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5-amino-3-(cyanomethyl)-1H-pyrazole-4-carbonitrile as Precursor for synthesis of some novel pyrazolo[1,5-a]pyrimidine derivatives

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Abstract

New pyrazolo[1,5-a]pyrimidine-3-carbonitrile **5** was obtained by reaction of 5-amino-3-cyanomethyl-1H-pyrazole-4-carbonitrile **3** with enamine of acetylacetone **2**. Coupling of compound **5** with aryldiazonium chloride **6a-c** afforded pyrimido[1',2':1,5]pyrazolo[3,4-d]pyridazine derivatives **8**. Also, condensation of compound **5** with aromatic aldehydes **9a-c** gives the corresponding arylidene derivatives **10**. stirring of compound **5** with phenyl isothiocyanate in presence of potassium hydroxide, followed by addition of phencyl bromide derivatives **13a-c** or chloroacetonitrile **18** afforded (thiophen-3-yl)-7-methylpyrazolo[1,5-a]pyrimidine-3-carbonitrile **16a-c** and **20** which cyclized by refluxing in ethanolic sodium ethoxide solution to afforded thieno[3",4":5',6']pyrido [4',3':3,4]pyrazolo[1,5-a]pyrimidine derivatives **17a-c** and **21**.

Keywords: pyrazolo, pyrimidine, arylidene, phencyl bromide.

1. Introduction

Pyrazolo[1,5-a]pyrimidine derivatives are an import-ant group of heterocyclic compounds with pharmaco-logical and biological activities, such as the antibact-erial [1], antiviral [2], cytotoxic [3], antidepressant [4], antihypertensive [5], analgesic [6], Antitumour [7] and antimicrobial activity [8-11]. The pyrazolo [1,5-a]pyrimidines as bicyclic heterocycles have an important synthetic value in preparing drugs with anticancer activities [12-19]. Pyrazolo[1,5-a]pyram-idine analogs have been extensively studied as kinase inhibitors [20-25]. The most common methods for synthesizing pyrazolo[1,5-a]pyrimidine derivatives are cyclocondensations of 5-aminopyrazoles with bifunctional reagents [26-29]. Consequently, synthetic methodologies for novel pyrazolo[1,5-a]pyramidine derivatives are of particular interest to organic and medicinal chemists. In our study we reported a convenient methods for the synthesis of some new pyrazolo[1,5-a]pyrimidine derivatives with expected biological activity.

2. Experimental

All analyses were done at the faculty of Science, Sohag University, Sohag (Egypt). IR spectra (KBr) were recorded on FTIR 5300 spectrometer (ν, cm^{-1}). The ^{1}HNMR and ^{13}CNMR spectra were recorded in DMSO-*d6* at 400MHz on a Varian Gemini NMR spectrometer (δ, ppm) using TMS as an internal standard.

2.1 Synthesis of 6-acetyl-2-(cyanomethyl)-7-methyl pyrazolo[1,5-a]pyrimidine-3-carbonitrile (5)

A mixture of acetylacetone (**1**) (0.01mol) with *N*,*N*- dimethylformamide dimethyl acetal (DMFDMA) (1.32 ml, 0.01 mol) was stirred at room temperature. for 24 h. Then was added 5-amino-3-(cyanomethyl)-1*H*-pyrazole-4-carbonitrile (**3**) (1.47g, 0.01mol) in glacial acetic acid. The mixture was heated under reflux for 4 h, then allowed to cool. The solid product was collected and recrystallized from ethanol as brown crystals. Yield: (1.85g, 77.41%), m.p. 218-220 °C; IR (KBr, cm^{-1}): 3075 (CH-aromatic), 2928 (CH-aliphatic), 2230 (C≡N) and 1688 (C=O); ^{1}HNMR (DMSO-d_6, 400MHz): 2.6 (s, 3H, CH_3), 3.05(s, 3H, CH_3CO), 4.5(s, 2H, CH_2) and 8.94 ppm (s, 1H, H-pyrimidine); ^{13}CNMR (DMSO-d_6, 100MHz): 16.22, 19.23, 28.52, 81.85, 114.2, 117.05, 126.1, 148.32, 150.21, 151.4, 158.06 and 197.42 ppm; Anal. Calcd. For $C_{12}H_9N_5O$: C, 60.25;

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H, 3.79; N, 29.27. Found: C, 60.08; H, 3.54; N, 29.12.

*2.2. General Procedure for Synthesis of pyrimido [1',2':1,5]pyrazolo[3,4-d]pyridazine derivatives (**8a-c**).*

A solution of compound (**5**) (0.01mol) in ethanol (30 ml) containing sodium acetate (2gm) was cooled to 0ºC, was stirred, and treated gradually with cooled solution of aryl diazonium chloride (**6a-c**). The solid product so formed was collected and recrystallized from ethanol.

*2.2.1. 3-Acetyl-10-imino-4-methyl-9-phenyl-9,10-dihydropyrimido[1',2':1,5]pyrazolo[3,4-d]pyridazine-7-carbonitrile (**8a**).*

As yellow brown crystals Yield: (2.4g, 69.9 %), m.p. 280-282 °C; IR (KBr, cm^{-1}): 3333 (NH), 3053 (CH-aromatic), 2924 (CH-aliphatic), 2222 (C≡N) and 1698 (C=O); ^{1}HNMR (DMSO-d_6, 400MHz): 2.38(s, 3H, CH_3), 2.81(s, 3H, CH_3CO), 7.25- 7.83(m, 5H,H-Aromatic), 8.69 (s, 1H, H-pyrimidine) and 11.63 ppm (s, 1H, D_2O exchange NH); ^{13}CNMR (DMSO-d_6, 100MHz): 15.12, 26.45, 90.78, 112.35, 125.18, 124.08, 126.24, 127.85, 131.20, 135.60, 140.49, 147.24, 148.92, 150.21, 152.29 and 197.12 ppm; Anal. Calcd. For $C_{18}H_{13}N_7O$: C, 62.97; H, 3.82; N, 28.56. Found: C, 62.74; H, 3.69; N, 28.38.

