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# A three step one-pot regioselective synthesis of highly substituted pyrazolo[1,5-*a*]pyrimidines assisted by $KHSO_4$ in aqueous media under ultrasound irradiation

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ABSTRACT

A simple and efficient synthesis of substituted pyrazolo[1,5-*a*]pyrimidine derivatives has been developed by the use of ultrasound. 5-Methyl-4-phenyl-1*H*-pyrazol-3-amine required for the synthesis of pyrazolo[1,5-*a*]pyrimidine derivatives has been easily obtained by the reaction of 3-(dimethylamino)-2-phenylacrylonitrile (formed from readily available 2-phenylacetonitrile) with hydrazine hydrate in refluxing ethanol. The 5-aminopyrazole was then reacted with various formylated active proton compounds in presence of $KHSO_4$ in aqueous medium under ultrasound irradiation to give the desired products. The chemical structures of the newly synthesized compounds were confirmed by IR, $^1$H NMR, $^{13}$C NMR and Mass spectral data. X-ray crystallographic study of a selected compound 6-(4-chlorophenyl)-2-methyl-3-phenylpyrazolo[1,5-*a*]pyrimidin-7-amine (7c) was performed to ascertain the regioselectivity of the reaction. Crystal data for compound 7c: Triclinic, space group P-1 (no. 2), $a$ = 8.0198(3) Å, $b$ = 14.0341(6) Å, $c$ = 14.2099(6) Å, $\alpha$ = 87.672(2)°, $\beta$ = 83.902(2)°, $\gamma$ = 89.120(2)°, $V$ = 1588.87(11) Å$^3$, $Z$ = 4, $T$ = 293(2) K, μ(MoKα) = 0.248 mm$^{-1}$, $D_{calc}$ = 1.400 g/cm$^3$, 12918 reflections measured (4.012° ≤ 2Θ ≤ 49°), 5152 unique ($R_{int}$ = 0.0411, $R_{sigma}$ = 0.0429) which were used in all calculations. The final $R_1$ was 0.0486 (I > 2σ(I)) and $wR_2$ was 0.1320 (all data).

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## 1. Introduction

Ultrasound irradiation has found application in material science, life sciences, medicinal chemistry, cleaning, sonar, electronics, agriculture and oceanography, etc. [1]. Ultrasound technology has also gained significant attention in the field of organic synthesis [2], due to its general commercial availability as well as its various advantages like enhanced reaction rates, greater selectivity, shorter reaction time, precipitation of practically pure products, use of less hazardous solvents, high to excellent yields and minimization of waste products [3,4]. It offers an alternative and convenient pathway for reactions to be carried out efficiently [1]. Ultrasound irradiation works on the principle of cavitation. During the process of irradiation, sound waves pass through the reaction medium whereby the molecules of the medium are separated generating millions of microscopic bubbles. These bubbles grow in size and reach a state of maximum strain ultimately leading to its collapse. These rapid and violent implosions of millions of bubbles generate localised hot spots with transient temperatures of about 5000 °C and pressures of about 1000 atmospheres [2,5]. Such localized hot spots act as micro-reactor which enhances the chemical reaction more effectively [6].

The synthesis of pyrazolo[1,5-*a*]pyrimidine derivatives have gained significant interest due to their various biological [7-11] and pharmacological activities. Recently, pyrazolo[1,5-*a*]pyrimidines as translocator protein 18 kDa (TSPO) ligands [12] have been studied. Hassan and co-workers [13] reported the synthesis of 2-[(4-methoxyphenyl)amino]-5,7-dimethyl-*N*-phenylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide and 7-amino-*N*-(4-chlorophenyl)-6-cyano-5-(4-methoxyphenyl)-2-[(4-methoxyphenyl)amino]pyrazolo[1,5-*a*]pyrimidine-3-carboxamide which were found to exhibit growth inhibitory activity against Ehrlich Ascites Carcinoma (EAC) cells when compared with doxorubicin drug. Also, pyrazolo[1,5-*a*]pyrimidine nucleus is an interesting and versatile scaffold for the preparation of various drugs like zaleplon, indiplon and ocinaplon [14-16].


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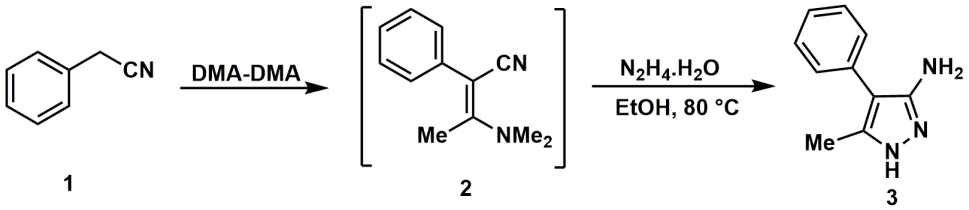



**Scheme 1**

Realising the importance of these molecules, we have recently reported [17-20] a general synthetic strategy and demonstrated the applicability for the synthesis of pyrazolo[1,5-*a*] pyrimidines. In view of the importance of these molecules we have extended our synthetic strategy for 5-methyl-4-phenyl pyrazolo[1,5-*a*]pyrimidine derivatives and the details are presented herein.

## 2. Experimental

### *2.1. Material and methods*

Melting points were recorded by open capillary method and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 983 spectrometer (Perkin-Elmer). High resolution $^1$H NMR and $^{13}$C NMR (400 MHz and 600 MHz) were measured on a DRX-400 Varian spectrometer and Bruker spectrometer, respectively. $CDCl_3$ and DMSO-$d_6$ were used as the solvent. The chemical shifts (σ, ppm) and the coupling constants (Hz) are reported in the standard fashion with reference to tetramethylsilane (TMS) as internal reference. In the NMR spectral data, the abbreviations d, dd, bs, s, m, and t, stand for doublet, double-doublet, broad-singlet, singlet, multiplet, and triplet, respectively. The X-ray diffraction data was solved with Olex2 [21]. The structure was worked out with the olex2.solve [21] structure solution program using Charge Flipping and refined with the SHELXL [22] refinement package using Least Squares minimization. Molecular graphics and preparation of material for publication were obtained using Olex2 1.3-beta [23]. The electron spray mass spectra were recorded on a THERMO Finnigan LCQ Advantage max ion trap mass spectrometer. Ultrasound irradiation was carried out in an EQUITRON Digital Ultrasonic Cleaner-2.5 L, model 8425.025. 424 at 170 Watt and 50 Hz. Formylated active proton compounds were synthesized by our previously reported procedure [24,25].

