of ester group), 2.4 (s, 3H, CH\textsubscript{3} of the ester group), 8.1 - 8.3 (t, 3H, Ar-H, three protons of pyridine ring), 8.5

Scheme II — Condensation of various active methylene compounds with 6a-b to obtain products 11-14 (a, i.e., X = H, b, i.e., X = Br)
(s, 1H, α-H to the enamine nitrogen), 9.2 (q, 1H, one proton of the pyridine ring); LC-MS (HR-MS): m/z 235.1083 [M+H]+.

Ethyl-2-[(5-bromopyridin-2-yl)amino)methylene]-3-oxo-butan-2-one, 3b: Yield 74%. m.p.105-108°C (methanol). IR (KBr): 3219-2810 (medium, broad, NH), 1726 and 1704 cm⁻¹ (strong, sharp, two C=O groups); ¹H NMR (DMSO-d6/TMS): δ 1.3, (s, 3H, CH₃), 4.2(q , 2H, CH₂ of ester protons), 2.4 (s, 3H, CH₃), 7.6 (q, 1H, Ar-H), 8.1 (t, 2H, Ar-H, two protons of pyridine ring), 8.5 (s, 1H, α-H to the enamine nitrogen), 8.9 (s, NH pyridine nitrogen); LC-MS (HR-MS): m/z 310.1021 [M+H]+.

Preparation of 3-acetyl-4H-pyrdo[1,2-a]pyrimidin-4-one, 4

Compound 3 (5 mmol) was added, portion-wise to hot diphenylether (25 mL) at 255°C, boiling the whole mixture for about 30 min. After the completion of reaction, as indicated by TLC for disappearance of 3, the mixture was cooled to RT and poured into n-hexane (50 mL). The separated solid was filtered, washed with n-hexane (2x20 mL) and dried. The crude product was recrystallized from a suitable solvent.

3-Acetyl-4H-pyrdo[1,2-a]pyrimidin-4-one, 4a: Yield 65%. m.p.151-54°C (ethyl acetate). IR (KBr): 1748 and 1698 cm⁻¹ (COCH₃ and C=O); ¹H NMR (DMSO-d6/TMS): δ 2.4 (s, 3H, CH₃), 8.2 (t, 3H, Ar-H, three protons of pyridine ring), 8.6 (s, 1H, α-H to the enamine nitrogen), 9.1 (s, 1H, Ar-H); LC-MS (HR-MS): m/z 189.0661 [M+H]+.

3-Acetyl-7-bromo-4H-pyrdo[1,2-a]pyrimidin-4-one, 4b: Yield 62%. m.p.170-74°C (ethyl acetate). IR (KBr): 3122-3073 region (medium, broad, -NH), 1748-1698 cm⁻¹ (strong, sharp two C=O groups); ¹H NMR (DMSO-d6/TMS): δ 2.5 (s, 3H, CH₃), 8.4 (s, 1H, pyridine ring proton), 9.2 (s, 1H, α-H to the enamine nitrogen); LC-MS (HR-MS): m/z 268.8895 [M+H]+.

Preparation of 3-(1-(2-phenylhydrazono)ethyl)-4H-pyrdo[1,2-a]pyrimidin-4-one, 5

A mixture of 4 (7 mmol), phenylhydrazine (7 mmol) and ethanol (20 mL) containing 3-4 drops of glacial acetic acid was stirred at RT for 3 h. The separated solid was filtered, washed, dried and purified by recrystallization from acetic acid.

3-(1-(2-Phenylhydrazono)ethyl)-4H-pyrdo[1,2-a]pyrimidin-4-one, 5a: Yield 76%. m.p.161-64°C (acetic acid). IR (KBr): 1748 and 1708 cm⁻¹ (strong, sharp, two C=O groups); ¹H NMR (DMSO-d6/TMS): δ 7.4-8.2 (m, 9H, Ar-H, pyridine, pyrazole and aryl ring protons), 8.4 (s, 1H, pyridine ring proton), 9.2 (s, 1H, α-H to the enamine nitrogen), 9.1 (d, 1H, NH, D₂O exch.), 10 (s, 1H, CHO); LC-MS: m/z 316 [M+H]+.

7-Bromo-3-(1-(2-phenylhydrazono)ethyl)-4H-pyrdo[1,2-a]pyrimidin-4-one, 5b: Yield 74%. m.p.169-72°C (acetic acid). IR (KBr): 3121-3072 (medium, broad, NH), 1748 cm⁻¹ (strong, sharp, C=O groups); ¹H NMR (DMSO-d6/TMS): δ 2.5 (s, 3H, CH₃), 6.8-8.0 (m, 7H, Ar-H and pyridine ring protons), 8.4 (s, 1H, pyridine ring proton), 8.8 (s, 1H, α-proton to the enamine nitrogen), 9.2 (s, 1H, NH, D₂O exch.); LC-MS: m/z 279 [M+H]+.