*2.2.2. 3-Acetyl-10-imino-4-methyl-9-(p-tolyl)-9,10-dihydropyrimido[1',2':1,5]pyrazolo[3,4-d]pyridazine-7-carbonitrile (**8b**).*

As reddish-brown crystals Yield: (2.8g, 75 %), m.p.= 265-267 °C; IR (KBr, cm^{-1}): 3382 (NH), 3034 (CH-aromatic), 2914 (CH-aliphatic), 2227 (C≡N) and 1703 (C=O); ^{1}HNMR (DMSO-d_6, 400MHz): 2.28, 2.56(2s, 6H, $2CH_3$), 2.94(s, 3H, CH_3CO), 7.38, 7.65(2d, 4H, H-Aromatic), 8.76 (s, 1H, H-pyrimidine) and 11.45 ppm (s, 1H, D_2O exchange NH); Anal. Calcd. For $C_{19}H_{15}N_7O$: C, 63.86; H, 4.23; N, 27.44. Found: C, 63.64; H, 4.15; N, 27.29

*2.2.3. 3-acetyl-10-imino-9-(4-methoxyphenyl)-4-methyl-9,10-dihydropyrimido[1',2':1,5] pyrazolo[3,4-d]pyridazine-7-carbonitrile (**8c**).*

As brown crystals Yield: (2.6g, 72.8 %), m.p. over 300 °C; IR (KBr, cm^{-1}): 3343 (NH), 3018 (CH-aromatic), 2894 (CH-aliphatic), 2211 (C≡N) and 1700 (C=O); ^{1}HNMR (DMSO-d_6, 400MHz): 2.45(s, 3H, CH_3), 2.92(s, 3H, CH_3CO), 3.84 (s, 3H, OCH_3), 7.18, 7.42(2d, 4H, H-Aromatic), 8.72 (s, 1H, H-pyrimidine) and 12.03 ppm (s, 1H, D_2O exchange NH); Anal. Calcd. For $C_{19}H_{15}N_7O_2$: C, 61.12; H, 4.05; N, 26.26. Found: C, 60.88; H, 3.92; N, 26.08.

*2.3. General Procedure for synthesis of arylidene derivatives (**10a-c**).*

A mixture of compound (**5)** (2.39g, 0.01mol) with aromatic aldehydes (**9a-c)** (0.01mol) in 30ml ethanol, 0.5ml triethylamine was heated under reflux for 4 h then allowed to cool. products were collected by filtration and recrystallized from ethanol.

*2.3.1. 6-Acetyl-2-(1-cyano-2-phenyl-vinyl)-7-methyl pyrazolo[1,5-a]pyrimidine-3-carbonitrile (**10a**).*

As yellow crystals Yield: (2.5g, 76.4 %), m.p.= 254-256 °C; IR (KBr, cm^{-1}): 3015 (CH-aromatic), 2928 (CH-aliphatic), 2189 (C≡N) and 1689 (C=O); ^{1}HNMR (DMSO-d_6, 400MHz): 2.54(s, 3H, CH_3), 2.82(s, 3H, CH_3CO), 7.31-7.57(m, 5H,H-Aromatic), 8.02(s, 1H, CH) and 8.58 ppm (s, 1H, H-pyrimidine); Anal. Calcd. For $C_{19}H_{13}N_5O$: C, 69.71; H, 4.00; N, 21.39. Found: C, 69.57; H, 3.85; N, 21.17.

*2.3.2 6-Acetyl-2-(1-cyano-2-(p-tolyl)vinyl)-7-methyl pyrazolo[1,5-a]pyramidine-3-carbo-nitrile (**10b**).*

As orange crystals Yield: (2.4g, 70.38 %), m.p.= 262-264 °C; IR (KBr, cm^{-1}): 2213 (C≡N) and 1695 (C=O); ^{1}HNMR (DMSO-d_6, 400MHz): 2.39, 2.62(2s, 6H, $2CH_3$), 2.96(s, 3H, CH_3CO), 7.15, 7.67(2d, 4H,H-Aromatic), 8.12(s, 1H, CH) and 8.82 ppm (s, 1H, H-pyrimidine); ^{13}CNMR (DMSO-d_6, 100MHz): 15.85, 21.12, 29.56, 78.87, 105.56, 114.25, 116.13, 124.85, 128.32, 130.14, 130.85, 139.36, 146.52, 147.13, 148.94, 151.24, 153.18 and 197.24 ppm; Anal. Calcd. For $C_{20}H_{15}N_5O$: C, 70.37; H, 4.43; N, 20.52. Found: C, 70.15; H, 4.28; N, 20.39.

