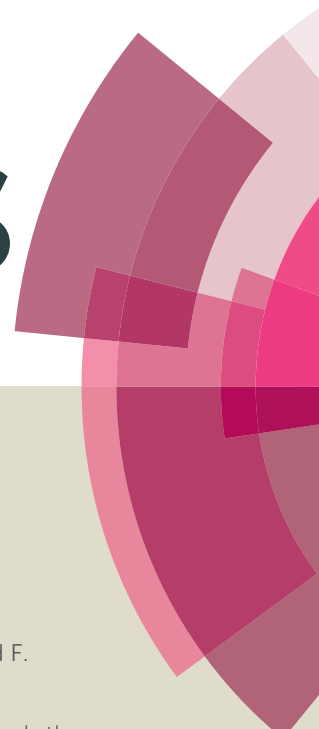


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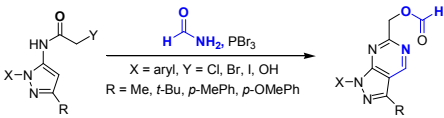
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Graphical abstract

Vilsmeier reagent mediated synthesis of 6-[(formyl)methyl]-pyrazolopyrimidines
via one-pot multiple tandem reaction

Shi-Han Lu, Po-Lin Liu, and Fung Fuh Wong*

Vilsmeier reagent mediated synthesis of pyrazolopyrimidine



**Vilsmeier reagent mediated synthesis of
6-[(formyloxy)methyl]-pyrazolopyrimidines via one-pot multiple
tandem reaction**

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Abstract

A new Vilsmeier reagent mediated one-pot reaction using 5-(2-chloroacetyl amino)pyrazoles as the starting material was developed for the efficient synthesis of 6-[(formyloxy)methyl]-1*H*-pyrazolo[3,4-*d*]pyrimidine. This new multiple tandem reactions involving Vilsmeier-Haack reaction, Morgan-Walls reaction, sequential elimination, substitution reaction, and final hydrolysis reaction efficiently afforded formyloxymethyl pyrazolo[3,4-*d*]pyrimidine products in good yields.

Introduction

As an expressly practical synthetic organic chemistry, the efficient, rapid and economical strategies were enthusiastically investigated to design the valuable chemical substances.^{1,2} One-pot tandem organic reactions have attracted great attentions for they can simplify the detection, isolation, and purification of intermediates in the operation procedure and also diminish the manufacture cost and environmental pollution.^{3,4} Additionally, the one-pot multiple processes were also recommended to the new synthetically efficient method and reaction designed approach for developing novel lead constructions of pharmaceuticals and even novel molecule-based materials.⁵

Vilsmeier-type reaction is a very versatile method for the construction of many heterocyclic compounds^{5,6} and acts an important organic synthetic tool for the introduction of a formyl group.⁶⁻¹⁰ Recently, we have evaluated new Vilsmeier-type reaction by studying the reactivity of amide reagents for the preparation of pyrazolone,¹¹ pyrazole,¹² dipyrazolylmethane,¹³ and fused pyrimidine derivatives.¹⁴ Those works indicated the chemoselective products resulted from the different reactivity of the substituted amides serving as the Vilsmeier reagent by reacting with POCl₃. On the other hands, Morgan-Walls cyclization reaction has been widely used for C–C bond formation to build various nitrogen ring systems.¹⁵ Herein, we reported the use of Vilsmeier reagent to initiate the Vilsmeier-Haack formylation reaction, Morgan-Walls cyclization reaction, sequential elimination, substitution reaction, and hydrolysis for synthesis of the pyrazole fused pyrimidine derivatives via a tandem multiple reaction.^{14,16}

Pyrimidines fused with a heterocycle such as furo-,¹⁷ pyrazolo-,¹⁸ pyrrolo-,¹⁹ pyridopyrazolo-,²⁰ and pyrazolotriazolo-pyrimidine²¹ are important classes of compounds and also currently of interest to the pharmaceutical industry due to their

remarkable pharmaceutical applications. Other synthesis approaches of pyrazolopyrimidines were also found through heterocyclization reaction using 5-amino-4-formypyrazoles,²² 5-amino-1*H*-4-pyrazolcarbonitriles,²³ 5-amino-1*H*-4-pyrazolcarboxamides²³ or other similar chemical reagents as the starting substrates.²⁴⁻²⁶ However, the reported synthetic manipulation for their preparation requires harsh conditions, long reaction times, complex synthetic procedures, and tedious purification steps.²⁷ Therefore, new convenient synthetic routes for the synthesis of pyrimidine fused heterocyclic systems have attracted considerable attention. In this work, we described a direct and convenient one-pot multiple method for the synthesis of a series of pyrazolo[3,4-*d*]pyrimidine derivatives from 5-(2-chloroacetyl amino)pyrazoles with formamide in the presence of PBr₃. This new multiple tandem reaction was developed to obtain formyloxymethyl pyrazolo[3,4-*d*]pyrimidine products in good yields (73–92%).

Result and discussion

Scheme 1 presents the typical reaction conditions for Vilsmeier reagent mediated synthesis of 1-aryl-6-[(formyloxy)methyl]-1*H*-pyrazolo[3,4-*d*]pyrimidines **17–32** from 5-(2-Chloroacetyl amino)pyrazoles **1–16**. Starting materials **1–16** were prepared from the reaction of 5-aminopyrazoles and 2-chloroacetyl chloride as previously reported.²⁸ Due to 5-(2-chloroacetyl amino)pyrazoles **1–16** possessed the activated α -chloro-*N*-arylacetamide moiety, we attempted to introduce the mild nucleophile iminium group on the C-4 position of pyrazolic ring of 5-(2-chloroacetyl amino)pyrazoles **1–16** via Vilsmeier-Haack reaction for evaluation the further intramolecular cyclization reaction condition for synthesis of 6-[(formyloxy)methyl]-1*H*-pyrazolo[3,4-*d*]pyrimidine in this work.

Scheme 1

To optimize the reaction conditions,

1,3-diphenyl-5-(2-chloroacetyl amino)pyrazole (**1**) was used as the model and reacted with formamide in the presence of various halogenating agents including benzoyl chloride (PhCOCl), oxalyl chloride (ClCOCOCl), phosphorous tribromide (PBr₃), phosphorous oxychloride (POCl₃), thionyl chloride (SOCl₂), and *p*-toluenesulfonic chloride (TsCl) at 50–60 °C for 5.0 h. Without the halogenating agent, virtually no reaction took place (see entry 1 in Table 1). When 3.0 equivalents of halogenating agents were added, the reaction gave the corresponding 1,3-diphenyl-6-[(formyloxy)methyl]-1*H*-pyrazolo[3,4-*d*]pyrimidine (**17**) in 26–88% yields (see entries 2–7 in Table 1). The use of PBr₃ provided the best result with the formation of product **17** in 88% yield (entry 2 in Table 1). The use of POCl₃ also gave a good yield of **17** (73%, entry 2 in Table 1).

Table 1

Employing the reliable procedure by use of PBr₃ as the brominating agent to 5-(2-chloroacetyl amino)pyrazoles **1–8** possessing methyl, chloro, and methoxy substituents, the tandem one-pot multiple reaction could readily take place to give the corresponding 1-aryl-6-[(formyloxy)methyl]-1*H*-pyrazolo[3,4-*d*]pyrimidines **17–24** in 73–92% yields (see Scheme 1 and Table 2). We found the *m*- and *p*-Me-Ph at the *N*-1 substituents in pyrazolic ring gave the 1-aryl-6-[(formyloxy)methyl]-1*H*-pyrazolo[3,4-*d*]pyrimidines **19** and **20** in better isolated yields (85% and 92%). Employing the same conditions to 5-(2-chloroacetyl amino)pyrazoles with methyl, *p*-NO₂-Ph and *p*-COOH-Ph substituents at the *N*-1 position of pyrazolic ring did not give the desired pyrazolo[3,4-*d*]pyrimidine products. As a result, we assumed the phenyl group with electron-donating group as the *N*-1 substituents would favor the proceeding of one-pot multiple reaction.

