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$K_2S_2O_8$-Promoted Consecutive Tandem Cyclization/Oxidative Halogenation: Access to 3-Halo-Pyrazolo[1,5-*a*]pyrimidines

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Cite This: *ACS Omega* 2023, 8, 23851−23859

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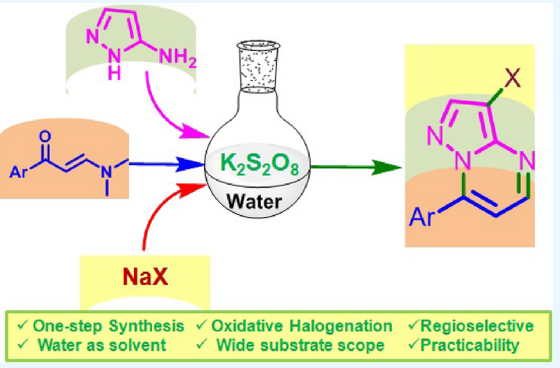
ABSTRACT: A one-pot methodology has been developed to synthesize 3-halo-pyrazolo[1,5-*a*]pyrimidine derivatives through the three-component reaction of amino pyrazoles, enaminones (or chalcone), and sodium halides. The use of easily accessible 1,3-biselectrophilic reagents like enaminones and chalcone offers a straightforward approach for the synthesis of 3-halo-pyrazolo[1,5-*a*]pyrimidines. The reaction proceeded through a cyclocondensation reaction between amino pyrazoles with enaminones/chalcone in the presence of $K_2S_2O_8$ followed by oxidative halogenations by NaX-$K_2S_2O_8$. Mild and environmentally benign reaction conditions, wide functional group tolerance, and scalability of the reaction are the attractive facet of this protocol. The combination of NaX-$K_2S_2O_8$ is also beneficial for the direct oxidative halogenations of pyrazolo[1,5-*a*]pyrimidines in water.



INTRODUCTION

Cascade cyclizations/C−H functionalizations have become an important strategy for synthesizing pharmaceutically active functionalized heterocycles.[1,2] Step- and time-efficiency and the use of easily available/accessible reagents make this approach more attractive and practicable. On the other hand, halogenated heterocycles are frequently found in natural products, pharmaceuticals, and dyes.[3] These are also very useful as synthetic intermediates for synthesizing functionalized heterocycles.[4] Recently, the efficiency of these derivatives as organocatalysts has been explored by chemists.[5] Consequently, much focus has been paid on synthesizing halogenated heterocycles as well as on the C−H halogenations of the heterocycles. Various halogenating agents are commercially available in the literature, such as X_2, NXS, trihaloisocyanuric acids, dihalo hydantoins, etc., for the late-stage electrophilic halogenations of heterocycles.[6] Among these, metal halides are bench-stable, safe, and inexpensive and have been employed in the oxidative halogenations of different heterocycles.[7] However, the literature has limited methodologies on the direct synthesis of halogenated heterocycles through cascade cyclization/oxidative halogenation.[8] Moreover, these developed strategies are mainly intramolecular cyclization followed by oxidative halogenation.

Pyrazolo[1,5-*a*]pyrimidines, an important class of fused heterocycles, are the core structure of various commercially available pharmaceuticals and agrochemicals like zaleplon (**I**, sedative-hypnotic), indiplon (**II**, sedative-hypnotic), lorediplon (**III**, useful to treat insomnia), ocinaplon (**IV**, anxiolytic drug), presatovir (**V**, anti-viral drug), reversan (**VI**, MRP1 inhibitor), dorsomorphin (**VII**, BMP inhibitor), anagliptin (**VIII**, anti-diabetic drugs), and pyrazophos (**IX**, fungicide and insecticide) (Figure 1).[9] These derivatives also exhibit various biological activities such as selective protein inhibitory, anticancer, psychopharmacological, etc.[10] Moreover, pyrazolo[1,5-*a*]-pyrimidines have various optoelectronic applications and are important in materials science.[11] Thus, the synthesis of functionalized pyrazolo[1,5-*a*]pyrimidine derivatives are always demanding.[12]

Halogenated pyrazolo[1,5-*a*]pyrimidines are important building blocks due to their usefulness in synthesizing various functionalized pyrazolo[1,5-*a*]pyrimidines through coupling reactions.[13] Moreover, some 3-halo derivatives exhibit anxiolytic properties (Scheme 1A).[14] Generally, the synthesis of halogenated pyrazolo[1,5-*a*]pyrimidines is carried out through the halogenations of pyrazolo[1,5-*a*]pyrimidines employing NXS as electrophilic halogenating agents and CCl_4 or THF as solvent (Scheme 1B).[15] Portilla et al. reported a one-pot synthesis of halogenated pyrazolo[1,5-*a*]pyrimidines through microwave-assisted in situ formation of pyrazolo[1,5-*a*]pyrimidines followed by electrophilic halogenations with NXS employing EDC as solvent (Scheme 1C).[15a] Although this methodology is beneficial for the synthesis of halogenated pyrazolo[1,5-*a*]pyrimidines, very high temperature and micro-