Preparation of 3-(4-oxo-4H-pyrdo[1,2-a]pyrimidin-3-yl)-1-phenyl-1H-pyrazole-4-carbaldehyde, 6

To cold DMF (10 mmol) was added drop-wise with stirring phosphorus oxychloride (10 mmol) over a period of 30 min. Stirring was continued for further 45 min keeping the reaction mixture at 0°C. Then 5a/5b (1 mmol) was added to the reaction mixture in small lots. After completion of addition, temperature was slowly allowed to rise to RT and then heated to 90°C for 1 h. The mixture was then cooled to RT, poured into minimum quantity of crushed ice followed by neutralization of the resulting solution using saturated sodium bicarbonate. The solid thus separated was collected by filtration, washed with distilled water (2x30 mL) and dried. The crude product was purified by recrystallization from acetic acid.

3-(4-Oxo-4H-pyrdo[1,2-a]pyrimidin-3-yl)-1-phenyl-1H-pyrazole-4-carbaldehyde, 6a: Yield 69%. m.p.161-64°C (acetic acid). IR (KBr): 3117-3080 (medium, broad, NH), 1742 and 1673 cm⁻¹ (strong, sharp, two C=O groups); ¹H NMR (DMSO-d6/TMS): δ 2.4 (s, 3H, CH₃), 7.4-8.2 (m, 9H, Ar-H, pyridine and vinylic proton), 8.5 (s, 1H, pyrazole ring proton), 9.1 (s, 1H, α-proton to the enamine nitrogen), 10.1 (s, 1H, CHO); LC-MS: m/z 397 [M+H]+.

3-(7-Bromo-4-oxo-4H-pyrdo[1,2-a]pyrimidin-3-yl)-1-phenyl-1H-pyrazole-4-carbaldehyde, 6b: Yield 66%. m.p.231-34°C (acetic acid). IR (KBr): 3119-3082 (medium, broad, NH), 1748 cm⁻¹ (strong, sharp, two C=O groups); ¹H NMR (DMSO-d6/TMS): δ 7.4-8.2 (m, 8H, pyridine and pyrazole ring protons), 8.4 (s, 1H, pyridine ring proton), 9.2 (s, 1H, α-proton to the enamine nitrogen), 9.1 (d, 1H, NH, D₂O exch.), 10 (s, 1H, CHO); LC-MS: m/z 396 [M+H]+.

Preparation of 11a-b, 12a-b, 13a-b, 14a-b and 15a-b

A mixture of 6a/6b (1 mmol), active methylene group compound (1 mmol), 3-4 drops of piperidine
and DMF (40 mL) was stirred at RT for 2 h. The completion of the reaction was monitored by TLC for disappearance of 6α/6β. Then, the reaction mixture was poured into ice-cold water. The separated solid was collected and dried. Recrystallization from a suitable solvent gave the pure product.

3-(4-(3-Methyl-5-oxo-1H-pyrazole-4(5H)-ylidene)methyl)-1-phenyl-1H-pyrazol-3-yl)-4H-pyrido[1,2-alpyrimidin-4-one, 11a: Yield 62%. m.p.>250°C (acetic acid). IR (KBr): 3119-3082 (medium, broad, NH), 1740 and 1675 cm\(^{-1}\) (strong, sharp, two C=O groups); \(^1\)H NMR (DMSO-d\(_6\)/TMS): δ 2.3 (s, 3H, CH\(_3\)), 7.4-8.2 (m, 9H, Ar-H, pyridine and vinylic proton), 8.4 (s, 1H, pyrazole ring proton), 9.2 (s, 1H, α-proton to the enamine nitrogen), 9.1 (s, 1H, NH, D\(_2\)O exch.), 10.1 (s, 1H, CHO); LC-MS: m/z 397 [M\(^{+}\)+1].

7-Bromo-3-(4-(3-methyl-5-oxo-1H-pyrazole-4(5H)-ylidene)methyl)-1-phenyl-1H-pyrazol-3-yl)-4H-pyrido[1,2-alpyrimidin-4-one, 11b: Yield 60%. m.p.>250°C (acetic acid). IR (KBr): 3119-3082 (medium, broad, NH), 1741 and 1690 cm\(^{-1}\) (strong, sharp, two C=O groups); \(^1\)H NMR (DMSO-d\(_6\)/TMS): δ 2.3 (s, 3H, CH\(_3\)), 7.4-8.2 (m, 8H, Aromatic, pyridine and vinylic proton), 8.4 (s, 1H, pyrazole ring proton), 9.2 (s, 1H, α-proton to the enamine nitrogen), 9.3 (s, 1H, NH, D\(_2\)O exch.); LC-MS: m/z 397 [M\(^{+}\)+1].