*2.3.3. 6-Acetyl-2-(1-cyano-2-(4-(dimethylamino) phenyl)vinyl)-7-methylpyrazolo[1,5-a]pyrimidine-3-carbonitrile (**10c**).*

As orange-red crystals Yield: (2.7g, 79.1 %), m.p.= 280-282 °C; IR (KBr, cm^{-1}): 3065 (CH-aromatic), 2921 (CH-aliphatic), 2221 (C≡N) and 1701 (C=O); ^{1}HNMR (DMSO-d_6, 400MHz): 2.45(s, 3H, CH_3), 2.72(s, 3H, CH_3CO), 3.16(s, 6H, $N(CH_3)_2$), 7.03, 7.77(2d, 4H,H-Aromatic), 8.05(s, 1H, CH) and 8.93 ppm (s, 1H, H-pyrimidine); Anal. Calcd. For $C_{21}H_{18}N_6O$: C, 68.09; H, 4.90; N, 22.69. Found: C, 67.94; H, 4.78; N, 22.49.

*2.4. General Procedure for Synthesis of (thiophen-3-yl)-7-methylpyrazolo[1,5-a]pyrimidine-3-carbonitrile (**16a-c**).*

A mixture of compound (**5**) (2.39g, 0.01mol) with potassium hydroxide (0.01mol) in dimethyl-formamide (15 ml) was stirred at room temperature. for 1 h, then phenyl isothiocyanate (0.01 mol) was adding to the resulting mixture with

continued stirring for 3 h followed by add phenacyl bromide derivatives (**13a-c**) (0.01 mol) with stirring for 4h. The mixture poured onto water and ice. The solid formed was filtered off, washed with water, and recrystallized from ethanol/DMF (3:1) mixture.

*2.4.1. 6-Acetyl-2-(4-amino-5-benzoyl-2-(phenylamino)thiophen-3-yl)-7-methylpyrazolo[1,5-a]pyramidine-3-carbonitrile (**16a**).*

As brownish crystals Yield: (3.2g, 65 %), m.p = 282-284°C; IR (KBr, cm^{-1}): 3412, 3332 (NH_2, NH), 2227 (C≡N) and 1698, 1682 (C=O); ^{1}HNMR (DMSO-d_6, 400MHz): 2.52(s, 3H, CH_3), 2.88(s, 3H, CH_3CO), 6.45(s, 2H, D_2O exchange NH_2), 6.95-7.74(m, 10H, H-Aromatic), 9.08 (s, 1H, H-pyrimidine) and 11.52 ppm (s, 1H, D_2O exchange NH); Anal. Calcd. For $C_{27}H_{20}N_6O_2S$: C, 65.84; H, 4.09; N, 17.06. Found: C, 65.72; H, 3.94; N, 16.93.

*2.4.2. 6-Acetyl-2-(4-amino-5-(4-methylbenzoyl)-2-(phenylamino)thiophen-3-yl)-7-methylpyrazolo[1,5-a]pyrimidine-3-carbonitrile (**16b**).*

As brown crystals Yield: (3.5g, 69.1 %), m.p =290-292°C; IR (KBr, cm^{-1}): 3416, 3343 (NH_2, NH), 2222 (C≡N) and 1697, 1687 (C=O); ^{1}HNMR (DMSO-d_6, 400MHz): 2.34, 2.55(2s, 6H, $2CH_3$), 2.85(s, 3H, CH_3CO), 6.48(s, 2H, D_2O exchange NH_2), 6.94-7.62(m, 9H, H-Aromatic), 8.96 (s, 1H, H-pyrimidine) and 10.86 ppm (s, 1H, D_2O exchange NH); Anal. Calcd. For $C_{28}H_{22}N_6O_2S$: C, 66.39; H, 4.38; N, 16.59. Found: C, 66.23; H, 4.19; N, 16.42.

*2.4.3 6-Acetyl-2-(4-amino-5-(4-methoxy benzoyl)-2-(phenylamino)thiophen-3-yl)-7-methylpyrazolo[1,5-a]pyrimidine-3-carbonitrile (**16c**).*

As deep brown crystals Yield, 67 %, m.p over 300°C; IR (KBr, cm^{-1}): 3398, 3314 (NH_2, NH), 2212 (C≡N) and 1692, 1680 (C=O); ^{1}HNMR (DMSO-d_6, 400MHz): 2.57(s, 3H, CH_3), 2.96(s, 3H, CH_3CO), 3.9(s, 3H, OCH_3), 6.60(s, 2H, D_2O exchange NH_2), 7.03-7.82(m, 9H,H-Aromatic), 8.88 (s, 1H, H-pyrimidine) and 11.24 ppm (s, 1H, D_2O exchange NH); ^{13}CNMR (DMSO-d_6, 100MHz): 16.27, 28.15, 56.43, 81.62, 99.85, 110.95, 113.16, 115.23, 120.24, 123.87, 126.12, 129.74, 130.88, 133.42, 139.47, 148.28, 150.64, 151.41, 152.18, 157.26, 163.84, 167.25, 190.27 and 197.64 ppm; Anal. Calcd. For $C_{28}H_{22}N_6O_3S$: C, 64.35; H, 4.24; N, 16.08; Found: C, 64.21; H, 4.13; N, 15.89.

*2.5. General Procedure for Synthesis of thieno[3'',4'':5',6']pyrido[4',3':3,4]pyrazolo[1,5-a]pyrimidine derivatives (**17a-c**).*

Compounds (**16a–c**) (0.01mol) were refluxed in sodium ethoxide solution for 4 h and then cooled. The solid so formed was filtered off and recrystallized from DMF.