Received: April 4, 2023
Accepted: June 9, 2023
Published: June 22, 2023

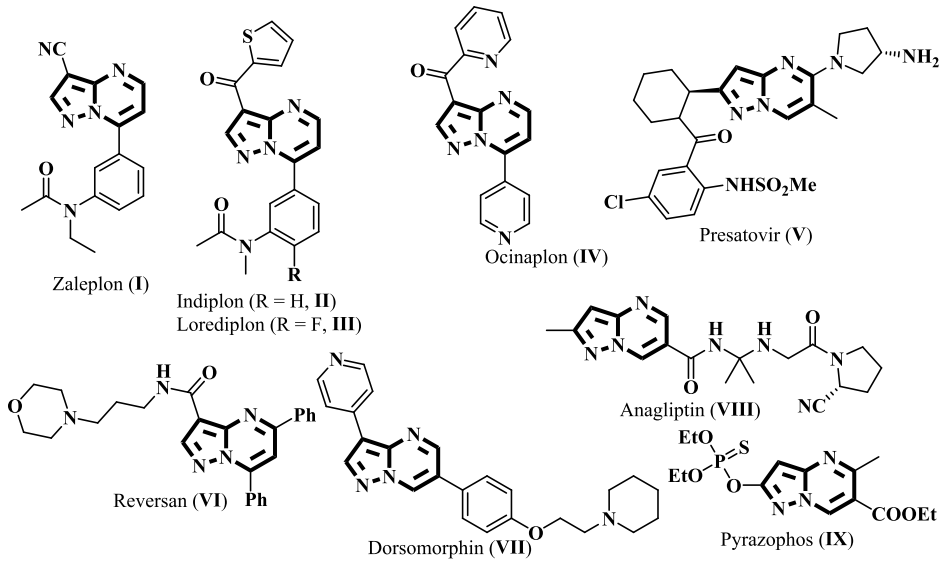
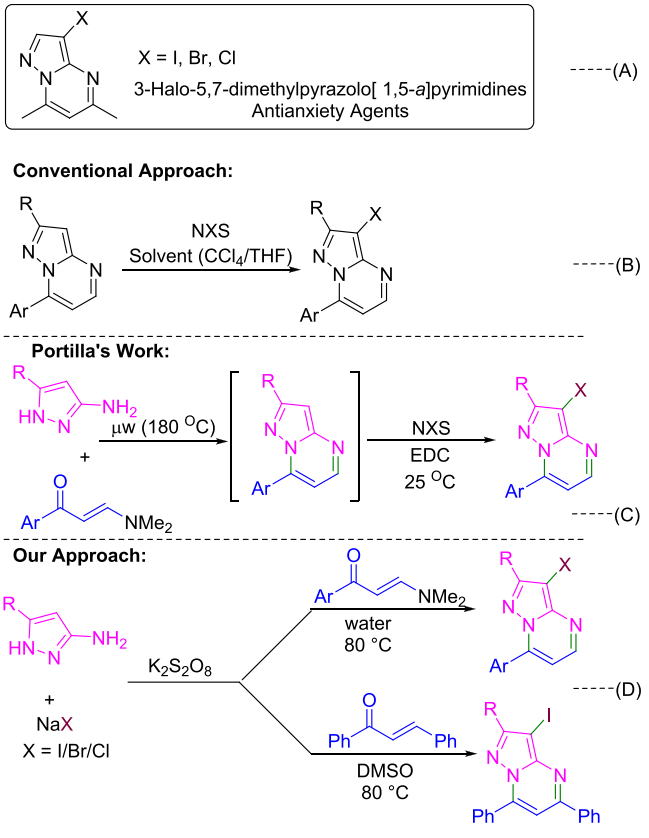


Figure 1. Pyrazolo[1,5-*a*]pyrimidine-containing pharmaceuticals and agrochemicals.

Scheme 1. Strategies Toward the Synthesis of Halogenated Pyrazolo[1,5-*a*]pyrimidines



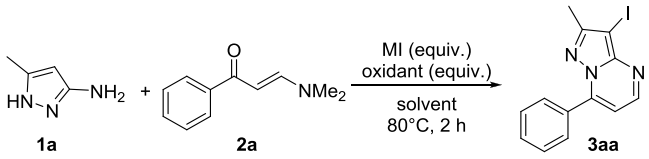
wave heating (180 °C) are required for this case. No such report is available in the literature on the oxidative halogenations of pyrazolo[1,5-*a*]pyrimidine derivatives. We have developed a simple, mild, and one-step protocol for the synthesis of halogenated pyrazolo[1,5-*a*]pyrimidines through a three-component reaction of amino pyrazoles, enaminones/chalcone, and sodium halides (NaI/NaBr/NaCl) (Scheme 1D). The oxidative halogenations of pyrazolo[1,5-*a*]-pyrimidines were also carried out employing sodium halides (NaI/NaBr/NaCl) as a halogenating agent and $K_2S_2O_8$ as an oxidant in water.