Table 2

For further investigation of the substitution effect, the same conditions were applied to 5-(2-chloroacetyl amino)pyrazoles **9–12** containing methyl, *t*-butyl, *p*-Me-Ph, *p*-Cl-Ph, or *p*-OMe-Ph groups at the *C*-3 position and phenyl substituent at the *N*-1 position. The reaction also successfully gave the corresponding **25–28** in 74–81% yields (see Scheme 1 and Table 2). In particular, compound **10** with *t*-butyl group at the *C*-3 position showed better yield (81%). For further demonstration of electronic effects of *meta*- or *para* substituent at the *N*-1 position of pyrazolic ring, compounds **13** and **14** were synthesized as the starting material to perform the reaction. The experimental results listed in Table 2 indicated that the *N*-1 *para*-Me phenyl displayed better yield than *meta*-Me substituent (84% vs. 74%). For compounds **15** and **16** bearing respective *ortho*- and *para*-Cl phenyl substituents at the *N*-1 position, the inducted effect of *N*-1 *para*-Cl substituent was also better than *ortho*-Cl (77% > 72%, see Table 2). All 6-[(formyloxy)methyl]-1*H*-pyrazolo[3,4-*d*]pyrimidines **17–30** were fully characterized by spectroscopic methods. Furthermore, the structure of 6-[(formyloxy)methyl]-1*H*-pyrazolo[3,4-*d*]pyrimidines **24** was also characterized by X-ray crystallographic analyses and the result (ORTEP) was presented in Figure 1.

Figure 1

We then investigated the effect of leaving group at the α position ($-(C=O)-CH-X$) for this new transformation. Starting materials including 5-(2-bromoacetyl amino)pyrazole **33**, 5-(2-iodoacetyl amino)pyrazole **34**, and 5-(2-hydroxyacetyl amino)pyrazole **35**²⁹ bearing Br, I, and OH at the α -C position were prepared (see Table 3). By employing the same reaction condition to compounds **33–35**, the better results were observed for compounds **33** and **34** in 86% and 87% yields, respectively (see entry 2 and 3 in Table 3). Although the hydroxyl group is not good leaving group, compound **35** was also successfully converted to the

corresponding pyrimidine fused product **22** in 73% yield due to the hydroxyl group was transformed into an efficient leaving group $\text{O}(\text{P}=\text{O})\text{Br}_2$ in the presence of PBr_3 (see Table 3). Based on the results, we found the reactivity of leaving group was $\text{I} > \text{Br} > \text{Cl} > \text{OH}$. To conceive economic cost and commercial available of reagents, we selected and synthesized a series of 5-(2-hydroxyacetyl amino)pyrazoles as the starting materials for our further evaluation.

Table 3

Following the experimental results, we proposed a plausible mechanism for this new one-pot multiple reaction in Scheme 2. Preliminarily, Vilsmeier reactive species **36** was generated from the reaction of formamide with PBr_3 *in situ*.^{11-14,30} 1,3-Diphenyl-5-(2-chloroacetyl amino)pyrazole **1** then reacted with **36** to undergo the Vilsmeier–Haack reaction to afford intermediate **37** with introducing imino group on C-4 position of pyrazoylic ring (see Scheme 2). In strong acidic conditions, excess amount of PBr_3 would catalyze the Morgan-Walls reaction to provide **38** and subsequently convert to generate **39** via intramolecular cyclization reaction.³¹ Intermediates **37** and **38** with electron-withdrawing groups, such as NO_2 and COOH , would decrease the nucleophilicity of imino group through conjugated effect and unfavorably took place the heterocyclization reaction. On the other hand, intermediates **38** including *N*-1 aliphatic methyl substituent was harmful for the co-plane formation to interfere with the intra-cyclization reaction. As a result, 5-(2-chloroacetyl amino)pyrazoles with methyl, *p*- NO_2 -Ph and *p*- COOH -Ph substituents in *N*-1 position of pyrazolic ring were unable to adapt in this new developed reaction condition. After the further deprotonation of intermediate **39**, 6-(chloromethyl)pyrazolo[3,4-*d*]pyrimidine intermediate **40** was formed. It is well known that formamide possesses two resonance contributors **42** and **43**.^{32,33} In the acidic condition, formamide was more favored the $\text{C}(\text{O}^-)=\text{N}^+\text{H}_2$ **42** contributor thus

replaced the chloro atom in **40** to give the substitution product **41**. After work-up, intermediate **41** was hydrolyzed to 6-[(formyl)methyl]-1*H*-pyrazolo[3,4-*d*]pyrimidine **17** as the major product (88% yield) and (1,3-diphenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)methanol **44** as the minor product (9% yield, see Scheme 2).

Scheme 2

During work-up and purification procedures, small amount of **44** was isolated as the by-product (see Scheme 2). This result led us to consider that compound **44** might be equilibria toward compound **17** under the acidic condition. Therefore, we isolated compound **44** and treated it with formamide and PBr₃ under the same condition. Compound **44** was successfully transferred to the corresponding pyrazolo[3,4-*d*]pyrimidine product **17** in 81% yield (see Scheme 3). Based on this controlled experimental result, compounds **44** should be hydrolyzed equilibrium expression product of compound **17** (see Scheme 3). For the further demonstration of this conception, the crude resulting solution was added with H₂O and kept at room temperature. The mixture was sampling each 30 mins and monitored by TLC and ¹H-NMR spectroscopic method. Following the result of TLC and ¹H-NMR spectroscopic characteristics, we found that compound **17** was gradually converted to the hydrolyzed product **44**. Therefore, the quenching neutralization procedure must be effectively carried out to diminish this hydrolysis product **44**.

Scheme 3

To gain insight into the reaction mechanism and to establish the formyloxylolation nature of the reaction, the further study was performed as shown in Scheme 2. For giving more evidences to the proposed mechanism, we also tried to convert compound **44** to the proposed intermediate 6-(chloromethyl)pyrazolo[3,4-*d*]pyrimidine **40** by treating it with thionyl chloride in

CH₂Cl₂ (80%, see Scheme 3).³⁴ Consequently, the synthesized intermediate **40** was reacted towards formamide with PBr₃ in the same condition. Fortunately, the corresponding product **17** was effectively isolated in 74% yield. The results gave more proof to our proposed mechanism.

Conclusions

We have successfully developed a new one-pot multiple reaction to prepare 6-(formyloxymethyl)pyrazolo[3,4-*d*]pyrimidine by treating 5-(2-chloroacetyl amino)pyrazoles with formamide in presence of PBr₃. Based on the study of leaving group, we found that the reactivity of leaving group effect is I > Br > Cl > OH. Following the further mechanistic study, key 6-(chloromethyl)pyrazolo[3,4-*d*]pyrimidine intermediate **40** was successfully synthesized from (1,3-diphenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)methanol **44** and then converted to the desired 6-[(formyloxy)methyl]-1*H*-pyrazolo[3,4-*d*]pyrimidine **17** under the same condition. The mechanistic study significantly demonstrated the plausible mechanism.

Experimental Section

All chemicals were reagent grade and used as purchased. All reactions were carried out under nitrogen atmosphere and monitored by TLC analysis. Flash column chromatography was carried out on silica gel (230–400 mesh). Commercially available reagents were used without further purification unless otherwise noted. ¹H NMR were recorded at 200, 400, or 500 MHz and ¹³C NMR recorded at 50, 100, or 125 MHz, respectively, in CDCl₃, CH₃OD, and DMSO-*d*₆ as solvent. The standard abbreviations s, d, t, q, and m refer to singlet, doublet, triplet, quartet, and multiplet, respectively. Coupling constant (*J*), whenever discernible, have been reported in Hz. Infrared spectra (IR) were recorded as neat solutions or solids; and mass spectra were recorded using electron impact or electrospray ionization techniques. The

wavenumbers reported are referenced to the polystyrene 1601 cm^{-1} absorption. Flash column chromatography purification of compounds was carried out by gradient elution using hexanes in ethyl acetate (EA) unless otherwise stated. High-resolution mass spectra were obtained by means of a JEOL JMS-HX110 mass spectrometer.

Standard procedure for synthesis of 5-(2-haloacetyl amino)pyrazoles 1–16 and 33–35.²⁸ 1-Aryl-3-aryl-5-aminopyrazoles (1.0 equiv) was dissolved in CH_2Cl_2 (10 mL) and stirred in ice-bath. 2-Chloroacetyl chloride, 2-chloroacetyl bromide, or 2-iodoroacetyl chloride (1.2 equiv) in 10 mL of CH_2Cl_2 or THF were slowly added to the reaction mixture at 0 °C under N_2 , respectively. The reaction was stirred at 0–10 °C for 3–4 h. The reaction mixture was washed with water (10 mL) and saturated aqueous NaHCO_3 (10 mL \times 2). The organic layer was dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give the corresponding acylation product 5-(2-haloacetyl amino)pyrazoles 1–6 and 33–35 in 73–87% yields.

5-(2-Chloroacetyl amino)-1-phenyl-3-phenylpyrazole (1). ^1H NMR (CDCl_3 , 200 MHz) δ 4.18 (s, 2 H, CH_2), 7.10 (s, 1 H), 7.23–7.55 (m, 8 H, ArH), 7.86 (dd, 2 H, J = 8.0, 4.0 Hz), 8.63 (br, 1 H, N–H).