*2.5.1. 1-(5-Amino-3-benzoyl-9-methyl-1-(phenylamino)thieno[3'',4'':5',6']pyrido[4',3':3,4]pyrazolo[1,5-a]pyrimidin-8-yl)ethan-1-one (**17a**).*

As red brown crystals Yield, (3.3g, 67 %), m.p over 300°C; IR (KBr, cm^{-1}): 3375, 3295 (NH_2, NH) and 1696, 1668 (2C=O); ^{1}HNMR (DMSO-d_6, 400MHz): 2.43(s, 3H, CH_3), 2.75(s, 3H, CH_3CO), 7.12-8.07(m, 12H, H-Aromatic+NH_2), 9.10 (s, 1H, H-pyrimidine) and 11.75 ppm (s, 1H, D_2O exchange NH); Anal. Calcd. For $C_{27}H_{20}N_6O_2S$: C, 65.84; H, 4.09; N, 17.06; Found: C, 65.69; H, 3.92; N, 16.98.

*2.5.2. 1-(5-Amino-9-methyl-3-(4-methyl benzoyl)-1-(phenylamino)thieno[3'',4'':5',6']pyrido[4',3':3,4]pyrazolo[1,5-a]pyrimidin-8-yl)ethan-1-one (**17b**).*

As brown crystals Yield, (3.6g, 71.14) %, m.p over 300°C; IR (KBr, cm^{-1}): 3354, 3286 (NH_2, NH) and 1701, 1672 (2C=O); ^{1}HNMR (DMSO-d_6, 400MHz): 2.42, 2.65(2s, 6H, $2CH_3$), 2.8(s, 3H, CH_3CO), 7.25-8.13(m, 11H,H-Aromatic+NH_2), 8.85 (s, 1H, H-pyrimidine) and 11.26 ppm (s, 1H, D_2O exchange NH); Anal. Calcd. For $C_{28}H_{22}N_6O_2S$: C, 66.39; H, 4.38; N, 16.59; Found: C, 66.29; H, 4.23; N, 16.36.

*2.5.3. 1-(5-Amino-3-(4-methoxybenzoyl)-9-methyl-1-(phenylamino)thieno[3'',4'':5',6']pyrido[4',3':3,4]pyrazolo[1,5-a]pyrimidin-8-yl)ethan-1-one (**17c**).*

As brown crystals Yield, (3.5g, 67.05 %), m.p over 300°C; IR (KBr, cm^{-1}): 3362, 3293 (NH_2, NH) and 1688, 1667 (2C=O); ^{1}HNMR (DMSO-d_6, 400MHz): 2.56(s, 3H, CH_3), 2.86(s, 3H, CH_3CO), 3.85(s, 3H, OCH_3), 7.05-7.93(m, 11H, H-Aromatic+NH_2), 8.92 (s, 1H, H-pyrimidine) and 10.95 ppm (s, 1H, D_2O exchange NH); Anal. Calcd. For $C_{28}H_{22}N_6O_3S$: C, 64.35; H, 4.24; N, 16.08; Found: C, 64.23; H, 4.12; N, 15.89.

*2.6. 6-Acetyl-2-(4-amino-5-cyano-2-(phenylamino)thiophen-3-yl)-7-methylpyrazolo[1,5-a]pyrimidine-3-carbonitrile (**20**).*

A mixture of compound (**5**) (2.39g, 0.01mol) with potassium hydroxide (0.01mol) in dimethylformamide (15 ml) was stirred at r. t. for 1 h, phenyl isothiocyanate (0.01mol) was added to the resulting mixture with continued stirring for 3 h, then chloroacetonitrile was added (**18**) (0.01mol) with continue stirring for 6h more. The mixture poured onto ice water. The solid product was filtered off, washed with water, and recrystallized from ethanol/DMF (3:1) mixture to afford brown crystals, yield, (2.8g, 68%), m.p. = 288-290 °C; IR (KBr, cm^{-1}): 3374, 3268 (NH_2, NH), 2230, 2207 (2C≡N) and 1697 (C=O); ^{1}HNMR (DMSO-d_6, 400MHz): 2.58(s, 3H, CH_3), 2.82(s, 3H, CH_3CO), 6.42(s, 2H, D_2O exchange NH_2), 7.23-7.78(m, 5H,H-Aromatic), 8.74 (s, 1H, H-pyrimidine) and 11.32 ppm (s, 1H, D_2O