RESULTS AND DISCUSSION

We started our investigation by choosing 5-methyl-1*H*-pyrazol-3-amine (**1a**) and (*E*)-3-(dimethylamino)-1-phenylprop-2-en-1-one (**2a**) as the model substrates (Table 1). Commercially available persulfates are highly useful as stable oxidants[16] and have been employed in various oxidative transformations under thermal[17] or photochemical conditions.[18] These are also well-known for converting iodide salt to iodine radical/iodine. So, we employed 20 mol % NaI and 1 equiv $K_2S_2O_8$ in MeCN at 80 °C under ambient air. Interestingly, the formation of 3-iodo-2-methyl-7-phenylpyrazolo[1,5-*a*]pyrimidine (**3aa**) as a major product along with 2-methyl-7-phenylpyrazolo[1,5-*a*]pyrimidine was observed within 2 h (Table 1, entry 1). Increasing the amount of NaI to 1 equiv increased the formation of **3aa** up to 50% (Table 1, entry 2). Further, increasing the amount of NaI (1.2 equiv) and $K_2S_2O_8$ (1.5 equiv) was very beneficial as the yield of **3aa** increased up to 70% (Table 1, entry 3). Then, we checked the effect of different solvents such as 1,2-DCE, MeOH, EtOH, DMSO, DMF, toluene, water, etc. (Table 1, entries 4−10). Satisfyingly, we observed that water was the best solvent for this three-component coupling reaction, and almost quantitative formation of **3aa** was observed (Table 1, entry 10). Other oxidants like $Na_2S_2O_8$, $(NH_4)_2S_2O_8$, PIDA, TBHP, H_2O_2, and oxygen were not so effective in the synthesis of **3aa** (Table 1, entries 11−16). On the other hand, KI and TBAI were less effective than NaI (Table 1, entries 17 and 18). The lower yield was observed upon decreasing the amount of $K_2S_2O_8$, whereas no product was formed without an oxidant (Table 1, entries 19−21). A detrimental effect was observed on decreasing the temperature as 72 and 52% yields were obtained at 60 °C and room temperature (Table 1, entries 22 and 23). Meanwhile, no significant increase of the yield was observed by carrying out the reaction at 100 °C (Table 1, entry 24). Thus, the optimum yield was obtained by carrying out the reaction employing 1.2 equiv NaI and 1.5 equiv $K_2S_2O_8$ in water under ambient air for 2 h (Table 1, entry 10).

https://doi.org/10.1021/acsomega.3c02270
ACS Omega 2023, 8, 23851−23859

Table 1. Optimization of the Reaction Conditions[a]



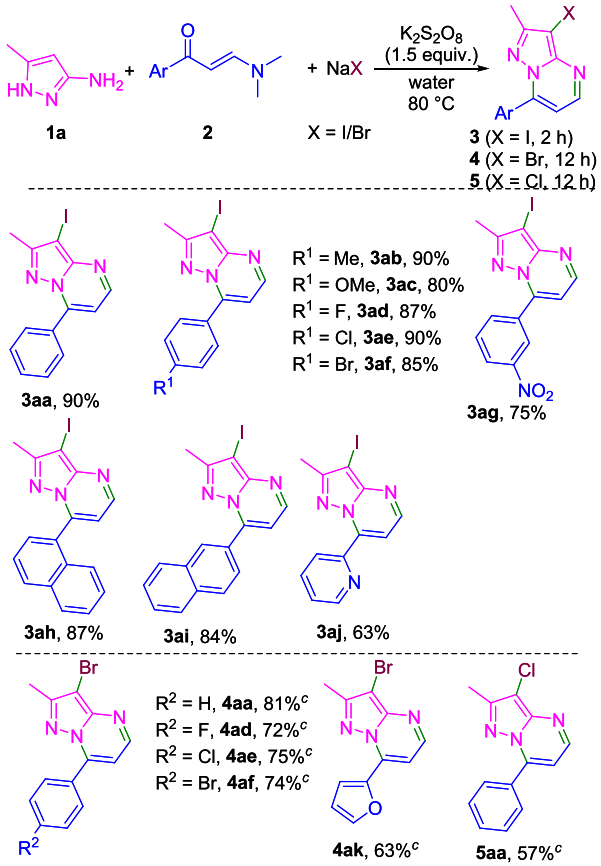
entry	iodide source (equiv)	oxidant (equiv)	solvent	yields[b]
1	NaI (0.2)	$K_2S_2O_8$ (1.0)	MeCN	20
2	NaI (1.0)	$K_2S_2O_8$ (1.0)	MeCN	50
3	NaI (1.2)	$K_2S_2O_8$ (1.5)	MeCN	70
4	NaI (1.2)	$K_2S_2O_8$ (1.5)	1,2-DCE	82
5	NaI (1.2)	$K_2S_2O_8$ (1.5)	MeOH	25
6	NaI (1.2)	$K_2S_2O_8$ (1.5)	EtOH	23
7	NaI (1.2)	$K_2S_2O_8$ (1.5)	DMSO	54
8	NaI (1.2)	$K_2S_2O_8$ (1.5)	DMF	12
9	NaI (1.2)	$K_2S_2O_8$ (1.5)	toluene	21
10	NaI (1.2)	$K_2S_2O_8$ (1.5)	water	90
11	NaI (1.2)	$Na_2S_2O_8$ (1.5)	water	75
12	NaI (1.2)	$(NH_4)_2S_2O_8$ (1.5)	water	85
13	NaI (1.2)	PIDA (1.5)	water	37
14	NaI (1.2)	TBHP (1.5)	water	NR
15	NaI (1.2)	H_2O_2 (1.5)	water	NR
16	NaI (1.2)	O_2	water	NR
17	KI (1.2)	$K_2S_2O_8$ (1.5)	water	84
18	TBAI (1.2)	$K_2S_2O_8$ (1.5)	water	20
19	NaI (1.2)	$K_2S_2O_8$ (0.5)	water	68
20	NaI (1.2)	$K_2S_2O_8$ (0.2)	water	33
21	NaI (1.2)		water	NR
22	NaI (1.2)	$K_2S_2O_8$ (1.5)	water	72[c]
23	NaI (1.2)	$K_2S_2O_8$ (1.5)	water	52[d]
24	NaI (1.2)	$K_2S_2O_8$ (1.5)	water	91[e]