### *2.1.1. Synthesis*

#### *2.1.1.1. Synthesis of 2-methyl-3-phenyl-7-arylpyrazolo[1,5-a]pyrimidine (5a-e)*

A mixture of aminopyrazole (**3**) (Scheme 1) (1 mmol), enaminones (**4**) (1 mmol), and $KHSO_4$ (2 mmol) was irradiated under the influence of ultrasound waves for 5-12 minutes in 5 mL of ethanol:water (1:1, *v*:*v*) mixture resulting in the formation of a precipitated product. After the completion of reaction monitored by thin layer chromatography (TLC) the precipitate was collected by filtration, washed repeatedly with water to ensure complete removal of acid and dried to give practically pure pyrazolopyrimidines (**5**) in 88-96 % yields. Further, purification was achieved by column chromatography using silica gel and 20 % EtOAc-Hexane (Scheme 2).

*2-Methyl-3, 7-diphenylpyrazolo[1, 5-a]pyrimid*ine (**5a**): Color: Yellow solid. Yield: 96 %. M.p.: 142-143 °C [251 °C] [26]. FT-IR (KBr, ν, cm$^{-1}$): 1605 (C=N), 1555 (C=C). $^1$H NMR (600 MHz, $CDCl_3$, *δ*, ppm): 2.65 (s, 3H, $CH_3$), 6.85 (d, 1H, $C_6$-H, *J* = 4.2 Hz), 7.32-7.34 (m, 1H, Ar), 7.48-7.51 (t, 2H, Ar), 7.57-7.58 (m, 3H, Ar), 7.73-7.74 (m, 2H, Ar), 8.08-8.10 (m, 2H, Ar), 8.51 (d, 1H, $C_5$-H, *J* = 4.2 Hz). $^{13}$C NMR (150 MHz, $CDCl_3$, *δ*, ppm): 14.5, 107.3, 109.7, 126.5, 128.7, 128.9, 129.2, 129.5, 131.2, 131.4, 132.6, 146.3, 147.5, 149.1, 152.6.
MS (EI, *m/z* (%)): 286 (MH)$^+$.

*2-Methyl-3-phenyl-7-(p-tolyl)pyrazolo[1, 5-a]pyrimidine* (**5b**): Color: Yellow solid. Yield: 95 %. M.p.: 179-181°C [178-180 °C] [27]. FT-IR (KBr, ν, cm$^{-1}$): 1600 (C=N), 1555 (C=C). MS (EI, *m/z* (%)): 300 (MH)$^+$.

*7-(4-Methoxyphenyl)-2-methyl-3-phenylpyrazolo[1,5-a]pyri midine* (**5c**): Color: Yellow solid. Yield: 88 %. M.p.: 176-177 °C. FT-IR (KBr, ν, cm$^{-1}$): 1602 (C=N), 1553 (C=C). $^1$H NMR (400 MHz, $CDCl_3$, *δ*, ppm): 2.63 (s, 3H, $CH_3$), 3.89 (s, 3H, $OCH_3$), 6.85 (d, 1H, $C_6$-H, *J* = 4 Hz), 7.07 (d, 2H, Ar, *J* = 8 Hz), 7.28-7.32 (t, 1H, Ar), 7.45-7.49 (t, 2H, $ArOCH_3$), 7.71 (d, 2H, Ar, *J* = 8 Hz), 8.11 (d, 2H, $ArOCH_3$, *J* = 8 Hz), 8.46 (d, 1H, $C_5$-H, *J* = 4 Hz). $^{13}$C NMR (100 MHz, $CDCl_3$, *δ*, ppm): 14.5, 106.5, 109.4, 114.2, 123.4, 126.4, 128.7, 129.1, 131.1, 132.7, 133.3, 146.0, 149.0, 152.4, 161.9. MS (EI, *m/z* (%)): 315 (M)$^+$.

*7-(4-Chlorophenyl)-2-methyl-3-phenylpyrazolo[1,5-a]pyrimi dine* (**5d**): Color: Yellow solid. Yield: 88 %. M.p.: 197-199°C [196-198 °C] [27]. MS (EI, *m/z* (%)): 320 (MH)$^+$.

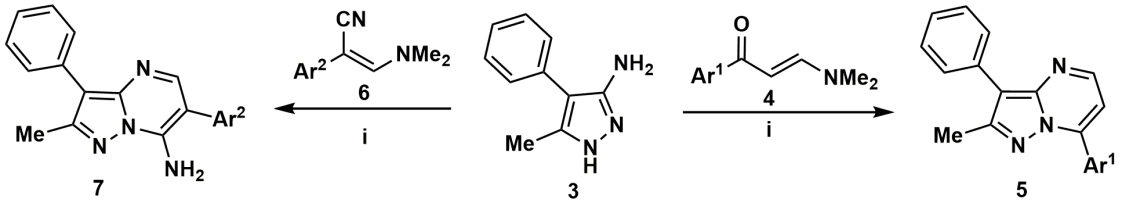
*2-Methyl-7-(4-nitrophenyl)-3-phenylpyrazolo[1, 5-a]pyrimidine* (**5e**): Color: Orange solid. Yield: 90 %. M.p.: 230-232 °C. FT-IR (KBr, ν, cm$^{-1}$): 1613 (C=N), 1554 (N=N). $^1$H NMR (400 MHz, DMSO-$d_6$, *δ*, ppm): 2.62 (s, 3H, $CH_3$), 6.89 (d, 1H $C_6$-H, *J* = 4 Hz), 7.31-7.34 (t, 1H, Ar), 7.46-7.50 (t, 2H, Ar), 7.69 (d, 2H, Ar, *J* = 7.6 Hz), 8.27 (d, 2H, Ar-$NO_2$, *J* = 8.8 Hz), 8.41 (d, 2H, $ArNO_2$, *J* = 8.8 Hz), 8.55 (d, 1H, $C_5$-H, *J* = 4 Hz). $^{13}$C NMR (100 MHz, DMSO-$d_6$, *δ*, ppm): 14.4, 107.8, 110.2, 124.0, 126.8, 128.8, 129.2, 130.6, 132.0, 137.3, 143.6, 146.7, 148.9, 149.1, 153.0. MS (EI, *m/z* (%)): 330 (M)$^+$.