5-(2-Chloroacetyl amino)-1-(2-methylphenyl)-3-phenylpyrazole (2). ^1H NMR (CDCl_3 , 200 MHz) δ 2.38 (d, J = 7.6 Hz, 3 H, CH_3), 4.10 (s, 2 H, CH_2), 6.96 (s, 1 H), 7.38–7.44 (m, 9 H, ArH).

5-(2-Chloroacetyl amino)-1-(3-methylphenyl)-3-phenylpyrazole (3). ^1H NMR (CDCl_3 , 200 MHz) δ 2.13 (s, 3 H, CH_3), 4.04 (s, 2 H, CH_2), 7.31–7.47 (m, 8 H, ArH), 7.91 (d, J = 3.0 Hz, 2 H, ArH), 8.82 (br, 1 H, N–H).

5-(2-Chloroacetyl amino)-1-(4-methylphenyl)-3-phenylpyrazole (4). ^1H NMR (CDCl_3 , 200 MHz) δ 2.42 (s, 3 H, CH_3), 4.18 (s, 2 H, CH_2), 7.09 (s, 1 H), 7.25–7.43 (m, 7H, ArH), 7.86 (dd, 2 H, J = 9.6, 8.0 Hz), 8.61 (br, 1 H, N–H).

5-(2-Chloroacetyl-amino)-1-(2-chlorophenyl)-3-phenylpyrazole (5). ^1H NMR (CDCl_3 , 200 MHz) δ 4.13 (s, 2 H, CH_2), 7.04 (s, 1 H), 7.25–7.55 (m, 9H, ArH), 8.29 (br, 1 H, N–H).

5-(2-Chloroacetyl-amino)-1-(3-chlorophenyl)-3-phenylpyrazole (6). Brown solid; mp 101–102 $^\circ\text{C}$; ^1H NMR (CDCl_3 , 200 MHz) δ 4.20 (s, 2 H, CH_2), 7.08 (s, 1 H, ArH), 7.31–7.47 (m, 5 H, ArH), 7.61 (s, 2 H, ArH), 7.85 (d, J = 7.6 Hz, 2 H, ArH), 8.61 (s, 1 H, N–H); ^{13}C NMR (CDCl_3 , 50 MHz) δ 42.64, 96.23, 122.00, 124.88, 125.76 ($2 \times \text{CH}$), 128.45, 128.66 ($3 \times \text{CH}$), 130.84, 132.42, 135.42, 135.81, 138.64, 152.42, 162.50; IR (KBr) 3046, 2955, 2924, 2853, 1721 (s, C=O), 1201, 764; EIMS m/z : 349 ($\text{M}^+ + 4$, 2), 347 ($\text{M}^+ + 2$, 9), 345 (M^+ , 16), 194 (100), 165 (11), 133 (79), 105 (42), 91 (74), 77 (30); HRMS Calcd for $\text{C}_{17}\text{H}_{13}\text{Cl}_2\text{ON}_3$: 345.0436, Found: 345.0433.

5-(2-Chloroacetyl-amino)-1-(4-chlorophenyl)-3-phenylpyrazole (7). ^1H NMR (CDCl_3 , 200 MHz) δ 4.18 (s, 2 H, CH_2), 7.04 (s, 1 H), 7.24–7.50 (m, 7H, ArH), 7.79 (dd, 2 H, J = 15.7, 7.8 Hz), 7.29 (br, 1 H, N–H).

5-(2-Chloroacetyl-amino)-1-(3-methoxyphenyl)-3-phenylpyrazole (8). ^1H NMR (CDCl_3 , 200 MHz) δ 3.86 (s, 3 H, CH_3), 4.17 (s, 2 H, CH_2), 7.01–7.07 (m, 3H, ArH), 7.39–7.46 (m, 5H, ArH), 7.83–7.84 (m, 2H, ArH), 8.54 (br, 1 H, N–H).

5-(2-Chloroacetyl-amino)-1-phenyl-3-methylpyrazole (9). ^1H NMR (CDCl_3 , 200 MHz) δ 2.30 (s, 3 H, CH_3), 4.13 (s, 2 H, CH_2), 6.55 (s, 1 H), 7.36–7.54 (m, 5H, ArH), 8.52 (br, 1 H, N–H).

5-(2-Chloroacetyl-amino)-1-phenyl-3-tetrabutanyl pyrazole (10). ^1H NMR (CDCl_3 , 200 MHz) δ 1.33 (s, 9 H, CH_3), 4.13 (s, 2 H, CH_2), 6.63 (s, 1 H), 7.46–7.48 (m, 5H, ArH), 8.58 (br, 1 H, N–H).

5-(2-Chloroacetyl-amino)-1-phenyl-3-(4-methylphenyl) pyrazole (11). ^1H NMR (CDCl_3 , 200 MHz) δ 2.36 (s, 3 H, CH_3), 4.15 (s, 2 H, CH_2), 6.74 (s, 1 H), 7.06–7.54 (m, 7H, ArH), 7.72 (d, J = 6.4 Hz, 2 H, ArH), 8.65 (br, 1 H, N–H).

5-(2-Chloroacetyl-amino)-1-phenyl-3-(4-methoxyphenyl) pyrazole (12). ^1H NMR (CDCl_3 , 200 MHz) δ 3.82 (s, 3 H, CH_3), 4.18 (s, 2 H, CH_2), 6.93 (d, $J = 8.8$ Hz, 2 H, ArH), 7.04 (s, 1 H), 7.43–7.55 (m, 5H, ArH), 7.80 (dd, 2 H, $J = 8.8$, 4.4 Hz), 8.62 (br, 1 H, N–H).

5-(2-Chloroacetyl-amino)-1-(3-methylphenyl)-3-(4-methoxyphenyl) pyrazole (13). ^1H NMR (CDCl_3 , 200 MHz) δ 2.42 (s, 3 H, CH_3), 3.82 (s, 3 H, CH_3), 4.17 (s, 2 H, CH_2), 6.92 (dd, 2 H, $J = 8.8$, 6.8 Hz), 7.03 (s, 1 H), 7.26–7.41 (m, 4H, ArH), 7.80 (dd, 2 H, $J = 8.8$, 6.8 Hz), 8.66 (br, 1 H, N–H).

5-(2-Chloroacetyl-amino)-1-(4-methylphenyl)-3-(4-methoxyphenyl) pyrazole (14). ^1H NMR (CDCl_3 , 200 MHz) δ 2.39 (s, 3 H, CH_3), 3.82 (s, 3 H, CH_3), 4.17 (s, 2 H, CH_2), 6.92 (dd, 2 H, $J = 8.8$, 4.4 Hz), 7.02 (s, 1 H), 7.30–7.42 (m, 4H, ArH), 7.78 (dd, 2 H, $J = 8.8$, 6.8 Hz), 8.60 (br, 1 H, N–H).

5-(2-Chloroacetyl-amino)-1-(2-chlorophenyl)-3-tetrabutanyl pyrazole (15). ^1H NMR (CDCl_3 , 200 MHz) δ 1.35 (s, 9 H, CH_3), 4.08 (s, 2 H, CH_2), 6.56 (s, 1 H), 7.38–7.56 (m, 4H, ArH), 8.20 (br, 1 H, N–H); ^{13}C NMR (CDCl_3 , 50 MHz) δ 30.27 (3 \times CH), 32.53, 42.49, 94.85, 128.24, 130.26, 130.58, 130.84, 131.61, 135.07, 135.55, 162.53, 163.29.

5-(2-Chloroacetyl-amino)-1-(4-chlorophenyl)-3-tetrabutanyl pyrazole (16). ^1H NMR (CDCl_3 , 200 MHz) δ 1.29 (s, 9 H, CH_3), 4.11 (s, 2 H, CH_2), 6.56 (s, 1 H), 7.39–7.46 (m, 4H, ArH), 8.49 (br, 1 H, N–H).

5-(2-Bromoacetyl-amino)-1-(3-chlorophenyl)-3-phenylpyrazole (33). Yellow solid; mp 106–107 $^\circ\text{C}$; ^1H NMR (CDCl_3 , 400 MHz) δ 4.01 (s, 2 H, CH_2), 7.05 (s, 1 H, ArH), 7.31–7.47 (m, 6 H, ArH), 7.61 (s, 1 H, ArH), 7.85 (d, $J = 7.6$ Hz, 2 H, ArH), 8.48 (s, 1 H, N–H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 42.63, 96.23, 121.99, 124.87, 125.76 (2 \times CH), 127.99, 128.66 (3 \times CH), 130.84, 132.40, 135.42, 135.81, 138.61, 152.43, 162.50; IR (KBr) 3046, 2955, 2924, 2853, 1721 (s, C=O), 1201, 764; EIMS m/z : 393

($M^+ + 4$, 25), 391 ($M^+ + 2$, 100), 389 (M^+ , 76), 296 (11), 271 (30), 269 (93), 233 (35), 102 (69), 77 (16); HRMS Calcd for $C_{17}H_{13}BrClON_3$: 388.9931, Found: 388.9932.