[a]Reaction conditions: A mixture of **1a** (0.2 mmol), **2a** (0.2 mmol), MI, and oxidant in solvent (1 mL) was heated at 80 °C for 2 h. [b]Isolated yields. [c]At 60 °C. [d]At room temperature. [e]At 100 °C.

Next, we investigated the substrate scope of this three-component synthesis of 3-halo-2-methyl-7-phenylpyrazolo[1,5-*a*]pyrimidine derivatives. Various enaminones, amino pyrazoles, and metal halides were employed under the optimized reaction conditions (Scheme 2). Aryl enaminones bearing electron-donating as well as electron-withdrawing substituents (such as -Me, -OMe, -F, -Cl, -Br, -NO_2, etc.) on the phenyl ring successfully afforded the 3-iodo-pyrazolo[1,5-*a*]pyrimidine derivatives with high to excellent yields (**3aa**−**3ag**). (*E*)-3-(Dimethylamino)-prop-2-en-1-ones with naphthalenyl moiety also produced the respective 3-iodinated pyrazolo[1,5-*a*]-pyrimidines with excellent yields (**3ah**−**3ai**). Moreover, heteroaryl enaminones like (*E*)-3-(dimethylamino)-1-(pyridin-2-yl)prop-2-en-1-one reacted well to selectively give 3-iodo-2-methyl-7-(pyridin-2-yl)pyrazolo[1,5-*a*]pyrimidine with 63% yield (**3aj**). We also investigated the synthesis of 3-bromo- and 3-chloro pyrazolo[1,5-*a*]pyrimidines using NaBr and NaCl, respectively. The methodology was beneficial for synthesizing 3-bromo-2-methyl-7-phenylpyrazolo[1,5-*a*]-pyrimidines employing NaBr, albeit a longer reaction time was required (**4aa**, **4ad**, **4ae**, **4af**, and **4ak**). NaCl was also effective under optimized reaction conditions to afford 3-chloro pyrazolo[1,5-*a*]pyrimidine (**5aa**) with moderate yield (57%).

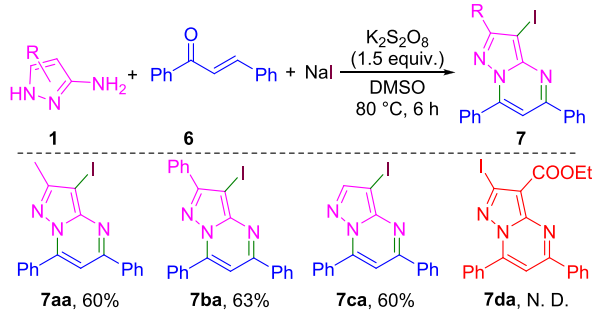
This tandem cyclization/halogenation was also useful for another enone like chalcone (Scheme 3). However, water was not a suitable solvent for this transformation, and DMSO was

Scheme 2. Substrate Scopes of Amino Pyrazoles, Enones, and Halogenating Agents (NaX)[a,b]



[a]Reaction conditions: A mixture of **1a** (0.2 mmol), **2** (0.2 mmol), NaX (1.2 equiv), and $K_2S_2O_8$ (1.5 equiv) in water (1 mL) was heated at 80 °C for 2 h. [b]Isolated yields. [c]A mixture of **1** (0.2 mmol), **2** (0.2 mmol), and $K_2S_2O_8$ (1.0 equiv) in water (1 mL) was heated at 80 °C for 1 h; after that, NaBr/NaCl (1.2 equiv) and $K_2S_2O_8$ (1.5 equiv) was added and heated for further 12 h.