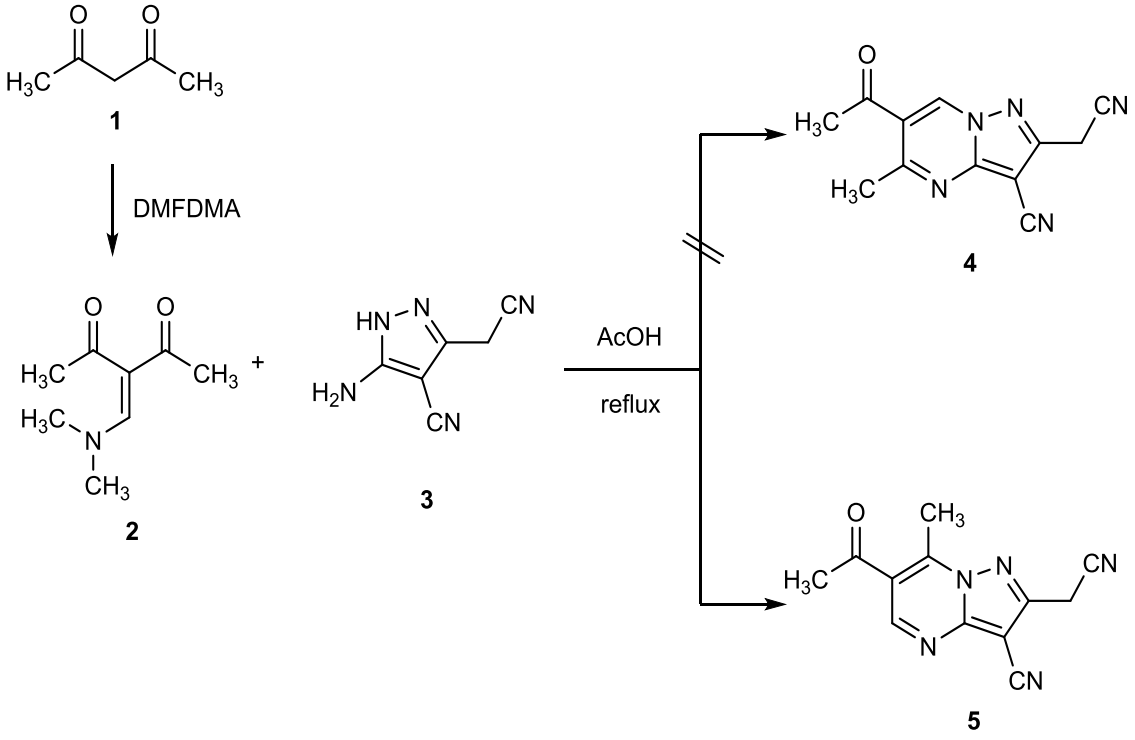
exchange NH); ^{13}CNMR (DMSO-d_6, 100MHz): 15.21, 27.92, 82.11, 95.88, 109.12, 115.54, 116.1, 121.75, 122.52, 127.26, 128.95, 139.71, 149.05, 150.18, 150.55, 151.55, 151.32, 154.14, 165.92 and 198.65 ppm; Anal. Calcd. For $C_{21}H_{15}N_7OS$: C, 61.01; H, 3.66; N, 23.71; Found: C, 60.92; H, 3.58; N, 23.63.

*2.7. 8-Acetyl-5-amino-9-methyl-1-(phenylamino) thieno[3'',4'':5',6']pyrido[4',3':3,4]pyra-zolo[1,5-a]pyrimidine-3-carbonitrile (**21**).*

Compounds (**20**) (0.01mol) was refluxed in sodium ethoxide solution for 4 h. then cooled. The solid so formed was filtered off and recrystallized from DMF as deep brown crystals, yield, 72%, m.p. over 300°C; IR (KBr, cm^{-1}): 3366, 3259 (NH_2, NH), 2212 (C≡N) and 1687 (C=O); ^{1}HNMR (DMSO-d_6, 400MHz): 2.63(s, 3H, CH_3), 2.72(s, 3H, CH_3CO), 7.15-7.92(m, 7H, H-Aromatic+NH_2), 8.89 (s, 1H, H-pyrimidine) and 11.52 ppm (s, 1H, D_2O exchange NH); ^{13}CNMR (DMSO-d_6, 100MHz): 15.32, 27.17, 91.11, 93.27, 103.1, 112.72, 121.55, 123.56, 128.61, 130.8, 138.77, 145.07, 147.63, 148.21, 148.77, 155.32, 161.79, 162.87 and 197.17 ppm.; Anal. Calcd. For $C_{21}H_{15}N_7OS$: C, 61.01; H, 3.66; N, 23.71; Found: C, 60.65; H, 3.52; N, 23.59.

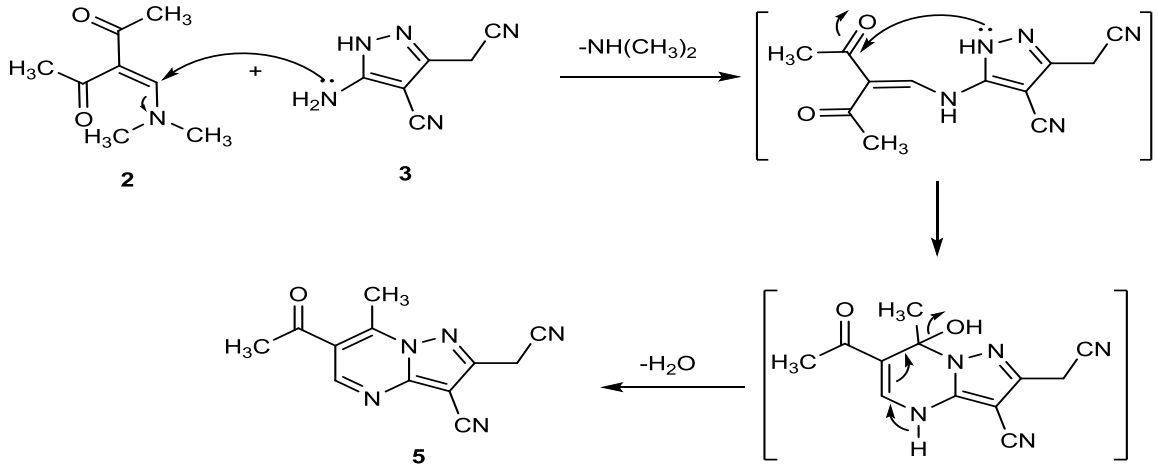
3. Results and Discussion

Refluxing of 5-amino-3-cyanomethyl-1*H*-pyrazole-4-carbonitrile (**3**) with 3-((dimethylamino) methylene)-pentane-2,4-dione (**2**) in glacial acetic acid may be afforded 6-acetyl-2-(cyanomethyl)-5-methylpyrazolo [1,5-a]pyrimidine-3-carbonitrile (**4**) or 6-acetyl-2-(cyanomethyl)-7-methylpyrazolo [1,5-a]pyrimidine-3-carbonitrile (**5**) (Scheme 1). The isolated compound is isomer 5 depending on nucleophilic attack of the exocyclic amino group [30]. Its elemental analyses and spectral data determined the structure of compound (**5**). Whereas IR spectrum showed the appearance of absorption band at 1688 cm^{-1} for carbonyl group, and disappearance of bands of amino and imino groups. ^{1}H NMR showed the appearance of singlet signals at 2.6, 3.05 and 8.94 ppm for CH_3, CH_3CO and proton of pyrimidine ring, respectively.