1-(3-Chlorophenyl)-5-(2-iodoacetyl-amino)-3-phenylpyrazole (34). Yellow solid; mp 103–104 °C; 1H NMR ($CDCl_3$, 200 MHz) δ 4.20 (s, 2 H, CH_2), 7.08 (s, 1 H, ArH), 7.22 (m, 2 H, ArH), 7.42 (m, 4 H, ArH), 7.61 (s, 1 H, ArH), 7.85 (m, 2 H, ArH), 8.62 (s, 1 H, N–H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 32.88, 90.21, 126.21, 127.26, 129.94 (2 \times CH), 128.45, 132.54 (3 \times CH), 134.52, 134.77, 135.69, 139.72, 1345.34, 152.43, 165.23; IR (KBr) 3229, 2920, 1674 (s, C=O), 1593, 1558, 1366, 1076, 763, 1201, 764; EIMS m/z : 439 ($M^+ + 2$, 13), 437 (M^+ , 52), 345 (32), 269 (100), 233 (39), 102 (90), 91 (12), 77 (27); HRMS Calcd for $C_{17}H_{13}ClIION_3$: 436.9792, Found: 436.9793.

Standard procedure for synthesis of 1,3-diphenyl-6-[(formyloxy)methyl]-1H-pyrazolo-[3,4-*d*]pyrimidine 17 and (1,3-diphenyl-1H-pyrazolo[3,4-*d*]pyrimidin-6-yl)methanol 44. The reliable procedure involved the treatment of 5-(2-chloroacetyl-amino)pyrazoles **1** (203 mg, 0.58 mmol, 1.0 equiv), with PBr_3 (1.77 mmol, \sim 0.2 mL, \sim 3.0 equiv) in formamide solution (2 mL) at 50–60 °C within 5 h. When the reaction was completed, the reaction mixture was added to saturate sodium bicarbonate (15 mL) and extracted with dichloromethane (15 mL \times 2). The combined organic layer was washed sodium bicarbonate (15 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue solution was purified by column chromatography on silica gel to give the corresponding 6-(formylmethyl)pyrazolo[3,4-*d*]pyrimidines **17** (168 mg, 0.51 mmol) in 88 % yield and by-product (1,3-diphenyl-1H-pyrazolo[3,4-*d*]pyrimidin-6-yl)methanol **44** (17.1 mg, 0.049 mmol) in 9% yield.

1,3-Diphenyl-6-[(formyloxy)methyl]-1H-pyrazolo[3,4-*d*]pyrimidine (17). Yellow solid; mp 126–127 °C; 1H NMR ($CDCl_3$, 200 MHz) δ 5.55 (s, 2 H, CH_2), 7.33–7.37 (m, 1 H, ArH), 7.46–7.58 (m, 5 H, ArH), 8.01 (dd, J = 1.6, 7.9 Hz, 2 H, ArH), 8.28

(dd, $J = 1.6, 7.9$ Hz, 2 H, ArH), 8.33 (s, 1 H, CHO), 9.43 (s, 1 H, Pyrimidine-H); ^{13}C NMR (CDCl_3 , 50 MHz) δ 65.60, 113.14, 121.16 ($2 \times \text{CH}$), 126.73, 127.26 ($2 \times \text{CH}$), 129.14, 129.63 ($4 \times \text{CH}$), 131.29, 138.39, 144.96, 152.97, 153.59, 160.50, 161.48; IR (KBr) 2955, 1721(s, C=O), 1585, 1497, 1416, 1200, 753; EIMS m/z : 330 (M^+ , 100), 301 (38), 286 (79), 273 (15), 271 (12), 180 (7), 142 (10), 91 (14), 77 (51); HRMS Calcd for $\text{C}_{19}\text{H}_{14}\text{O}_2\text{N}_4$: 330.1117, Found: 330.1121.

(1,3-Diphenyl-1H-pyrazolo[3,4-*d*]pyrimidin-6-yl)methanol (44). Yellow solid; mp 101–102 °C; ^1H NMR (CDCl_3 , 400 MHz) δ 4.99 (s, 2 H, CH_2), 7.34–7.38 (m, 1 H, ArH), 7.48–7.57 (m, 5 H, ArH), 8.04 (d, $J = 7.2$ Hz, 2 H, ArH), 8.26 (d, $J = 7.2$ Hz, 2 H, ArH), 9.44 (s, 1 H, Pyrimidine-H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 64.85, 113.21, 121.49 ($2 \times \text{CH}$), 126.92, 127.36 ($2 \times \text{CH}$), 129.22 ($4 \times \text{CH}$), 129.70, 131.40, 138.39, 145.25, 152.82, 153.55, 166.22; IR (KBr) 3395 (OH, Br), 2916, 1651, 1543, 748; EIMS m/z : 302 (M^+ , 100), 301 (53), 273 (25), 273 (15), 271 (20), 91 (16), 77 (49); HRMS Calcd for $\text{C}_{18}\text{H}_{14}\text{ON}_4$: 302.1168, Found: 302.1161.

Standard Procedure for Synthesis of 6-(Formyloxymethyl)pyrazolo[3,4-*d*]pyrimidines 18–32. The reliable procedure involved the treatment of 5-(2-chloroacetyl amino)pyrazoles (**2–16**, 1.0 equiv), with PBr_3 (~3.0 equiv) in formamide solution (2 mL) at 50–60 °C within 5 h. When the reaction was completed, the reaction mixture was added to saturate sodium bicarbonate (15 mL) and extracted with dichloromethane (15 mL \times 2). The combined organic layer was washed sodium bicarbonate (15 mL), dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue solution was purified by column chromatography on silica gel to give the corresponding 6-(formylmethyl)pyrazolo[3,4-*d*]pyrimidines **18–32** in 73–92 % yields.

6-[(Formyloxy)methyl]-1-(2-methylphenyl)-3-phenyl-1H-pyrazolo[3,4-*d*]pyrimidine (18). White solid; mp 133–134 °C; ^1H NMR (CDCl_3 , 400 MHz) δ 2.22 (s, 3 H,

CH₃), 5.47 (s, 2 H, CH₂), 7.37–7.57 (m, 7 H, ArH), 8.03 (d, J = 7.6 Hz, 2 H, ArH), 8.23 (s, 1 H, CHO), 9.53 (s, 1 H, Pyrimidine-H); ¹³C NMR (CDCl₃, 100 MHz) δ 18.44, 65.69, 111.90, 126.69, 127.29 (2 \times CH), 127.61, 129.24 (2 \times CH), 129.41, 129.58, 131.43, 131.63, 135.40, 136.11, 145.16, 153.04, 154.55, 160.47, 161.72; IR (KBr) 2920, 2851, 1721 (s, C=O), 1589, 1458, 1265, 1184, 752; EIMS m/z : 344 (M^+ , 13), 299 (32), 298 (100), 256 (17), 202 (11), 189 (17), 155 (14), 133 (31), 91 (41), 88 (28), 77 (17); HRMS Calcd for C₂₀H₁₆O₂N₄: 344.1273, Found: 344.1274.

6-[(Formyloxy)methyl]-1-(3-methylphenyl)-3-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (19). White solid; mp 127–128 °C; ¹H NMR (CDCl₃, 200 MHz) δ 2.22 (s, 3 H, CH₃), 5.47 (s, 2 H, CH₂), 7.34–7.59 (m, 5 H, ArH), 7.53 (d, J = 7.5 Hz, 2 H, ArH), 8.04 (dd, J = 1.4, 7.8 Hz, 2 H, ArH), 8.23 (s, 1 H, CHO), 9.49 (s, 1 H, Pyrimidine-H); ¹³C NMR (CDCl₃, 50 MHz) δ 18.43, 65.66, 111.88, 126.68, 127.27 (2 \times CH), 127.60, 129.23 (2 \times CH), 129.39, 129.57, 131.42, 131.60, 135.38, 136.08, 145.14, 153.03, 154.53, 160.46, 161.70; IR (KBr) 3059 (m), 2916, 2847, 1724 (s, C=O), 1589, 1504, 1458, 1184, 1134, 760; EIMS m/z : 344 (M^+ , 15), 298 (100), 256 (19), 163 (20), 146 (47), 134 (35), 120 (55), 115 (58), 99 (84), 77 (30); HRMS Calcd for C₂₀H₁₆O₂N₄: 344.1273, Found: 344.1268.