Scheme 3. One-Pot Three Component Reaction of Amino Pyrazoles, Chalcone, and NaI[a,b]

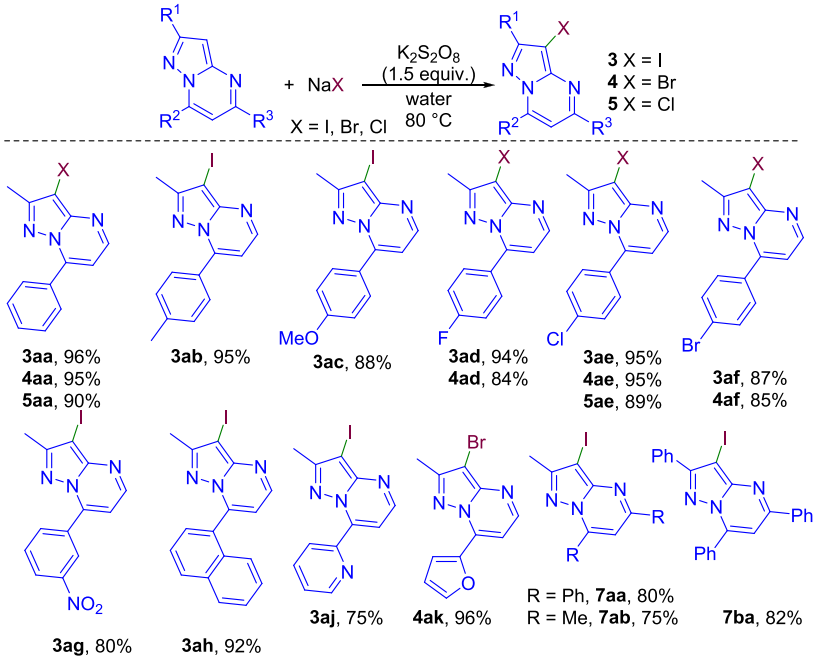


[a]Reaction conditions: A mixture of **1** (0.2 mmol), **6** (0.2 mmol), NaX (1.2 equiv), and $K_2S_2O_8$ (1.5 equiv) in DMSO (1 mL) was heated at 80 °C for 6 h. [b]Isolated yields.

proven to be a suitable solvent in this case. 5-Methyl-1*H*-pyrazol-3-amine and 5-phenyl-1*H*-pyrazol-3-amine efficiently reacted with chalcone to afford the respective 3-iodopyrazolo-[1,5-*a*]pyrimidines; however, a longer reaction time was required (**7aa** and **7ba**). Importantly, only the formation of 3-iodinated pyrazolo[1,5-*a*]pyrimidine (**7ca**) was observed

https://doi.org/10.1021/acsomega.3c02270
ACS Omega 2023, 8, 23851−23859

Scheme 4. Substrate Scope of the Oxidative Halogenations of Pyrazolo[1,5-*a*]pyrimidines[a,b]



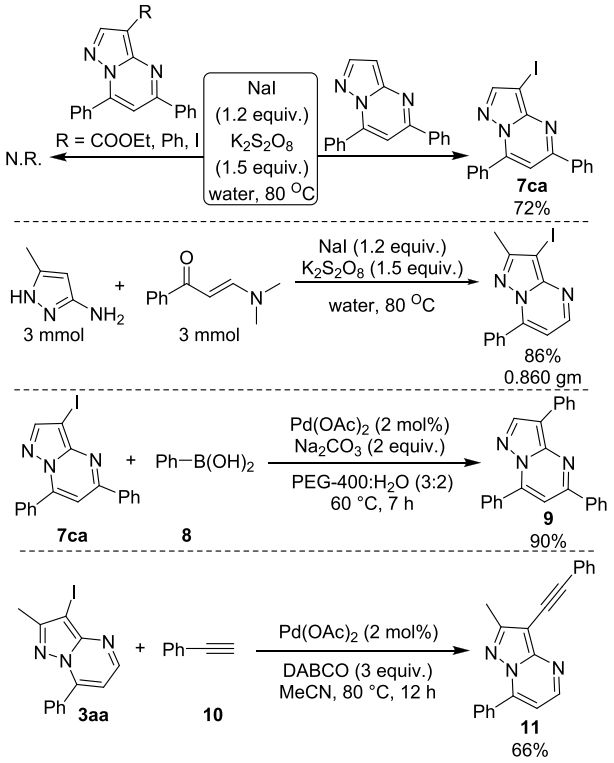
[a]Reaction conditions: A mixture of pyrazolo[1,5-*a*]pyrimidines (0.2 mmol), NaX (1.2 equiv), and $K_2S_2O_8$ (1.5 equiv) in water (1 mL) was heated at 80 °C for 1 h. [b]Isolated yields.

even when 1*H*-pyrazol-3-amine was employed, whereas no formation of iodinated pyrazolo[1,5-*a*]pyrimidine (**7da**) was observed using methyl 3-amino-1*H*-pyrazole-4-carboxylate.

We also checked the efficiency of the combination of NaX/$K_2S_2O_8$ in the direct oxidative C−H halogenations of pyrazolo[1,5-*a*]pyrimidine derivatives in water (Scheme 4). Various 7-aryl pyrazolo[1,5-*a*]pyrimidines afforded 3-iodinated pyrazolo[1,5-*a*]pyrimidine derivatives with excellent yields (**3aa**−**3ag**). The iodination of 2-methyl-7-(pyridin-2-yl)-pyrazolo[1,5-*a*]pyrimidine took place selectively on the pyrazole ring among three heterocyclic units—pyrazole, pyrimidine, and pyridine (**3aj**). The iodination took place with ease in the case of 5,7-diphenylpyrazolo[1,5-*a*]pyrimidine, 2,5,7-trimethylpyrazolo[1,5-*a*]pyrimidine and 2,5,7-triphenylpyrazolo[1,5-*a*]pyrimidine (**7aa**, **7ab**, and **7ba**). This protocol was also applicable for oxidative bromination and chlorination of various aryl/heteroaryl substituted pyrazolo-[1,5-*a*]pyrimidines (**4aa**, **4ad**, **4ae**, **4af**, **4ak**, **5aa**, and **5ae**). In the case of chlorination, much better yields were obtained compared to the one-pot strategy.