#### *2.1.1.2. Synthesis of 2-methyl-3-phenyl-6-arylpyrazolo[1,5-a]pyrimidin-7-amine (7a-c)*

A mixture of aminopyrazole (**3**) (1 mmol) and enamino nitriles (**6**) (1 mmol) and $KHSO_4$ (2 mmol) was irradiated under the influence of ultrasound waves for 8-21 minutes in 5 mL of ethanol:water (1:1, *v*:*v*) mixture to give a precipitated product. After the completion of reaction monitored by TLC the precipitate was collected by filtration, washed repeatedly with ethanol:water (1:1, *v*:*v*) to ensure complete removal of acid and dried to give practically pure pyrazolopyrimidines (**7**) in 75-84 % yields. Further, purification was achieved by column chromatography (silica gel, 20 % EtOAc-hexane) (Scheme 2).

*2-Methyl-3, 6-diphenylpyrazolo[1, 5-a]pyrimidin-7-amine* (**7a**): Color: Pale white solid. Yield: 75 %. M.p.: 219-220 °C [215-216 °C] [28]. FT-IR (KBr, ν, cm$^{-1}$): 3364 (N-H), 1599 (C=N), 1523 (N=N).

*6-(4-Methoxyphenyl)-2-methyl-3-phenylpyrazolo[1,5-a]pyri midin-7-amine* (**7b**): Color: Pale white solid. Yield: 83 %. M.p.: 235-237 °C. FT-IR (KBr, ν, cm$^{-1}$): 3362 (N-H), 1592 (C=N), 1525 (C=C). $^1$H NMR (400 MHz, $CDCl_3$, *δ*, ppm): 2.62 (s, 3H, $CH_3$), 3.86 (s, 3H, $OCH_3$), 6.04 (s, 2H, $NH_2$), 7.03 (d, 2H, ArH, *J* = 8.6 Hz), 7.29-7.31 (m, 1H, ArH), 7.39 (d, 2H, ArH, *J* = 8.6 Hz), 7.45-7.49 (t, 2H, ArH), 7.71 (d, 2H, ArH, *J* = 7.4 Hz), 8.25 (s, 1H, $C_5$-H).




i = US, 60 °C, $KHSO_4$, EtOH:$H_2O$

| Compounds | $Ar^1$ | Compounds | $Ar^2$ |
|---|---|---|---|
| 5a | $C_6H_5$ | 7a | $C_6H_5$ |
| 5b | 4-$CH_3C_6H_4$ | 7b | 4-$CH_3OC_6H_4$ |
| 5c | 4-$CH_3OC_6H_4$ | 7c | 4-$ClC_6H_4$ |
| 5d | 4-$ClC_6H_4$ | | |
| 5e | 4-$NO_2C_6H_4$ | | |

**Scheme 2**

$^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$, ppm): 14.3, 55.5, 102.1, 106.3, 108.1, 114.9, 115.1, 126.3, 128.7, 128.8, 129.7, 130.5, 144.8, 149.2, 152.4, 159.4. MS (EI, *m/z* (%)): 330 $(M)^+$.

*6-(4-Chlorophenyl)-2-methyl-3-phenylpyrazolo[1,5-a]pyrimidin-7-amine* (**7c**): Color: Off white solid. Yield: 84 %. M.p.: 248-250 °C. FT-IR (KBr, ν, $cm^{-1}$): 3344 (NH), 1601 (C=N), 1522 (C=C). $^1$H NMR (600 MHz, $CDCl_3$, $\delta$, ppm): 2.61 (s, 3H, $CH_3$), 7.23-7.25 (m, 1H, ArH), 7.42-7.44 (m, 2H, ArH), 7.49 (m, 4H, 2-ArH, 2-$NH_2$), 7.72-7.74 (m, 2H, ArH), 7.85-7.86 (m, 2H, Ar), 8.11 (s, 1H, $C_5$-H). $^{13}$C NMR (150 MHz, $CDCl_3$, $\delta$, ppm): 13.4, 100.2, 106.3, 124.5, 127.2, 127.3, 127.4, 128.1, 129.7, 131.8, 131.9, 143.6, 148.6, 148.8, 150.3. MS (EI, *m/z* (%)): 334 $(M)^+$.

### *2.1.1.3. Synthesis of 2-methyl-3-phenyl-7-heteroaryl pyrazolo[1,5-a]pyrimidines (9a-d)*

A mixture of aminopyrazole (**3**) (1 mmol) and enaminone (**8a** or **8b**) (1 mmol), in the presence of $KHSO_4$ (2 mmol) was irradiated under the influence of ultrasound waves for 11-16 minutes in 5 mL of ethanol:water (1:1, *v*:*v*) mixture to give a precipitated product. After the completion of the reaction monitored by TLC, the precipitate thus formed was collected by filtration, washed repeatedly with ethanol:water (1:1, *v*:*v*) to ensure complete removal of acid and dried to give practically pure pyrazolopyrimidine (**9**) in 85-87 % yields. Further, purification was achieved by column chromatography (silica gel, 20 % EtOAc-hexane) (Scheme 3).

In case of the reaction between compounds **3** and **8c** under similar conditions, two regio-isomeric products **9c** and **9d** were isolated in 49 and 44 % yields, respectively.

*2-Methyl-3-phenyl-7-(pyridin-4-yl)pyrazolo[1, 5-a]pyrimidine* (**9a**): Color: Yellow solid. Yield: 87 %. M.p.: 204-206 °C. FT-IR (KBr, ν, $cm^{-1}$): 1601 (C=N), 1553 (C=C). $^1$H NMR (400 MHz, $CDCl_3$, $\delta$, ppm): 2.66 (s, 3H, $CH_3$), 6.89-6.92 (m, 1H, $C_6$-H), 7.32-7.36 (t, 1H, ArH), 7.48-7.51 (t, 2H, ArH), 7.72 (d, 2H, ArH, *J* = 8 Hz), 8.00 (bs, 2H, pyridine), 8.53-8.55 (m, 1H, $C_5$-H), 8.86 (br, 2H, pyridine). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$, ppm): 14.4, 107.5, 123.2, 126.8, 128.8, 129.1, 132.1, 138.7, 143.2, 147.3, 148.9, 150.6, 153.0, 152.9. MS (EI, *m/z* (%)): 287 $(MH)^+$.