6-[(Formyloxy)methyl]-1-(4-methylphenyl)-3-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (20). White solid; mp 107–108 °C; ¹H NMR (CDCl₃, 400 MHz) δ 2.42 (s, 3 H, CH₃), 5.55 (s, 2 H, CH₂), 7.34 (d, J = 8.0 Hz, 2 H, ArH), 7.56 (s, 1 H, ArH), 8.04 (d, J = 8.0 Hz, 2 H, ArH), 8.14 (d, J = 8.0 Hz, 2 H, ArH), 8.23 (s, 1 H, CHO), 9.46 (s, 1 H, Pyrimidine-H); ¹³C NMR (CDCl₃, 50 MHz) δ 21.10, 65.68, 113.06, 121.35 (2 \times CH), 127.34 (2 \times CH), 129.22 (2 \times CH), 129.71, 129.73 (2 \times CH), 131.46, 135.97, 136.79, 144.87, 152.99, 153.45, 160.53, 161.42; IR (KBr) 2922, 1726 (s, C=O), 1514, 1454, 1184, 1172, 957, 816, 766; EIMS m/z : 344 (M^+ , 100), 301 (37), 208 (11), 91 (19), 77 (10); HRMS Calcd for C₂₀H₁₆O₂N₄: 344.1273, Found: 344.1276.

1-(2-Chlorophenyl)-6-[(formyloxy)methyl]-3-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (21). Yellow solid; mp 81–82 °C; ¹H NMR (CDCl₃, 200MHz) δ 5.47 (s, 2 H, CH₂), 7.45–7.64 (m, 7 H, ArH), 8.02 (dd, *J* = 1.4, 7.7 Hz, 2 H, ArH), 8.24 (s, 1 H, CHO), 9.48 (s, 1 H, Pyrimidine–H); ¹³C NMR (CDCl₃, 50 MHz) δ 65.61, 112.02, 127.37 (2 × CH), 127.59, 129.24 (2 × CH), 129.61, 129.72, 130.69, 130.78, 131.35, 132.09, 134.74, 145.79, 153.03, 154.99, 160.45, 161.92; IR (KBr) 3059, 2922, 2851, 1722 (s, C=O), 1591, 1503, 1410, 1184, 1132, 980, 756; EIMS *m/z*: 366 (*M*⁺ + 2, 35), 364 (*M*⁺, 100), 335 (34), 329 (13), 320 (83), 307 (15), 271 (13), 133 (29), 91 (24), 77 (27); HRMS Calcd for C₁₉H₁₃ClO₂N₄: 364.0721, Found: 364.0725.

1-(3-Chlorophenyl)-6-[(formyloxy)methyl]-3-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (22). Yellow solid; mp 128–129 °C; ¹H NMR (CDCl₃, 400 MHz) δ 5.58 (s, 2 H, CH₂), 7.32 (d, *J* = 7.2 Hz, 1 H, ArH), 7.44–7.59 (m, 3 H, ArH), 7.57 (s, 1 H, ArH), 8.04 (d, *J* = 8.0, 2 H, ArH), 8.31 (d, *J* = 8.0 Hz, 1 H, ArH), 8.34 (s, 1 H, ArH), 8.44 (s, 1 H, Pyrimidine–H), 9.46 (s, 1 H, CHO); ¹³C NMR (CDCl₃, 100 MHz) δ 65.46, 113.42, 118.81, 121.05, 126.58, 127.37 (2 × CH), 129.24 (2 × CH), 129.88, 130.15, 131.09, 134.90, 139.52, 145.51, 153.12, 153.97, 160.38, 161.88; IR (KBr) 3059, 2922, 2851, 1722 (s, C=O), 1591, 1503, 1410, 1184, 1132, 980, 756; EIMS *m/z*: 366 (*M*⁺ + 2, 34), 364 (*M*⁺, 100), 355 (16), 335 (53), 320 (77), 307 (22), 281 (18), 221 (18), 111 (12), 77 (18); HRMS Calcd for C₁₉H₁₃ClO₂N₄: 364.0721, Found: 364.0725.

1-(4-Chlorophenyl)-6-[(formyloxy)methyl]-3-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (23). Yellow solid; mp 127–128 °C; ¹H NMR (CDCl₃, 200MHz) δ 5.56 (s, 2 H, CH₂), 7.48–7.57 (m, 5 H, ArH), 8.03 (dd, *J* = 1.5, 8.4, 2 H, ArH), 8.31 (d, *J* = 8.4, 2 H, ArH), 8.33 (s, 1 H, CHO), 9.46 (s, 1 H, Pyrimidine–H); ¹³C NMR (CDCl₃, 100 MHz) δ 65.61, 113.36, 122.26, 125.75, 127.40, 129.32, 129.90 (2 × CH), 131.18, 132.21, 137.08, 145.41, 153.19, 153.78, 160.50, 161.81; IR (KBr) 3059, 2922, 2851, 1722 (s, C=O), 1591, 1503, 1410, 1184, 1132, 980, 756; EIMS *m/z*: 366 (*M*⁺ + 2, 2), 364 (*M*⁺,

7), 284 (21), 217 (11), 135 (100), 91 (16), 77 (9); HRMS Calcd for $C_{19}H_{13}ClO_2N_4$: 364.0721, Found: 364.0718.

6-[(Formyloxy)methyl]-1-(3-methoxyphenyl)-3-phenyl-1*H*-pyrazolo-[3,4-*d*]pyrimidine (24). Yellow solid; mp 90–91 °C; 1H NMR ($CDCl_3$, 400 MHz) δ 3.87 (s, 3 H, CH_3), 5.54 (s, 2 H, CH_2), 7.06 (d, J = 8.0 Hz, 2 H, ArH), 7.48–7.57 (m, 2 H, ArH), 7.55 (s, 1 H, ArH), 8.03 (d, J = 8.0 Hz, 2 H, ArH), 8.14 (dd, J = 2.0, 8.0 Hz, 2 H, ArH), 8.32 (s, 1 H, CHO), 9.45 (s, 1 H, Pyrimidine-H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 55.58, 65.73, 112.91, 114.38 (2 \times CH), 123.01 (2 \times CH), 127.32 (2 \times CH), 129.22 (2 \times CH), 129.57, 131.55, 131.72, 144.71, 153.01, 153.29, 158.45, 160.51, 161.46; IR (KBr) 2924, 1728 (s, C=O), 1585, 1512, 1458, 1250, 1173, 1030, 829, 764; EIMS m/z : 360 (M^+ , 100), 331 (13), 316 (12), 77 (10); HRMS Calcd for $C_{20}H_{16}O_3N_4$: 360.1222, Found: 360.1224.

6-[(Formyloxy)methyl]-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (25). Brown solid; mp 85–86 °C; 1H NMR ($CDCl_3$, 400 MHz) δ 2.69 (s, 3 H, CH_3), 5.52 (s, 2 H, CH_2), 7.29–7.33 (m, 1 H, ArH), 7.48–7.52 (m, 1 H, ArH), 7.50 (s, 1 H, ArH), 8.19 (d, J = 8.0 Hz, 2 H, ArH), 8.30 (s, 1 H, CHO), 9.12 (s, 1 H, Pyrimidine-H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.58, 65.74, 114.77, 120.87 (2 \times CH), 126.41, 129.11 (2 \times CH), 138.44, 143.41, 151.95, 153.12, 160.45, 161.58; IR (KBr) 2924, 2854, 1732 (s, C=O), 1589, 1508, 1458, 1161, 752; EIMS m/z : 268 (M^+ , 89), 239 (46), 224 (100), 211 (20), 142 (12), 91 (13), 77 (53); HRMS Calcd for $C_{14}H_{12}O_2N_4$: 268.0960, Found: 268.0963.