Selectivity and practical applicability have been also demonstrated (Scheme 5). When 5,7-diphenylpyrazolo[1,5-*a*]pyrimidine was employed, mono-iodination regioselectively occurred at the 3-position (**7ca**), whereas no reaction occurred when methyl 5,7-diphenylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate, 3,5,7-triphenylpyrazolo[1,5-*a*]pyrimidine (**9**) and 3-iodo-5,7-diphenylpyrazolo[1,5-*a*]pyrimidine (**7ca**) were employed under the optimized reaction conditions. These results indicate that this C−H halogenation is highly regioselective. One-step synthesis was also applicable for the gram-scale preparation of 3-iodo pyrazolo[1,5-*a*]pyrimidine with excellent yields (**3aa**). The synthesized 3-iodo pyrazolo[1,5-*a*]pyrimidine may be transformed to other substituted pyrazolo[1,5-*a*]pyrimidine derivatives via cross-coupling reactions. We have synthesized 3,5,7-triphenylpyrazolo[1,5-*a*]pyrimidine (**9**) and 2-methyl-7-

Scheme 5. Selectivity and Practical Applicability of the Methodology and Transformation of 3-Iodo Pyrazolo[1,5-*a*]pyrimidine to Functionalized Pyrazolo[1,5-*a*]pyrimidines



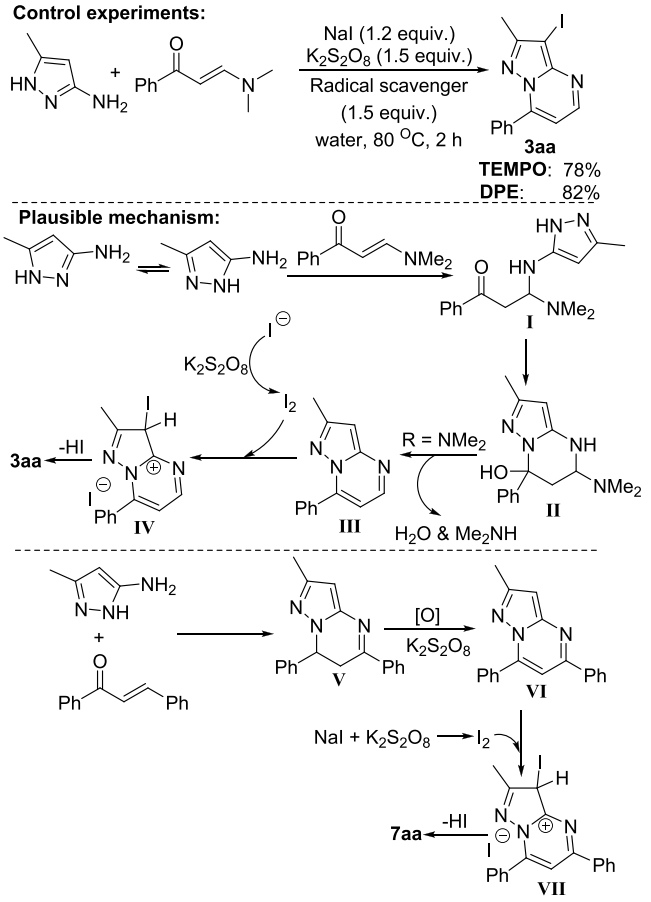
phenyl-3-(phenylethynyl)pyrazolo[1,5-*a*]pyrimidine (**11**) from 3-iodo pyrazolo[1,5-*a*]pyrimidines through Suzuki coupling and Sonogashira coupling, respectively.[19]

The yield of the one-pot reaction was not significantly hampered in presence of radical scavengers like TEMPO and

https://doi.org/10.1021/acsomega.3c02270
ACS Omega 2023, 8, 23851−23859

DPE, which signify that the reaction proceeded through a non-radical pathway (Scheme 6). The reaction proceeded through

Scheme 6. Control Experiments and Plausible Mechanism



the initial formation of pyrazolo[1,5-*a*]pyrimidine (**III**) by the reaction of enaminones with amino pyrazoles in presence of $K_2S_2O_8$ through cascade cyclization. The Michael addition of amino pyrazole to enaminones afforded the intermediate **I**, which, on intramolecular cyclization, produced the intermediate **II**. The intermediate **II** through the elimination of water and Me_2NH afforded the pyrazolo[1,5-*a*]pyrimidines. In the next step, pyrazolo[1,5-*a*]pyrimidine **III** reacted with the in situ generated I_2 to afford the intermediate **IV**, which, on proton elimination, produced the final product **3aa**. Meanwhile, in case of chalcone, the intermediate **V** is formed by the reaction of chalcone with amino pyrazoles through Michael addition followed by intramolecular cyclization and dehydration.[11c] The intermediate **V**, on oxidation, afforded the pyrazolo[1,5-*a*]pyrimidine **VI**, which, on electrophilic iodination by in situ generated I_2 followed by deprotonation, produced the final product **7aa**.