*2-Methyl-3-phenyl-7-(pyridin-3-yl)pyrazolo[1, 5-a]pyrimidine* (**9b**): Color: Yellow solid. Yield: 85 %. M.p.: 149-151 °C. FT-IR (KBr, ν, $cm^{-1}$): 1608 (C=N), 1554 (C=C). $^1$H NMR (400 MHz, $CDCl_3$, $\delta$, ppm): 2.51 (s, 3H, $CH_3$), 6.88 (d, 1H, $C_6$-H, *J* = 4.4 Hz), 7.31-7.35 (t, 1H, Ar), 7.47-7.53 (m, 3H, 2H-Ar, 1H-pyridine), 7.72 (d, 2H, Ar, *J* = 8 Hz), 8.52-8.57 (m, 2H, pyridine) 8.78 (d, 1H, $C_5$-H, *J* = 4.4 Hz), 9.2 (s, 1H, pyridine). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$, ppm): 14.4, 107.2, 110.1, 123.4, 126.7, 127.6, 128.8, 129.1, 132.2, 137.0, 143.1, 147.3, 149.0, 149.8, 151.8, 152.8. MS (EI, *m/z* (%)): 287 $(MH)^+$.

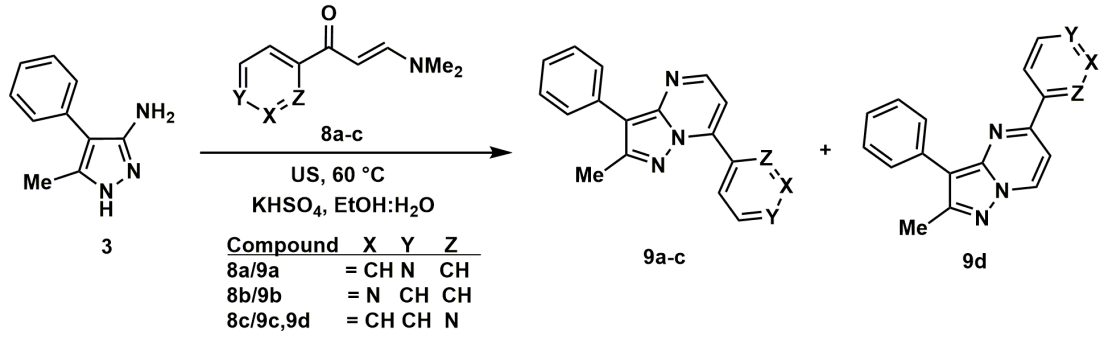
*2-Methyl-3-phenyl-7-(pyridin-2-yl)pyrazolo[1, 5-a]pyrimidine* (**9c**): Color: Yellow solid. Yield: 49 %. M.p.: 131-133 °C. FT-IR (KBr, ν, $cm^{-1}$): 1604 (C=N), 1542 (C=C). $^1$H NMR (400 MHz, $CDCl_3$, $\delta$, ppm): 2.67 (s, 3H, $CH_3$), 7.29-7.33 (t, 1H, Ar), 7.43-7.50 (m, 3H, 2H-Ar, 1H-pyridine), 7.61 (d, 1H, $C_6$-H, *J* = 4.4 Hz), 7.73 (d, 2H, Ar, *J* = 6.8 Hz), 7.91-7.95 (m, 1H, pyridine), 8.59 (d, 1H, $C_5$-H, *J* = 4.4 Hz), 8.80 (bs, 1H, pyridine), 9.09 (d, 1H, pyridine, *J* = 7.6 Hz). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$, ppm): 14.5, 107.9, 125.9, 126.2, 126.6, 128.7, 129.2, 132.4, 136.8, 143.7, 148.7, 149.1, 150.1, 152.4. MS (EI, *m/z* (%)): 287 $(MH)^+$.

*2-Methyl-3-phenyl-5-(pyridin-2-yl)pyrazolo[1, 5-a]pyrimidine* (**9d**): Color: Yellow solid. Yield: 44 %. M.p.: 152-154 °C. FT-IR (KBr, ν, $cm^{-1}$): 1606 (C=N), 1552 (C=C). $^1$H NMR (400 MHz, $CDCl_3$, $\delta$, ppm): 2.66 (s, 3H, $CH_3$), 7.30-7.35 (m, 2H, Pyridine), 7.48-7.52 (t, 2H, Ar), 7.79-7.84 (m, 3H, Ar), 7.98 (d, 1H, $C_7$-H, *J* = 7.6 Hz), 8.52 (d, 1H, pyridine, *J* = 8 Hz), 8.63-8.68 (m, 2H, $C_6$-1H, 1H-pyridine). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$, ppm): 14.6, 105.2, 109.8, 121.9, 124.8, 126.4, 128.6, 128.9, 132.5, 134.6, 137.0, 145.0, 149.2, 153.1, 154.3, 155.1. MS (EI, *m/z* (%)): 287 $(MH)^+$.

### *2.1.1.4. Synthesis of 6-acetyl/carboalkoxy-2,7-dimethyl-3-phenylpyrazolo[1,5-a]pyrimidine-3-carboxamide (12)*

In order to synthesize the target pyrazolo[1,5-*a*]pyrimidine (**12**), formylated active proton compounds of type **11** were required. This was synthesized by the irradiation of acyclic active proton compounds (**10**) (1 mmol) with DMF-DMA in microwave digester for 5 minutes. The reaction mixture (monitored by TLC) was evaporated to dryness under reduced pressure. To this, aminopyrazole (**3**) (1 mmol) as synthesized in Scheme 1 was added and dissolved in 5 mL of ethanol:water mixture (1:1, *v*:*v*). $KHSO_4$ (2 mmol) was then added and subjected to ultrasound irradiation for 6-20 minutes to give a precipitated product. After the completion of reaction (monitored by TLC), the precipitate was collected by filtration, washed repeatedly with ethanol-water (1:1, *v*:*v*) and dried over anhydrous $CaCl_2$ to give practically pure products (**12**) in 85-88 % yields. Further, purification was achieved by column chromatography (silica gel, 5 % EtOAc-hexane) (Scheme 4).

*1-(2, 7-Dimethyl-3-phenylpyrazolo[1, 5-a]pyrimidin-6-yl) ethanone* (**12a**): Color: Yellow solid. Yield: 88 %. M.p.: 105-107 °C. FT-IR (KBr, ν, $cm^{-1}$): 1683 (CO), 1586 (C=N), 1524 (C=C). $^1$H NMR (400 MHz, $CDCl_3$, $\delta$, ppm): 2.66 (s, 3H, $CH_3$), 2.67 (s, 3H, $CH_3$), 3.16 (s, 3H, $COCH_3$), 7.33-7.35 (m, 1H, Ar), 7.48-7.50 (m, 2H, Ar), 7.68-7.69 (m, 2H, Ar), 8.83 (s, 1H, $C_5$-H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$, ppm): 14.7, 15.3, 29.9, 111.0, 117.5, 127.0, 128.8, 129.1, 131.7, 145.3, 149.2, 150.3, 155.6, 196.6. MS (EI, *m/z* (%)): 266 $(MH)^+$.