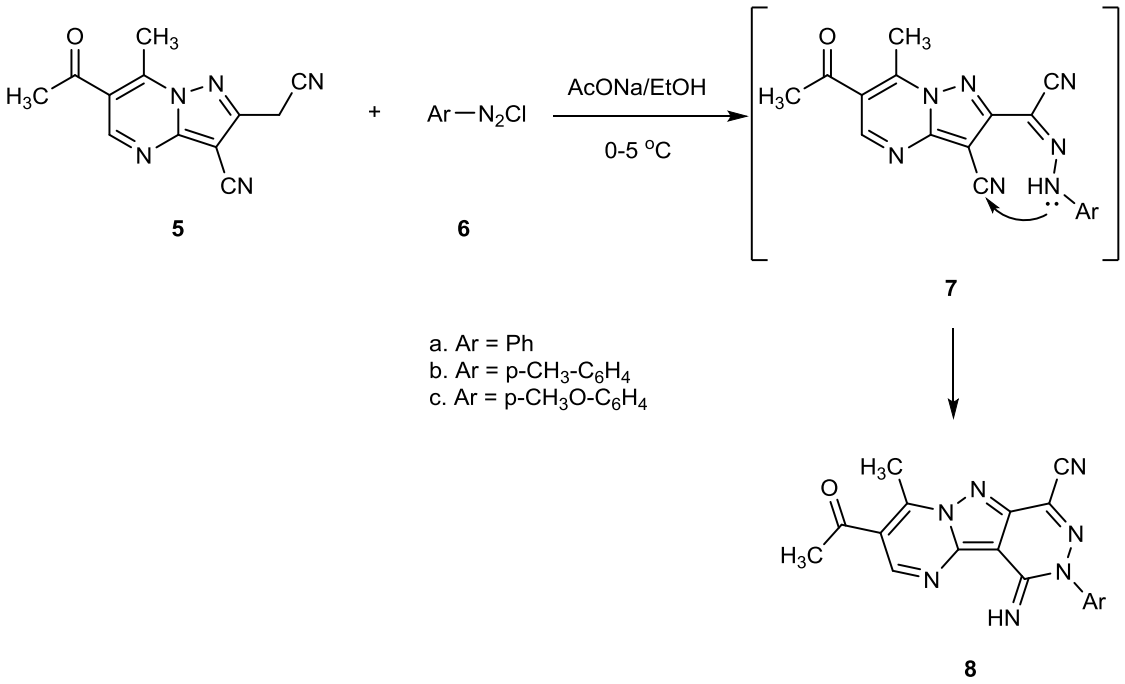
Scheme 1; synthesis of 6-acetyl-2-(cyanomethyl)-7-methylpyrazolo[1,5-a]pyrimidine-3-carbonitrile (**5**).

The formation of compound (**5**) can be explained by the reaction pathway depicted in (Scheme 2). The formation of (**5**) is assumed to proceed *via* the *Michael* addition of the exocyclic amino group in the aminopyrazole (**3**) to enamine (**2**) and elimination of $NH(CH_3)_2$ followed by elimination of water molecule.



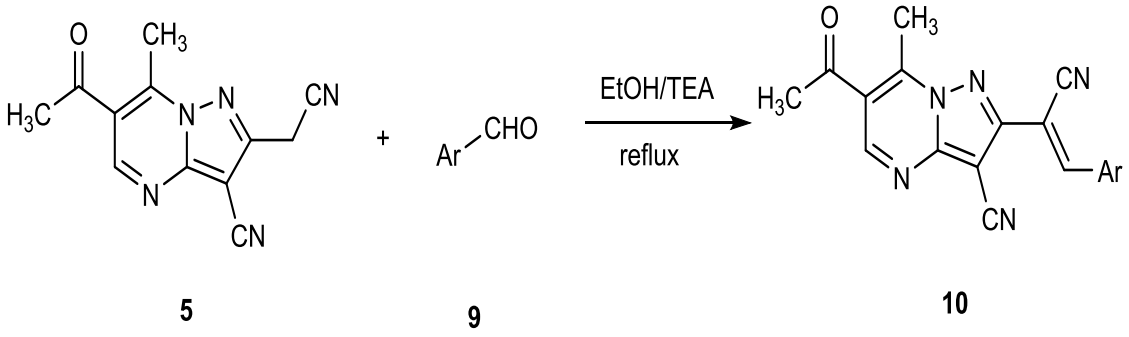
Scheme 2; mechanism reaction of formation of compound (**5**).

On the other hand, compounds (**5**) was coupled with aromatic diazonium chloride (**6a-c**) to afford of pyrimido[1',2':1,5]pyrazolo[3,4-d]pyridazine derivatives **8a-c**, *via* intramolecular cyclization of (**7a-c**) through nucleophilic addition of the imino group to cyano group (scheme 3). Their elemental analyses and spectral data confirmed the structure of compounds (**8a-c**); where IR spectra showed the appearance of a new band about 3300 cm^{-1} for NH group and ^1H NMR spectra showed the appearance of D_2O exchangeable signal δ_H 11-12 ppm for NH group.



Scheme 3; synthesis of pyrimido[1',2':1,5]pyrazolo[3,4-d]pyridazine derivatives (**8a-c**).