CONCLUSIONS

In conclusion, we have developed a new one-step methodology for synthesizing halogenated pyrazolo[1,5-*a*]pyrimidine derivatives through cyclization between amino pyrazoles and enaminones in an aqueous medium. The mixture of NaX-$K_2S_2O_8$ played an important role in this cascade cyclization−oxidative halogenation. This strategy is also applicable to chalcone for synthesizing densely substituted 3-iodopyrazolo[1,5-*a*]pyrimidines. The combination of NaX-$K_2S_2O_8$ also acted as useful reagents for the oxidative halogenations of pyrazolo[1,5-*a*]pyrimidines with various functionalities. A library of halogenated pyrazolo[1,5-*a*]pyrimidines has been synthesized employing this protocol. The synthesized 3-iodo pyrazolo[1,5-*a*]pyrimidine has been transformed into other substituted pyrazolo[1,5-*a*]pyrimidines through cross-coupling reactions. Simple and mild reaction conditions, the use of easily available and accessible reagents, water as a solvent, wide substrate scopes, and large-scale applicability are the attractive features of this methodology.

EXPERIMENTAL SECTION

General Information. All the reagents and solvents were purchased from commercial sources and used as is. Pyrazolo-[1,5-*a*]pyrimidine derivatives were prepared by following the literature reports.[15] All the reactions were carried out using an oven-dried reaction tube. The reactions were monitored by using aluminum TLC silica plates and visualized in a UV chamber (254 or 365 nm). Column chromatography was carried out using 60−120 mesh silica gel and a mixture of ethyl acetate−hexane as eluent. ^{1}H NMR and ^{13}C NMR were recorded in 400 and 100 MHz NMR spectrometers, respectively, using $CDCl_3$ as solvent. Chemical shifts were given in parts per million (δ), and coupling constants (J) were expressed in Hertz. The signals were expressed as s for singlet, d for doublet, dd for doublet of doublet, t for triplet. Melting points were recorded using capillary tubes in the melting point apparatus and data were uncorrected.

*General Procedure for the One-Pot Synthesis of 3-Halo Pyrazolo[1,5-a]pyrimidines (**GP 1A**) for **3**, **4**, and **5**.* In an oven-dried reaction tube, enaminone (0.2 mmol) and amino pyrazole (0.2 mmol) were taken, and 1 mL of H_2O was added. Then, NaI (1.2 equiv, 36 mg) and $K_2S_2O_8$ (1.5 equiv, 81 mg) were added into the reaction tube. The reaction mixture was then stirred in air at 80 °C. After the completion of the reaction (monitored by TLC), the reaction mixture was extracted with DCM−water and dried over anhydrous sodium sulfate (Na_2SO_4). The DCM was then evaporated to get the crude product, which was purified by column chromatography employing a mixture of ethyl acetate and hexane as eluent. (In the case of NaBr and NaCl, initially, a mixture of enaminone (0.2 mmol), amino pyrazole (0.2 mmol), and $K_2S_2O_8$ (1 equiv) in 1 mL of H_2O was heated at 80 °C for 1 h; after that, NaBr/NaCl (1.2 equiv) and $K_2S_2O_8$ (1.5 equiv, 81 mg) were added into the reaction tube. Then, the reaction mixture was stirred in air at 80 °C for 12 h. After the completion of the reaction (monitored by TLC), the reaction mixture was extracted with DCM−water and dried over anhydrous sodium sulfate (Na_2SO_4). The DCM was then evaporated to get the crude product, which was purified by column chromatography employing a mixture of ethyl acetate and hexane as eluent.)

*General Procedure for the One-Pot Synthesis of 3-Halo Pyrazolo[1,5-a]pyrimidines (**GP 1B**) for **7**.* In an oven-dried reaction tube, chalcone (0.2 mmol) and amino pyrazole (0.2 mmol) were taken and 1 mL of DMSO was added. Then, NaI (1.2 equiv, 36 mg) and $K_2S_2O_8$ (1.5 equiv, 81 mg) were added into the reaction tube. Then, the reaction mixture was stirred in air at 80 °C. After the completion of the reaction (monitored by TLC), the reaction mixture was extracted with DCM−water and dried over anhydrous sodium sulfate (Na_2SO_4). The DCM was then evaporated to get the crude

https://doi.org/10.1021/acsomega.3c02270
ACS Omega 2023, 8, 23851−23859

product, which was purified by column chromatography employing a mixture of ethyl acetate and hexane as eluent.

*General Procedure for the Oxidative Halogentations of Phenylpyrazolo[1,5-a]Pyrimidines (**GP 2**).* A mixture of phenylpyrazolo[1,5-*a*]pyrimidine derivatives (**PP**, 0.2 mmol), NaI (36 mg, 1.2 equiv), and $K_2S_2O_8$ (81 mg, 1.5 equiv) in H_2O (1 mL) was taken in an oven-dried reaction tube. Then, the mixture was heated at 80 °C for 1 h. After the completion of the reaction (monitored by TLC), the reaction mixture was extracted with DCM−water and dried over anhydrous sodium sulfate (Na_2SO_4). Then, DCM was evaporated to obtain the crude product. In some cases, the crude product was sufficiently pure, and in other cases, the crude product was purified by column chromatography using ethyl acetate−hexane as eluent.