**Scheme 3**

*Methyl 2, 7-dimethyl-3-phenylpyrazolo[1, 5-a]pyrimidine-6-carboxylate* (**12b**): Color: Yellow solid. Yield: 85 %. M.p.: 110-112 °C. FT-IR (KBr, ν, $cm^{-1}$): 1725 (CO), 1602 (C=N), 1523 (C=C). $^1$H NMR (600 MHz, $CDCl_3$, *δ*, ppm): 2.66 (s, 3H, $CH_3$), 3.21 (s, 3H, $CH_3$), 3.96 (s, 3H, $OCH_3$), 7.32-7.34 (t, 1H, Ar), 7.47-7.49 (t, 2H, Ar), 7.68 (d, 2H, Ar, *J* = 8.4 Hz), 8.92 (s, 1H, $C_5$-H). $^{13}$C NMR (150 MHz, $CDCl_3$, *δ*, ppm): 14.6, 15.2, 52.5, 110.1, 111.1, 126.9, 128.8, 129.1, 131.7, 146.0, 149.9, 151.2, 155.1, 165.5. MS (EI, *m/z* (%)): 281 $(M)^+$.

*Ethyl 2, 7-dimethyl-3-phenylpyrazolo[1, 5-a]pyrimidine-6-carboxylate* (**12c**): Color: Yellow solid. Yield: 90 %. M.p.: 104-106 °C. FT-IR (KBr, ν, $cm^{-1}$): 1711 (CO), 1602 (C=N), 1531 (C=C). $^1$H NMR (600 MHz, $CDCl_3$, *δ*, ppm): 1.42-1.44 (t, 3H, $CH_3$), 2.66 (s, 3H, $CH_3$), 3.21 (s, 3H, $CH_3$) 4.41-4.44 (q, 2H, $CH_2$), 7.32-7.34 (t, 1H, Ar), 7.47-7.49 (m, 2H, Ar), 7.68-7.69 (m, 2H, Ar), 8.94 (s, 1H, $C_5$-H). $^{13}$C NMR (150 MHz, $CDCl_3$, *δ*, ppm): 14.1, 14.3, 14.9, 61.3, 110.1, 110.8, 126.6, 128.5, 128.8, 131.5, 145.7, 149.7, 150.7, 154.7, 164.8. MS (EI, *m/z* (%)): 296 $(MH)^+$.

## 3. Results and discussion

### *3.1. Chemistry*

For the synthesis of the target pyrazolo[1,5-*a*]pyrimidine we first required 3-aminopyrazole of type **3**. This was synthesized as shown in Scheme 1 starting from easily accessible phenyl acetonitrile (**1**) which was acylated by its reaction with *N*,*N*-dimethylacetaldimethylacetamide (DMA-DMA). The intermediate (**2**) without further purification was reacted with hydrazine hydrate in refluxing ethanol [29]. After the completion of the reaction, monitored by TLC, the reaction mixture was evaporated and cooled. To this, water was added whereby brown solid was formed, which was collected by filtration and washed with water. Aminopyrazole (**3**) thus obtained was dried over anhydrous $CaCl_2$ and was used for subsequent reaction without further purification.

3-Aminopyrazole (**3**) was then irradiated with an equimolar quantity of enaminones (**4**) in the presence of $KHSO_4$ (2 equivalents) in 5 mL of water-ethanol mixture (1:1, *v*:*v*) in an ultrasonic bath at 60 °C (Scheme 2). The progress of the reaction was monitored by thin layer chromatography. The products were obtained in 88-96 % yields in 5-12 minutes. The reaction mixture was allowed to cool to room temperature and the precipitate was collected by filtration, washed with ethanol-water (1:1, *v*:*v*) and finally dried over anhydrous $CaCl_2$ to give practically pure product **5**. Encouraged by this, the reaction of enaminonitriles **6** with aminopyrazole **3** (Scheme 2) was subsequently explored and the expected 7-aminopyrazolo pyrimidines **7** were obtained in 75-84 % overall yields in 8-21 minutes under similar conditions.

The structures of the synthesised compounds were confirmed by their spectral data (IR, $^1$H NMR, $^{13}$C NMR and MS spectroscopy). Also X-ray crystallography for compound **7c** as model was performed for ascertaining the structure. The $^1$H NMR spectra of compounds **5a-e**, showed doublet for the $C_5$-H and $C_6$-H protons at around δ 8.51 and 6.85 ppm, respectively.

The $^1$H NMR spectra of compound **7b-c**, showed sharp singlet for $C_5$-H protons at about δ 8.20 ppm, whereas, the -$NH_2$ protons for compound **7b** resonated as singlet at δ 6.04 ppm and that for compound **7c**, the signal get mixed with the aromatic protons.

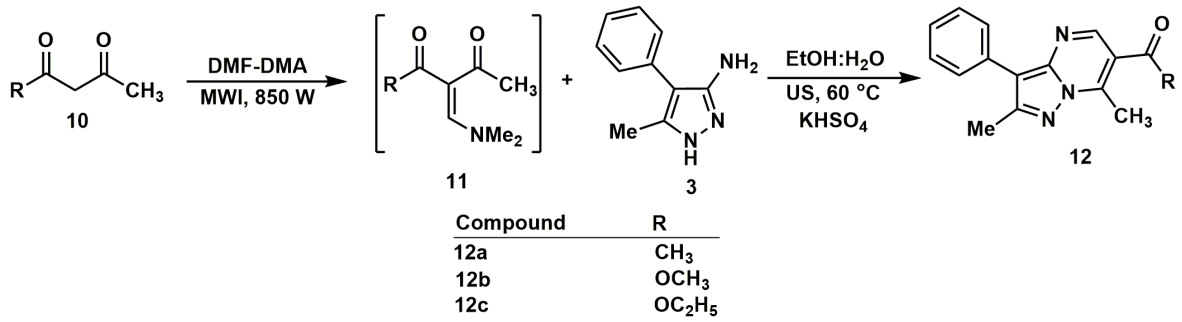
Also, the reaction of aminopyrazole **3** with 3-(dimethyl amino)-1-(heteroaryl)prop-2-en-1-ones was investigated under similar conditions whereby the desired 2-methyl-3-phenyl-7-heteroaryl-pyrazolo[1,5-*a*]pyrimidine (**9**) was formed (Scheme 3) in 12-16 minutes in 83-85 % yields. Surprisingly, in case of the reaction of aminopyrazole **3** with compound **8c**, regioisomeric products **9c** and **9d** were formed (Scheme 3). The regioisomeric products **9c** and **9d** showed $R_f$ value at 0.2 and 0.4, respectively, and were therefore easily isolated by column chromatography using silica gel (60-120 mesh) and 20 % EtOAc-hexane as eluent. The products isolated were differentiated with the help of $^1$H NMR.