3-tetra-Butanyl-6-[(formyloxy)methyl]-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (26). Brown solid; mp 91–92 °C; 1H NMR ($CDCl_3$, 200 MHz) δ 1.56 (s, 9 H, CH_3), 5.51 (s, 2 H, CH_2), 7.25–7.33 (m, 1 H, ArH), 7.46–7.53 (m, 2 H, ArH), 7.50 (s, 1 H, ArH), 8.22 (d, J = 8.0 Hz, 2 H, ArH), 8.30 (s, 1 H, CHO), 9.29 (s, 1 H, Pyrimidine-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 30.02 (3 \times CH), 65.74, 113.02, 120.99 (2 \times CH),

126.28, 129.08 (2 × CH), 138.62, 153.07, 153.53, 154.98, 160.54, 160.90; IR (KBr) 2963, 2924, 1732 (s, C=O), 1582, 1508, 1420, 1366, 1157, 756; EIMS m/z: 310 (M⁺, 21), 295 (30), 265 (12), 159 (15), 113 (12), 98 (13), 91 (100), 77 (20); HRMS Calcd for C₁₇H₁₈O₂N₄: 310.1434, Found: 310.1430.

6-[(Formyloxy)methyl]-3-(4-methylphenyl)-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (27). Yield: 87%; yellow liquid; ¹H NMR (CDCl₃, 200 MHz) δ 2.44 (s, 3 H, CH₃), 5.55 (s, 2 H, CH₂), 7.36 (d, *J* = 8.1 Hz, 2 H, ArH), 7.53 (dd, *J* = 8.0, 7.4 Hz, 2 H, ArH), 7.94 (d, *J* = 8.1 Hz, 2 H, ArH), 8.30 (d, *J* = 8.1 Hz, 2 H, ArH), 8.32 (s, 1 H, CHO), 9.44 (s, 1 H, Pyrimidine-H); ¹³C NMR (CDCl₃, 50 MHz) δ 29.69, 65.70, 113.28, 121.27 (2 × CH), 126.72, 127.24 (2 × CH), 128.58, 129.16 (2 × CH), 129.93 (2 × CH), 138.53, 139.89, 145.19, 153.05, 153.68, 160.51, 160.51, 161.51; IR (KBr) 2920, 2851, 1717 (s, C=O), 1589, 1501, 1411, 1200, 1134, 980, 756 cm⁻¹; EIMS m/z: 344 (M⁺, 100), 315 (36), 300 (51), 287 (11), 91 (13), 77 (17); HRMS Calcd for C₂₀H₁₆O₂N₄: 344.1273, Found: 344.1275.

6-[(Formyloxy)methyl]-3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazolo-[3,4-*d*]pyrimidine (28). Yellow solid; mp 165–167 °C; ¹H NMR (CDCl₃, 200MHz) δ 3.88 (s, 3 H, CH₃), 5.55 (s, 2 H, CH₂), 7.07 (d, *J* = 8.8 Hz, 2 H, ArH), 7.33–7.37(m, 1 H, ArH), 7.49–7.57 (m, 2 H, ArH), 8.29 (dd, *J* = 1.0, 8.8 Hz, 2 H, ArH), 8.32 (s, 1 H, CHO), 9.41 (s, 1 H, Pyrimidine-H); ¹³C NMR (CDCl₃, 100 MHz) δ 55.42, 65.69, 113.19, 114.66 (2 × CH), 121.19 (2 × CH), 123.96, 126.24, 128.66 (2 × CH), 129.14 (2 × CH), 138.52, 144.92, 152.97, 153.61, 160.51, 160.83, 161.46; IR (KBr) 2922, 1715 (s, C=O), 1585, 1504, 1412, 1199, 1030, 982, 787 cm⁻¹; EIMS m/z: 360 (M⁺, 100), 331 (24), 316 (29), 77 (15); HRMS Calcd for C₂₀H₁₆O₃N₄: 360.1222, Found: 360.1217.

6-[(Formyloxy)methyl]-1-(3-methlyphenyl)-3-(4-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (29). Yellow solid; mp 138–139 °C; ¹H NMR (CDCl₃, 400MHz) δ 2.47 (s, 3 H, CH₃), 3.89 (s, 3 H, OCH₃), 5.55 (s, 2 H, CH₂), 7.08 (d, *J* = 8.4 Hz, 2 H,

ArH), 7.17 (m, 1 H, ArH), 7.41 (m, 1 H, ArH), 7.99 (d, $J = 8.4$ Hz, 2 H, ArH), 8.08 (m, 2 H, ArH), 8.32 (s, 1 H, CHO), 9.42 (s, 1 H, Pyrimidine-H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 21.62, 55.45, 65.73, 113.19, 114.72 ($2 \times \text{CH}$), 118.50, 121.94, 124.10, 127.54, 128.72 ($2 \times \text{CH}$), 128.97, 138.46, 139.19, 144.89, 152.97, 153.65, 160.49, 160.88, 161.46; IR (KBr) 2953, 1717 (s, C=O), 1585, 1503, 1408, 1175, 1134, 837, 787; EIMS m/z : 374 (M^+ , 100), 345 (19), 330 (24), 91 (8); HRMS Calcd for $\text{C}_{21}\text{H}_{18}\text{O}_3\text{N}_4$: 374.1379, Found: 374.1383.

6-[(Formyloxy)methyl]-1-(4-methoxyphenyl)-3-(4-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (30). Yellow solid; mp 152–154 °C; ^1H NMR (CDCl_3 , 200 MHz) δ 2.42 (s, 3 H, CH_3), 3.89 (s, 3 H, OCH_3), 5.54 (s, 2 H, CH_2), 7.07 (d, $J = 8.0$ Hz, 2 H, ArH), 7.33 (d, $J = 8.0$ Hz, 2 H, ArH), 7.98 (d, $J = 8.0$ Hz, 2 H, ArH), 8.13 (d, $J = 8.0$ Hz, 2 H, ArH), 8.31 (s, 1 H, CHO), 9.41 (s, 1 H, Pyrimidine-H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 21.62, 55.45, 65.73, 113.19, 114.72 ($2 \times \text{CH}$), 118.50, 121.94, 124.10, 127.54, 128.72 ($2 \times \text{CH}$), 128.97, 138.46, 139.19, 144.89, 152.97, 153.65, 160.49, 160.88, 161.46; IR (KBr) 2922, 1732 (s, C=O), 1585, 1504, 1412, 1199, 1136, 839, 754; EIMS m/z : 374 (M^+ , 100), 345 (19), 330 (25), 226 (22), 210 (13), 180 (15), 167 (36), 135 (18), 125 (20), 111 (40), 97 (51), 91 (17); HRMS Calcd for $\text{C}_{21}\text{H}_{18}\text{O}_3\text{N}_4$: 374.1379, Found: 374.1381.

3-tetra-Butyl-1-(2-chlorophenyl)-6-[(formyloxy)methyl]-1*H*-pyrazolo[3,4-*d*]pyrimidine (31). Yellow solid; mp 138–139 °C; ^1H NMR (CDCl_3 , 200 MHz) δ 1.56 (s, 9 H, CH_3), 5.52 (s, 2 H, CH_2), 7.25–7.33 (m, 1 H, ArH), 7.46–7.53 (m, 2 H, ArH), 8.22 (d, $J = 8.0$ Hz, 2 H, ArH), 8.23 (s, 1 H, CHO), 9.46 (s, 1 H, Pyrimidine-H); ^{13}C NMR (CDCl_3 , 50 MHz) δ 30.01 ($3 \times \text{CH}$), 67.54, 112.03, 121.97 ($2 \times \text{CH}$), 128.72, 129.08 ($2 \times \text{CH}$), 139.63, 153.07, 153.53, 154.98, 156.35, 161.93; IR (KBr) 2916, 1721 (s, C=O), 1578, 1558, 1458, 1261, 1165, 760, 694; EIMS m/z : 346 ($\text{M}^+ + 2$, 30), 344 (M^+ , 100), 345 (19), 330 (25), 226 (22), 210 (13), 180 (15), 167 (36), 135 (18), 125 (20),

111 (40), 97 (51), 91 (17); HRMS Calcd for $C_{17}H_{17}ClO_4N_2$: 344.1040, Found: 344.1044.

3-Tetrabutanyl-1-(4-chlorophenyl)-6-[(formyloxy)methyl]-1*H*-pyrazolo[3,4-*d*]pyrimidine (32). Yellow solid; mp 147–148 °C; 1H NMR ($CDCl_3$, 200 MHz) δ 1.55 (s, 9 H, CH_3), 5.51 (s, 2 H, CH_2), 7.49 (m, 2 H, ArH), 8.25 (m, 2H, ArH), 8.30 (s, 1 H, CHO), 9.29 (s, 1 H, Pyrimidine-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 30.27 (3 \times CH), 65.70, 128.24 (2 \times CH), 130.26, 130.58, 130.84 (2 \times CH), 131.61, 135.07, 135.55, 145.19, 153.05, 162.53, 163.29; IR (KBr) 2922, 1721 (s, C=O), 1585, 1252, 1175, 1026, 781; EIMS m/z : 346 ($M^+ + 2$, 37), 344 (M^+ , 94), 345 (19), 330 (25), 226 (22), 210 (13), 180 (15), 167 (36), 135 (18), 125 (20), 111 (40), 97 (51), 91 (17); HRMS Calcd for $C_{17}H_{17}ClO_4N_2$: 344.1040, Found: 344.1043. (100), 55 (44); HRMS calcd. for $C_{17}H_{22}N_4O_3$, 330.1692; found 330.1696.