3-(4-(3-Methyl-5-oxo-1-phenyl-1H-pyrazole-4(5H)-ylidene)methyl)-1-phenyl-1H-pyrazol-3-yl)-4H-pyrido[1,2-alpyrimidin-4-one, 12a: Yield 68%. m.p.>250°C (acetic acid). IR (KBr): 3119-3082 (medium, broad, NH), 1745 and 1680 cm\(^{-1}\) (strong, sharp, two C=O groups); \(^1\)H NMR (DMSO-d\(_6\)/TMS): δ 2.3 (s, 3H, CH\(_3\)), 2.5 (s, 3H, CH\(_3\)), 7.4-8.2 (m, 13H, Ar-H, pyridine and vinylic proton), 8.4 (s, 1H, pyrazole ring proton), 9.2 (s, 1H, α-H to the enamine ring nitrogen); LC-MS: m/z 473 [M\(^{+}\)+1].

7-Bromo-3-(4-(3-methyl-5-oxo-1-phenyl-1H-pyrazole-4(5H)-ylidene)methyl)-1-phenyl-1H-pyrazol-3-yl)-4H-pyrido[1,2-alpyrimidin-4-one, 12b: Yield 63%. m.p.>250°C (acetic acid). IR (KBr): 3119-3082 (medium, broad, NH), 1748 and 1682 cm\(^{-1}\) (strong, sharp, two C=O groups); \(^1\)H NMR (DMSO-d\(_6\)/TMS): δ 2.3 (s, 3H, CH\(_3\)), 7.4-8.2 (m, 12H, Aromatic protons, pyridine and vinylic proton), 8.4 (s, 1H, pyrazole ring proton), 9.2 (s, 1H, α-H to the enamine nitrogen), 9.3 (s, 1H, NH, D\(_2\)O exch.); LC-MS: m/z 551 [M\(^{+}\)+1].

2,2-Dimethyl-5-((3-(4-oxo-4H-pyrido[1,2-alpyrimidin-3-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)-1,3-dioxane-4,6-dione, 13a: Yield 68%. m.p.>250°C (acetic acid). IR (KBr): 3115-3080 (medium, broad, NH), 1750 and 1685 cm\(^{-1}\) (strong, sharp, two C=O groups); \(^1\)H NMR (DMSO-d\(_6\)/TMS): δ 1.6 (s, 2H, CH\(_2\)), 7.4-8.2 (m, 12H, Aromatic proton, pyridine and vinylic proton), 8.4 (s, 1H, pyrazole ring proton), 9.2 (s, 1H, α-proton to the enamine nitrogen); LC-MS: m/z 443 [M\(^{+}\)+1].

5-((3-(7-Bromo-4-oxo-4H-pyrido[1,2-alpyrimidin-3-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)-2,2-dimethyl-1,3-dioxane-4, 6-dione, 13b: Yield 63%. m.p.>250°C (acetic acid). IR (KBr): 3115-3080 (medium, broad, NH), 1740 and 1673 cm\(^{-1}\) (strong, sharp, two C=O groups); \(^1\)H NMR (DMSO-d\(_6\)/TMS): δ 1.6 (s, 2H, CH\(_2\)), 7.4-8.2 (m, 7H, Aromatic proton, pyridine and vinylic proton), 8.4 (s, 1H, pyrazole ring proton), 9.2 (s, 1H, α-proton to the enamine nitrogen); LC-MS: m/z 522 [M\(^{+}\)+1].

2,2-Diethyl-5-((3-(4-oxo-4H-pyrido[1,2-alpyrimidin-3-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)-1,3-dioxane-4,6-dione, 14a: Yield 64%. m.p.>250°C (acetic acid). IR (KBr): 3130-3080 (medium, broad, NH), 1735 and 1670 cm\(^{-1}\) (strong, sharp, two C=O groups); \(^1\)H NMR (DMSO-d\(_6\)/TMS): δ 6.5 (s, 1H, HC=CH), 7.9 (s, 1H, C=CH), 7.7-8.2 (m, 3H, three protons of pyridine ring), 8.6 (s, 1H, α-H to the enamine nitrogen), 9.2 (s, 1H, NH pyridine nitrogen), 12.3 (s, 2H, NH); LC-MS: m/z 441 [M\(^{+}\)+1].

5-((3-(7-Bromo-4-oxo-4H-pyrido[1,2-alpyrimidin-3-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione, 14b: Yield 64%. m.p.>250°C (acetic acid). IR (KBr): 3130-3080 (medium, broad, NH), 1739 and 1671 cm\(^{-1}\) (strong, sharp, two C=O groups); \(^1\)H NMR (DMSO-d\(_6\)/TMS): δ 6.5 (s, 1H, HC=CH), 7.9 (s, 1H, C=CH), 7.7 (s, 1H, pyridine ring proton), 8.7 (s, 1H, pyridine ring proton), 8.6 (s, 1H, α-H to the enamine nitrogen), 9.2 (s, 1H, NH pyridine nitrogen), 12.4 (s, 2H, NH); LC-MS: m/z 520 [M\(^{+}\)+1].

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References