A plausible mechanism for the formation of the products has been rationalized as follows: Assisted by $KHSO_4$, the enaminone undergoes Aza-Michael addition-elimination reaction to give an adduct which subsequently undergoes cyclodehydration to yield the proposed pyrazolo[1,5-*a*]pyrimidines **9**. The nucleophilic attack by aminopyrazole could follow two routes. Route 1 result in the formation compound **9c** and route 2 gives compound **9d** as shown in the following Scheme 5.

The analysis and the identities of the compounds were established using $^1$H NMR. The $C_5$-H, $C_6$-H protons for compounds **9b**, **9c** appeared as doublets in the range δ 8.59-8.78 and δ 6.88-7.61 ppm, respectively, with coupling constant of 4.4 Hz. For compound **9a**, the $C_5$-H, $C_6$-H protons appeared as multiplet at δ 8.53-8.55 and δ 6.89-6.92 ppm, respectively. In case of regioisomeric product **9d** clear distinction of the substitution at C-5 were made as observed in the coupling constant [30]. The $C_7$-H proton showed doublet at δ 7.98 ppm with coupling constant 7.6 Hz [30] and the doublet of $C_6$-H proton gets buried with the proton of the heteroaryl group.

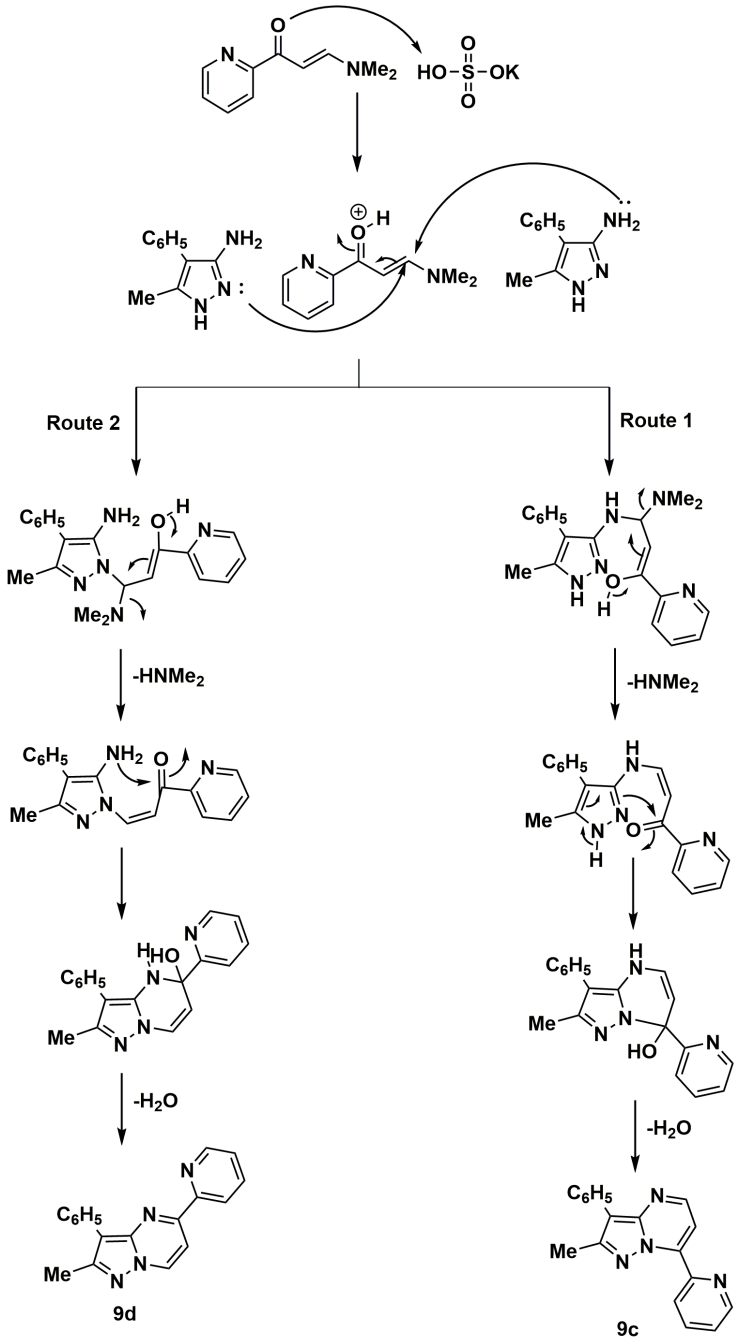
In order to further examine, the generality of this green methodology, we finally took up the reaction of aminopyrazole **3** with formylated active proton compounds **11** (Scheme 4) derived from 1,3-diketones in *in situ*. It was utterly pleasing to observe that the reactions went to completion giving the expected product **12** within 6-20 minutes in 88-90 % yields. The identities of these products and its distinction were established with the help of spectral analytic data.

In the case of compounds **12b-c**, the $C_5$-H protons gave singlet at about δ 8.92 ppm and for compound **12a**, it appeared as singlet at δ 8.83 ppm. The methyl protons at C-2, for all the synthesised compounds gave a sharp singlet at around δ 2.62 ppm.




| Compound | R |
|---|---|
| 12a | $CH_3$ |
| 12b | $OCH_3$ |
| 12c | $OC_2H_5$ |

**Scheme 4**




**Scheme 5**

**Table 1.** Synthesis of pyrazolo[1,5-*a*]pyrimidine derivatives.

| Compounds | Time (in minutes) | Yield experimental/literature (%) | M.p./Lit M.p. (°C) |
|---|---|---|---|
| 5a | 5 | 96/76 | 142-143/251 [26] |
| 5b | 6 | 95/75 | 179-180/178-180 [27] |
| 5c | 6 | 88/Unreported | 176-177 |
| 5d | 12 | 88/67 | 197/196-198 [27] |
| 5e | 5 | 90/Unreported | 230-232 |
| 7a | 12 | 75/81 | 219-220/215–216 [28] |
| 7b | 21 | 83/Unreported | 235 |
| 7c | 8 | 84/Unreported | 248-250 |
| 9a | 12 | 87/Unreported | 204-206 |
| 9b | 16 | 85/Unreported | 149-151 |
| 9c | 11 | 49/Unreported | 131 |
| 9d | 11 | 44/Unreported | 152-154 |
| 12a | 20 | 88/Unreported | 265 |
| 12b | 6 | 85/Unreported | 110-112 |
| 12c | 9 | 90/Unreported | 104-106 |