1-(3-Chlorophenyl)-3phenyl-5-(2-hydroxyacetylaminopyrazole (35)²⁹ A solution of 5-(2-chloroacetylaminopyrazole (6, 1.0 equiv) and cesium formate (HCO_2Cs , 3.0 equiv) in dry MeOH (10 mL) was heated at reflux for >2.0 h. When the reaction was completed, the solution was filtered to remove the excess amount of HCO_2Cs and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel or re-crystallization to give the corresponding 5-(2-hydroxyacetylaminopyrazole **35** in 84% yield. yellow solid; mp 98–99 °C; 1H NMR ($CDCl_3$, 200 MHz) δ 4.15 (s, 2 H, CH_2), 7.06 (s, 1 H, ArH), 7.32–7.44 (m, 7 H, ArH), 7.56 (m, 1 H, ArH), 7.83 (dd, $J = 4.5, 8.2$ Hz, 2 H, ArH), 8.79 (s, 1 H, NH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 62.12, 95.94, 122.08, 124.87, 125.78 (2 \times CH), 128.46, 128.54, 128.66 (2 \times CH), 130.74, 132.44, 135.61, 136.03, 138.75, 152.51, 168.37; IR (KBr) 3429, 2359, 1591, 1184, 966, 756; EIMS m/z : 329 ($M^+ + 2$, 33), 327 (M^+ , 73), 329 (33), 270 (32), 235 (20), 220 (39), 207 (25), 195 (58), 180 (97), 162 (24), 135 (94), 121 (100), 102 (36), 91 (56), 81 (77); HRMS Calcd for $C_{17}H_{14}ClO_2N_3$: 327.0775,

Found: 327.0776.

6-(Chloromethyl)pyrazolo[3,4-*d*]pyrimidine (40). The treatment of 1,3-diphenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)methanol (**44**, 1.0 equiv), with SOCl₂ (~3.0 equiv) in formamide solution (2 mL) at 50–60 °C within 3 h. When the reaction was completed, the reaction mixture was added to saturate sodium bicarbonate (15 mL) and extracted with dichloromethane (15 mL × 2). The combined organic layer was washed sodium bicarbonate (15 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue solution was purified by column chromatography on silica gel to give the corresponding 6-(chloromethyl)pyrazolo[3,4-*d*]pyrimidine **40** in 80 % yields: yellow solid; mp 133–134 °C; ¹H NMR (CDCl₃, 200 MHz) δ 4.89 (s, 2 H, CH₂), 7.32–7.40 (m, 1 H, ArH), 7.49–7.61 (m, 5 H, ArH), 8.05 (dd, *J* = 7.2, Hz, 2 H, ArH), 8.26 (dd, *J* = 7.2 Hz, 2 H, ArH), 9.49 (s, 1 H, Pyrimidine-H); ¹³C NMR (CDCl₃, 50 MHz) δ 47.33, 112.95, 121.33 (2 × CH), 126.87, 127.37 (2 × CH), 129.24 (3 × CH), 129.73, 131.38, 138.50, 145.07, 153.37, 153.88, 162.99; IR (KBr) 2920, 1581, 1501, 1226, 1134, 976, 756, 691; EIMS *m/z*: 320 (M⁺, 100), 319 (38), 294 (35), 251 (24), 221 (20), 207 (48), 140 (15), 91 (39), 77 (56); HRMS Calcd for C₁₈H₁₃ClN₄: 320.0829; Found: 320.0828.

Acknowledgments

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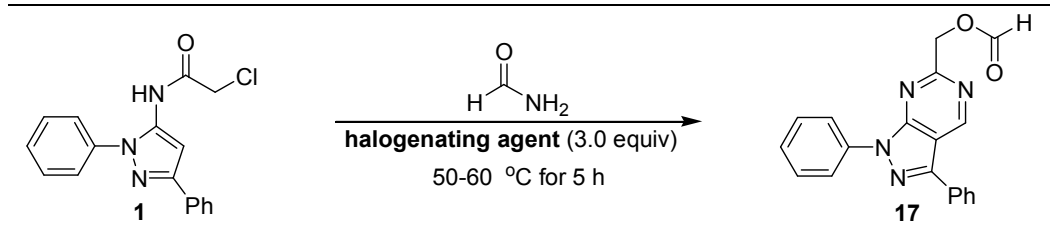
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Table 1 Optimization of the One-pot Multiple Tandem Reaction by Various of Halogenating Agents.



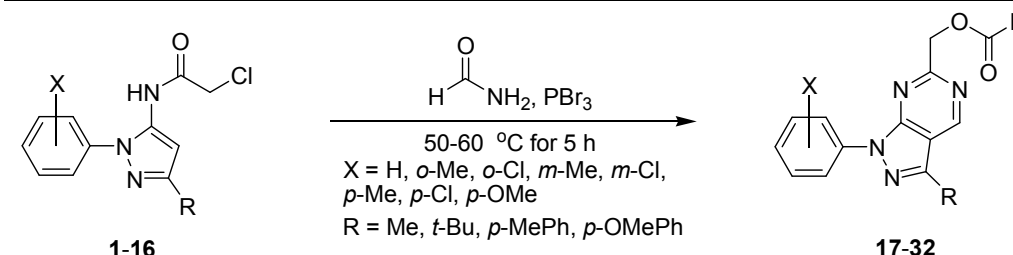
entry	halogenating agents (3.0 equiv)	yields of 17 (%) ^{a, b}
1	—	— ^c
2	PBr ₃	88
3	POCl ₃	73
4	SOCl ₂	41
5	TsCl	31
6	PhCOCl	26
7	CICOCOC	33

^abased on the weight of starting material 5-(2-chloroacetyl)amino)pyrazole **1**.

^bAll of results were the isolated yields.

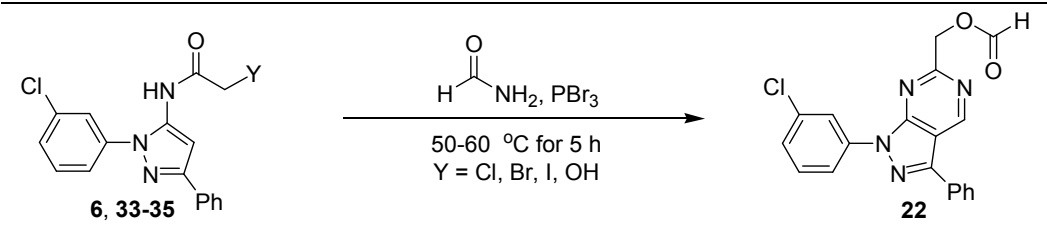
^cnot detectable

Table 2 Synthesis of 1-Aryl-6[(formyloxy)methyl]-1*H*-pyrazolo[3,4-*d*]pyrimidines **17–32** via the Tandem One-pot Multiple reaction.

				
S.M.	X	R	No.	Yields (%) ^a
1	H	Ph	17	88
2	<i>o</i> -Me	Ph	18	77
3	<i>m</i> -Me	Ph	19	85
4	<i>p</i> -Me	Ph	20	92
5	<i>o</i> -Cl	Ph	21	83
6	<i>m</i> -Cl	Ph	22	81
7	<i>p</i> -Cl	Ph	23	84
8	<i>p</i> -OMe	Ph	24	73
9	H	Me	25	78
10	H	<i>t</i> -Bu	26	81
11	H	<i>p</i> -Me-Ph	27	74
12	H	<i>p</i> -OMe-Ph	28	75
13	<i>m</i> -Me	<i>p</i> -OMe-Ph	29	74
14	<i>p</i> -Me	<i>p</i> -OMe-Ph	30	84
15	<i>o</i> -Cl	<i>t</i> -Bu	31	72
16	<i>p</i> -Cl	<i>t</i> -Bu	32	77

^aAll of results were the isolated yields.

Table 3 Optimization of the One-pot Multiple Tandem Reaction by Various of Leaving Groups.



Entry	S.M.	Y	Products	Yields (%) ^a
1	6	Cl	22	81
2	33	Br	22	86
3	34	I	22	87
4	35	OH	22	73

^aAll of results were the isolated yields.