Condensation of compounds (**5**) with various aromatic aldehydes (**9a-c**) in ethanol containing triethylamine afforded the corresponding arylidene derivatives (**10a-c**) (Scheme 4). Their elemental analyses and spectral data established the structures of the isolated compounds (**10a-c**). For example, the H^1 NMR spectrum of compound (**10b**) showed the disappearance of methylene protons and the appearance of additional signals after δ_H 8 ppm.



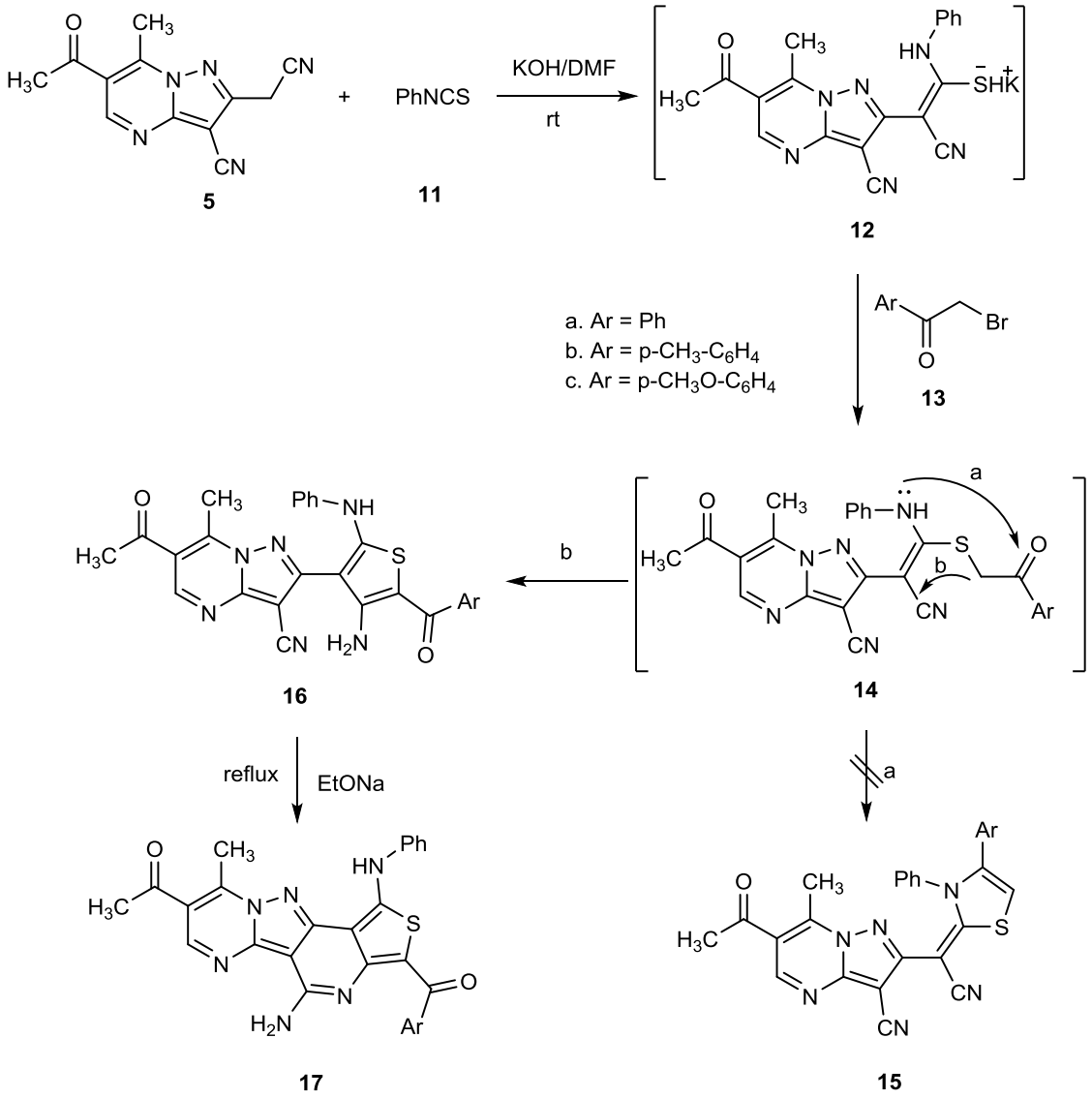
5 **9** **10**

a. Ar = Ph
b. Ar = p-CH_3-C_6H_4
c. Ar = p-$(CH_3)_2$N-C_6H_4

Scheme 4; synthesis of arylidene derivatives 10a-c.

Compound (**5**) reacted with phenylisothiocyanate in (DMF) in the presence of potassium hydroxide, followed by the addition of phenacyl bromide derivatives (**13a-c**) at room temperature, to afford thiophene derivatives (**16a-c**) (passway b) rather than the expected thiazole derivatives (**15a-c**) (passway a) through intermediate (**14a-c**). The structure of compounds (**16a-c**) was confirmed based on their elemental analyses and spectral data. Whereas IR spectra of compounds (**16a-c**) showed the appearance of bands indicated the presence of NH_2 and NH groups. For example, IR spectrum of compound (**16a**) showed bands at 3412, 3332 for NH_2 and NH groups beside absorption bands at 2227, 1698, 1682 for cyano and two carbonyl groups, respectively. Also**,** ^{1}H NMR of compound (**16a**) showed the appearance of D_2O exchangeable signals for amino and imino groups and multiplet signals at 6.95 - 7.74 ppm for aromatic protons.