**Table 2.** Crystal data and structure refinement for compound **7c**.

| | |
|---|---|
| Empirical formula | $C_{19}H_{15}N_4Cl$ |
| Formula weight | 334.80 |
| Temperature (K) | 293(2) |
| Crystal system | Triclinic |
| Space group | P-1 |
| a (Å) | 8.0198(3) |
| b (Å) | 14.0341(6) |
| c (Å) | 14.2099(6) |
| α (°) | 87.672(2) |
| β (°) | 83.902(2) |
| γ (°) | 89.120(2) |
| Volume (Å$^3$) | 1588.87(11) |
| Z | 4 |
| $\rho_{calc}$ (g/cm$^3$) | 1.400 |
| μ (mm$^{-1}$) | 0.248 |
| F(000) | 696.0 |
| Crystal size (mm$^3$) | 0.27 x 0.23 x 0.17 |
| Radiation | MoKα (λ = 0.71073) |
| 2Θ range for data collection (°) | 4.012 to 49 |
| Index ranges | $-8 \le h \le 9$, $-16 \le k \le 16$, $-16 \le l \le 16$ |
| Reflections collected | 12918 |
| Independent reflections | 5152 [$R_{int}$ = 0.0411, $R_{sigma}$ = 0.0429] |
| Data/restraints/parameters | 5152/0/449 |
| Goodness-of-fit on F$^2$ | 1.071 |
| Final R indexes [I≥2σ (I)] | $R_1$ = 0.0486, $wR_2$ = 0.1176 |
| Final R indexes [all data] | $R_1$ = 0.0737, $wR_2$ = 0.1320 |
| Largest diff. peak/hole / (e Å$^{-3}$) | 0.30/-0.30 |

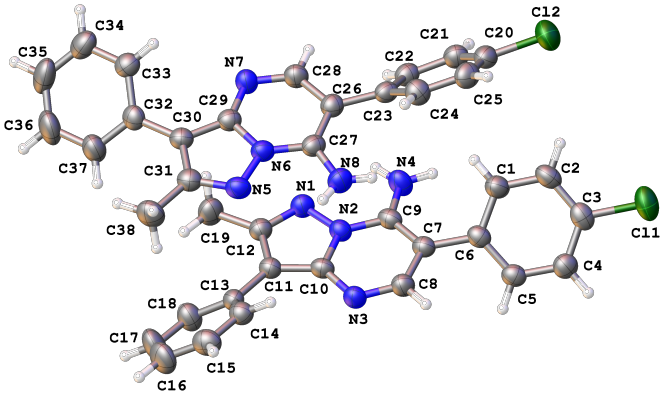



**Figure 1.** Molecular structure of compound **7c**.

Further, $^{13}C$ NMR and mass spectroscopy were in support of the structure. A summary of the synthesized pyrazolo[1,5-*a*] pyrimidines is presented in Table 1.

### *3.2. X-ray crystallography*

The confirmation and regioselectivity of the structure was done with the help of X-ray crystal structure by taking compound 6-(4-chlorophenyl)-2-methyl-3-phenylpyrazolo[1, 5-*a*] pyrimidin-7-amine **7c** (Figure 1) as a model.

Single crystals of $C_{19}H_{15}N_4Cl$ practicable for X-ray data analysis were crystallized with methanol. A suitable crystal was selected and mounted on a CCD (Charge-Coupled Device) area detector diffractometer. The crystal was kept at 293(2) K during data collection. X-ray data for compound **7c** was solved using Olex2. (Experimental section). Yellow crystals of compound **7c** suitable for single X-ray diffraction measurements were grown by the slow crystallisation in methanol. The crystallographic data for the structure were deposited to the Cambridge Crystallographic Data Center (CCDC no. 967390).

**Table 3.** Bond lengths for compound **7c**.

| Atom | Atom | Length (Å) | Atom | Atom | Length (Å) |
|---|---|---|---|---|---|
| N8 | C27 | 1.346(4) | C13 | C14 | 1.390(4) |
| Cl1 | C3 | 1.742(3) | C13 | C18 | 1.392(4) |
| Cl2 | C20 | 1.742(3) | C5 | C6 | 1.382(4) |
| N2 | C9 | 1.354(3) | C5 | C4 | 1.389(4) |
| N2 | N1 | 1.372(3) | C12 | C19 | 1.500(4) |
| N2 | C10 | 1.390(3) | C20 | C25 | 1.375(4) |
| N6 | C27 | 1.356(3) | C20 | C21 | 1.383(4) |
| N6 | N5 | 1.368(3) | C23 | C22 | 1.393(4) |
| N6 | C29 | 1.391(3) | C23 | C24 | 1.393(4) |
| N3 | C8 | 1.319(3) | N5 | C31 | 1.336(4) |
| N3 | C10 | 1.364(3) | C30 | C31 | 1.408(4) |
| N7 | C28 | 1.316(4) | C30 | C32 | 1.464(4) |
| N7 | C29 | 1.363(3) | C6 | C1 | 1.400(4) |
| C7 | C9 | 1.399(4) | C2 | C1 | 1.384(4) |
| C7 | C8 | 1.413(3) | C32 | C37 | 1.387(4) |
| C7 | C6 | 1.485(4) | C32 | C33 | 1.402(4) |
| C29 | C30 | 1.388(4) | C14 | C15 | 1.375(4) |
| N4 | C9 | 1.347(3) | C33 | C34 | 1.370(4) |
| C26 | C27 | 1.393(4) | C24 | C25 | 1.383(4) |
| C26 | C28 | 1.417(4) | C22 | C21 | 1.380(4) |
| C26 | C23 | 1.478(4) | C31 | C38 | 1.497(4) |
| N1 | C12 | 1.337(3) | C18 | C17 | 1.375(4) |
| C10 | C11 | 1.385(4) | C15 | C16 | 1.380(4) |
| C11 | C12 | 1.412(3) | C36 | C35 | 1.376(5) |
| C11 | C13 | 1.471(3) | C36 | C37 | 1.388(5) |
| C3 | C2 | 1.379(4) | C34 | C35 | 1.378(5) |
| C3 | C4 | 1.386(4) | C16 | C17 | 1.371(5) |