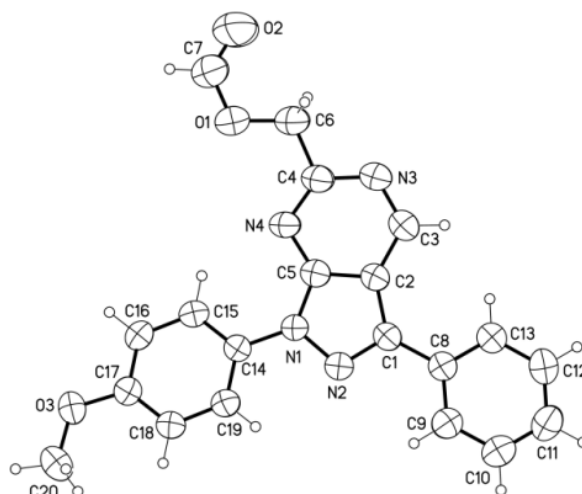
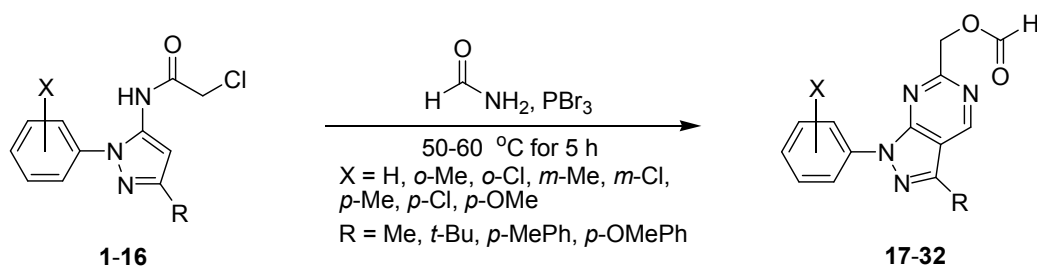
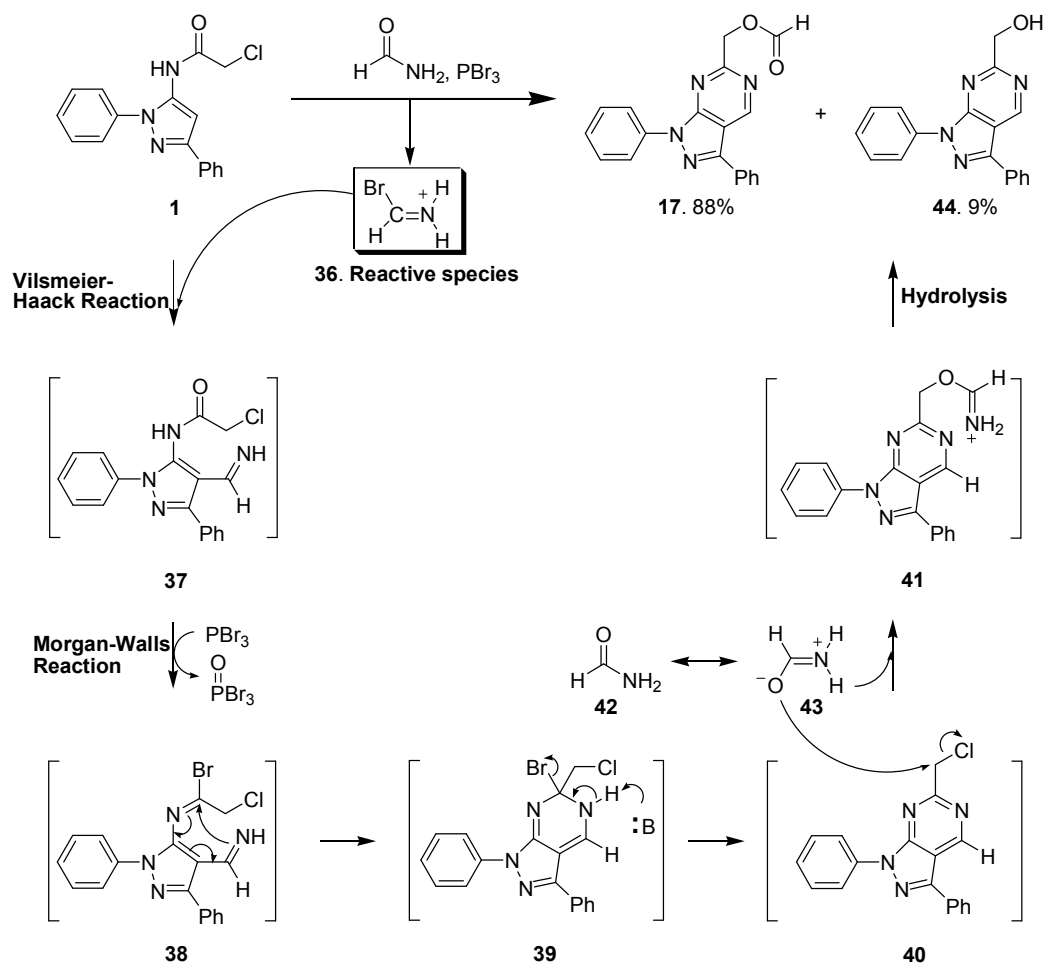


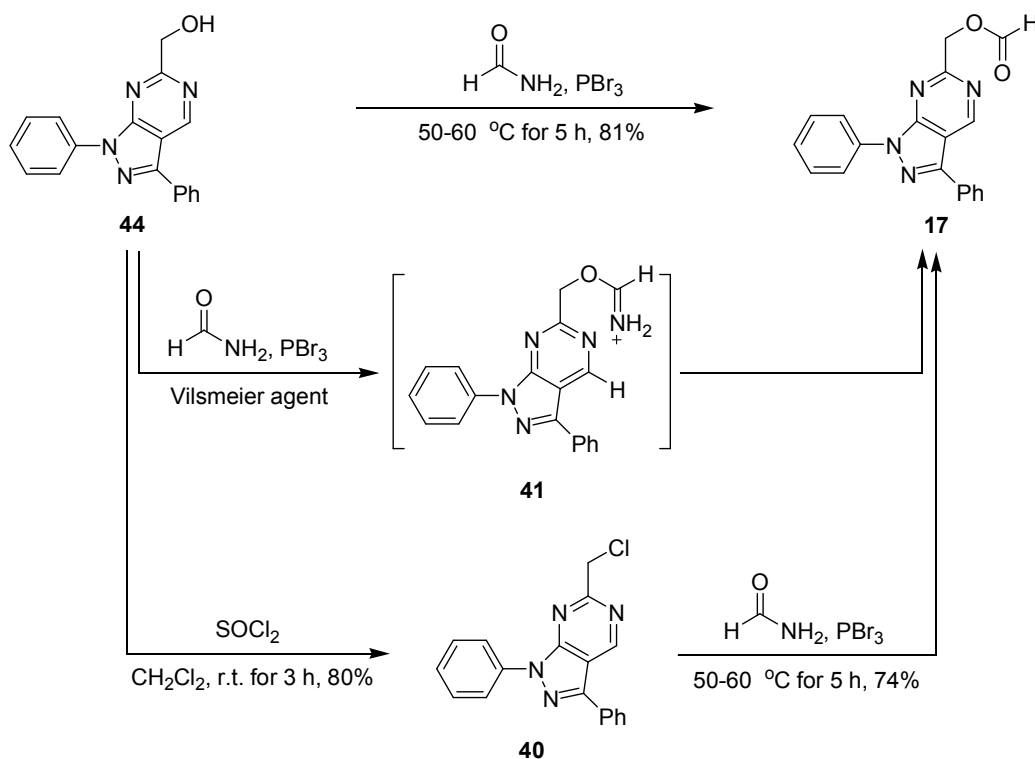
Figure 1 An ORTEP Diagram of 1-(*p*-Methoxyphenyl)-3-phenyl-6-[(formyl)methyl]-1*H*-pyrazolo[3,4-*d*]pyrimidine (**24**).



Scheme 1 The New One-pot Multiple Reaction for the Synthesis of 1-Aryl-6-[(formyloxy)methyl]-1*H*-pyrazolo[3,4-*d*]pyrimidines **17–32**.



Scheme 2 Proposed Mechanism for Synthesis of 1-Aryl-6-[(formyl)methyl]-1H-pyrazolo[3,4-d]pyrimidines **17-32** from 5-(2-chloroacetyl-amino)pyrazoles **1-16**.



Scheme 3. The Conversion Study of 1,3-Diphenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-ylmethanol (**44**) and 6-(Chloromethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine Intermediate (**40**) to 6-[(Formyl)methyl]-1*H*-pyrazolo[3,4-*d*]pyrimidine (**17**).