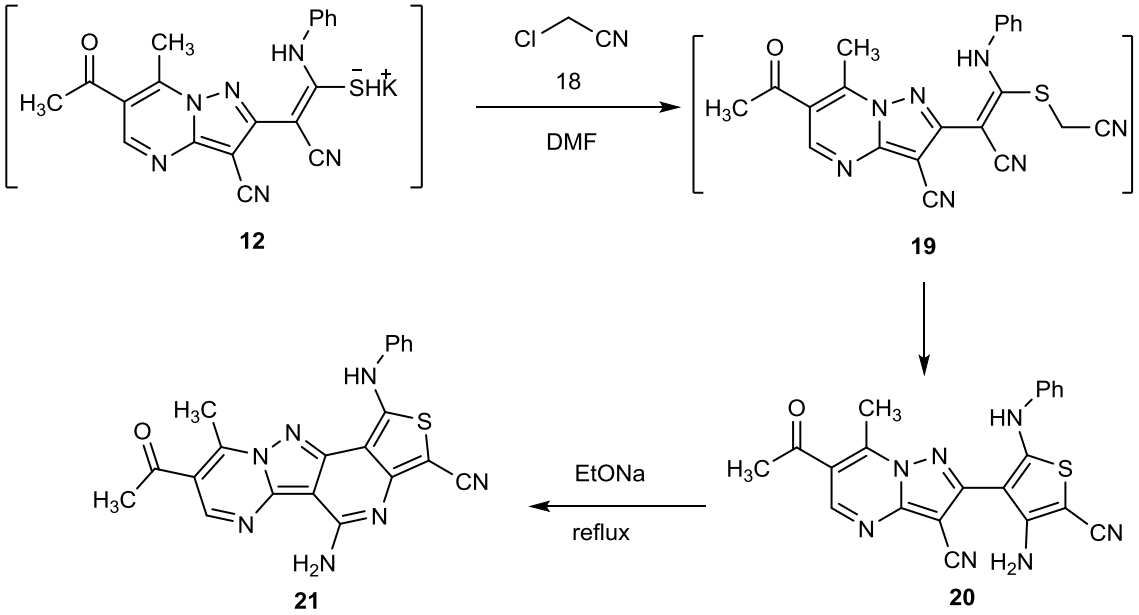
Also, we can confirmed the structure of compounds (**16a-c**) chemically by refluxing them in ethanolic sodium ethoxide solution to afforded thieno [3",4":5',6']pyrido[4',3':3,4]pyrazolo[1,5-a]pyrimidine derivatives (**17a-c**). The structures of isolated compounds were confirmed by spectral analyses. Where IR spectra of compounds (**17a-c**) showed disappearance of cyano groups (scheme 5).



Scheme 5; synthesis of (thiophen-3-yl)-7-methylpyrazolo[1,5-a]pyrimidine-3-carbonitrile (**16a-c**) and thieno[3",4": 5',6']pyrido [4',3':3,4]pyrazolo[1,5-a]pyrimidine derivatives (**17a-c**).

In the same manner, the reaction of the non-isolable potassium salt of pyrazolo[1,5-a]pyrimidine (**12**) with chloroacetonitrile (**18**) in DMF at room temperature, afforded 6-acetyl-2-(4-amino-5-cyano-2-(phenylamino)thiophen-3-yl)-7-methylpyrazolo[1,5-a]pyramidine-3-carbonitrile (**20**) (scheme 6). The IR spectrum of compound (**20**) showed absorption bands for amino and imino groups and two cyano groups. ^{1}H NMR showed the appearance of D_2O exchangeable signals at 6.42 and 11.32 ppm for amino and imino groups and multiplet signals at 7.23-7.78 ppm for aromatic protons.

Finally, refluxing of compound (**20**) in ethanolic sodium ethoxide solution afforded 8-acetyl-5-amino-9-methyl-1-(phenylamino)thieno[3",4":5',6']pyrido [4',3':3,4]pyrazolo[1,5-a]pyramidine-3-carbonitrile (**21**) (scheme 6). The structure of compound (**21**) was established by spectroscopic tools as well as elemental analyses data. IR spectrum of compound (**21**) showed appearance of absorption bands at 3366, 3259, 2212, and 1687 for NH_2, NH, C≡N, and carbonyl groups, respectively**.** Also, ^{1}H NMR of compound (**21**) showed singlet signals at 2.63, 2.72, 8.89, and 11.52 ppm for CH_3, CH_3CO, proton of pyrimidine, and NH groups, respectively, and multiplet signals at 7.15-7.92 ppm for NH_2 and aromatic protons.



Scheme 6; synthesis of (thiophen-3-yl)-7-methylpyrazolo[1,5-a]pyrimidine (**20)** and thieno[3",4":5',6']pyrido [4',3': 3,4]pyrazolo[1,5-a]pyrimidine (**21)**.

4. Conclusion

In this work, new pyrazolo[1,5-a]pyrimidine-3-carbonitrile has been synthesized and used for synthesis of new fused pyrazolo[1,5-a]pyrimidine derivatives by coupling with aryldiazonium chloride to afforded pyrimido[1',2':1,5]pyrazolo[3,4-d]pyridazine derivatives. Condensation with aromatic aldehydes gives the corresponding arylidenes and reaction with phenyl isothiocyanate and halogenated compounds to afforded thiophen-3-yl)-7-methyl pyrazolo[1,5-a]pyrimidine-3-carbonitrile and thieno [3",4":5',6']pyrido[4',3':3,4]pyrazolo[1,5-a]pyrimidine derivatives.

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