**Table 4.** Bond angles for compound **7c**.

| Atom | Atom | Atom | Angle (°) | Atom | Atom | Atom | Angle (°) |
|---|---|---|---|---|---|---|---|
| N8 | C27 | N6 | 115.6(3) | C9 | N2 | N1 | 123.2(2) |
| N8 | C27 | C26 | 127.9(3) | N6 | C27 | C26 | 116.5(2) |
| C9 | N2 | C10 | 124.3(2) | N3 | C8 | C7 | 127.5(3) |
| N1 | N2 | C10 | 112.4(2) | N5 | N6 | C29 | 112.2(2) |
| C27 | N6 | N5 | 124.1(2) | C8 | N3 | C10 | 114.9(2) |
| C27 | N6 | C29 | 23.7(2) | C25 | C24 | C23 | 122.4(3) |
| C34 | C33 | C32 | 121.1(3) | C21 | C22 | C23 | 121.6(3) |
| C28 | N7 | C29 | 114.8(2) | C30 | C29 | N6 | 105.9(2) |
| C9 | C7 | C6 | 122.6(2) | C22 | C21 | C20 | 119.6(3) |
| N7 | C29 | C30 | 133.0(2) | C3 | C4 | C5 | 119.3(3) |
| C8 | C7 | C6 | 120.8(2) | C28 | C26 | C23 | 119.6(2) |
| N7 | C29 | N6 | 21.1(2) | C20 | C25 | C24 | 118.8(3) |
| C27 | C26 | C28 | 16.5(3) | C11 | C10 | N2 | 105.9(2) |
| C27 | C26 | C23 | 23.8(2) | C2 | C3 | C4 | 120.7(3) |
| C12 | N1 | N2 | 103.69(19) | C2 | C3 | Cl1 | 119.2(2) |
| N3 | C10 | C11 | 133.5(2) | C14 | C13 | C11 | 120.4(2) |
| C10 | C11 | C12 | 105.0(2) | C6 | C5 | C4 | 121.5(2) |
| C12 | C11 | C13 | 127.8(2) | N1 | C12 | C1 | 113.0(2) |
| C4 | C3 | Cl1 | 120.1(3) | C11 | C12 | C19 | 128.5(2) |
| N7 | C28 | C26 | 127.4(2) | N3 | C10 | N2 | 120.6(2) |
| N4 | C9 | C7 | 128.0(3) | C2 | C1 | C6 | 121.6(3) |
| N1 | C12 | C1 | 113.0(2) | C10 | C11 | C13 | 127.2(2) |
| C25 | C20 | C21 | 120.7(3) | N5 | C31 | C30 | 113.1(2) |
| C31 | N5 | N6 | 104.0(2) | C30 | C31 | C38 | 127.9(3) |
| C29 | C30 | C32 | 126.3(2) | C18 | C13 | C11 | 121.8(2) |
| C5 | C6 | C7 | 121.7(2) | N4 | C9 | N2 | 115.9(2) |
| N5 | C31 | C30 | 113.1(2) | N1 | C12 | C19 | 118.4(2) |
| C14 | C13 | C18 | 117.8(2) | C25 | C20 | Cl2 | 119.5(2) |
| C17 | C18 | C13 | 120.9(3) | C31 | C30 | C32 | 128.9(2) |
| N2 | C9 | C7 | 116.1(2) | C33 | C32 | C30 | 120.2(2) |
| C14 | C15 | C16 | 120.3(3) | C37 | C32 | C30 | 122.1(3) |

Compound **7c** crystallizes in a triclinic cell (space group P-1) with a = 8.0198 (3) Å, b = 14.0341 (6) Å, c = 14.2099 (6) Å, α = 87.672 (2)°, β = 83.902 (2)°, γ = 89.120 (2)°, V = 1588.87 (11) Å$^3$ and Z = 4. The molecular graphic was performed using Olex2 1.3-beta (Figure 1).

Crystal data, data collection and structure refinement details are listed in Table 2. The crystal structure consists of two independent molecules per asymmetric unit, the pyrazolo[1,5-*a*]pyrimidine nucleus arranged in an opposite manner. The interaction of H1 with the Cg ring C20--C25 stabilize the crystal packing. Also, the π-π interaction of the pyrazolo[1,5-*a*] pyrimidine ring between C10-C11-C12-N1-N2 and C31-C30-C29-N6-N5, C10-N3-C8-C7-C9-N2 and C29-N6-C27-C26-C28-N7 rings interactions could be the contributing factor to this arrangement and stacking [31]. In both molecules, the pyrazolo[1,5-*a*]pyrimidine rings are planar with torsional angles C30-C29-N6-C27 -178.56°, N5-N6-C29-N7 -178.91°, C31-C30-C29-N6 -0.04°. The bond length and angles are within the normal ranges [32]. The bond length C10-N3 and C29-N7 which is single bond does not differ very much from bond lengths of N1-C12, N3-C8 and N5-C31, N7-C28 which are double bonds. Similarly, C11-C12, C8-C7 and C30-C31, C28-C26 which are single bonds does not vary much with that of C11-C10, C7-C8 and C30-C29, C26-C27 which are formally double bonds. This pattern could be due to the delocalization of the ring system. Selected bond lengths and bond angles are given in Tables 3 and 4. The phenyl groups at C3 and C6 position in both the molecules are oriented to the plane of the pyrazolo[1,5-*a*]pyrimidine nucleus with torsion angles of C1-C6-C7-C9 and C18-C13-C11-C12 as 44.67° and 36.78°, respectively, and C24-C23-C26-C27 and C37-C32-C30-C31 as -41.63° and -41.05°, respectively.

## 4. Conclusion

We have developed an efficient, facile and environmental friendly synthetic strategy for the synthesis of hitherto unknown pyrazolo[1,5-*a*]pyrimidine derivatives with formylated acetophenones and its equivalent in the presence of $KHSO_4$ in aqueous medium in good to excellent yields. Use of $KHSO_4$ led to mild reaction conditions with precipitation of practically pure products that could be easily isolated by filtration, ensuring complete removal of the acid by washing with EtOH:$H_2O$ (1:1, *v*:*v*).

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## Supporting information

CCDC-967390 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033.

## Disclosure statement

Conflict of interests: The authors declare that they have no conflict of interest.
Author contributions: All authors contributed equally to this work.
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Sample availability: Samples of the compounds are available from the author.

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