3-Iodo-2-methyl-7-phenylpyrazolo[1,5-a]pyrimidine[15a] *(**3aa**).* Yellow crystalline solid, (**GP 1A**: 60 mg, 90%. **GP 2**: 64 mg, 96%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.47 (d, J = 4.4 Hz, 1H), 7.95−7.92 (m, 2H), 7.49−7.47 (m, 3H), 6.79 (d, J = 4.0 Hz, 1H), 2.45 (s, 3H) ppm; ^{13}C{H}NMR ($CDCl_3$, 100 MHz): δ 156.5, 149.9, 149.5, 147.0, 131.3, 130.3, 129.3, 128.7, 107.6, 52.9, 15.3 ppm.

*3-Iodo-2-methyl-7-(p-tolyl)pyrazolo[1,5-a]pyrimidine (**3ab**).* Yellow crystalline solid, (**GP 1A**: 63 mg, 90%. **GP 2**: 66 mg, 95%); Mp = 112−114 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.46 (d, J = 4.4 Hz, 1H), 7.86 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 6.79 (d, J = 4.4 Hz, 1H), 2.46 (s, 3H), 2.38 (s, 3H) ppm; ^{13}C{H}NMR ($CDCl_3$, 100 MHz): δ 156.4, 149.9, 149.5, 147.2, 141.9, 129.4, 129.2, 127.5, 107.3, 52.7, 21.6, 15.2 ppm; HRMS (ESI-TOF), m/z, [M + Na]$^+$: calcd mass for $C_{14}H_{12}IN_3Na^+$: 371.9968; found: 371.9961.

*3-Iodo-7-(4-methoxyphenyl)-2-methylpyrazolo[1,5-a]-pyrimidine (**3ac**).* Yellow crystalline solid, (**GP 1A**: 59 mg, 80%. **GP 2**: 64 mg, 88%); Mp = 123−125 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.53 (d, J = 4.0 Hz, 1H), 8.08 (d, J = 8.8 Hz, 2H), 7.08 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 4.4 Hz, 1H), 3.92 (s, 3H), 2.55 (s, 3H) ppm; ^{13}C{H}NMR ($CDCl_3$, 100 MHz): δ 161.9, 156.3, 149.9, 149.7, 146.7, 131.1, 122.5, 114.2, 106.8, 55.5, 52.6, 15.3 ppm; HRMS (ESI-TOF), m/z, [M + H]$^+$: calcd mass for $C_{14}H_{13}IN_3O^+$: 366.0098; found: 366.0063.

*7-(4-Fluorophenyl)-3-iodo-2-methylpyrazolo[1,5-a]-pyrimidine (**3ad**).* Yellow crystalline solid, (**GP 1A**: 61 mg, 87%. **GP 2**: 67 mg, 94%); Mp = 132−134 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.46−8.45 (m, 1H), 8.00−7.96 (m, 2H), 7.19−7.14 (m, 2H), 6.77−6.76 (m, 1H), 2.44 (s, 3H) ppm; ^{13}C{H}NMR ($CDCl_3$, 100 MHz): δ 164.6 ($J_{C\text{-}F}$ = 296 Hz), 156.6, 149.9, 149.5, 145.9, 131.6 ($J_{C\text{-}F}$ = 8 Hz), 126.4, 116.0 ($J_{C\text{-}F}$ = 21 Hz), 107.4, 53.1, 15.2 ppm; HRMS (ESI-TOF), m/z, [M + H]$^+$: calcd mass for $C_{13}H_{10}FIN_3^+$: 353.9898; Found: 353.9879.

7-(4-Chlorophenyl)-3-iodo-2-methylpyrazolo[1,5-a]-pyrimidine[15a] *(**3ae**).* Yellow crystalline solid, (**GP 1A**: 67 mg, 90%. **GP 2**: 70 mg, 95%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.43 (d, J = 4.4 Hz, 1H), 7.89 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 6.75 (d, J = 4.4 Hz, 1H), 2.42 (s, 3H) ppm; ^{13}C{H}NMR ($CDCl_3$, 100 MHz): δ 156.6, 149.8, 149.5, 145.6, 137.5, 130.6, 129.0, 128.6, 107.4, 53.2, 15.2 ppm.

*7-(4-Bromophenyl)-3-iodo-2-methylpyrazolo[1,5-a]-pyrimidine (**3af**).* Yellow crystalline solid, (**GP 1A**: 70 mg, 85%. **GP 2**: 72 mg, 87%); Mp = 158−160 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.43 (d, J = 4.4 Hz, 1H), 7.82 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H), 7.75 (d, J = 4.4 Hz, 1H), 2.42 (s, 3H) ppm; ^{13}C{H}NMR ($CDCl_3$, 100 MHz): δ 156.6, 149.8, 149.5, 145.7, 132.0, 130.8, 129.1, 125.9, 107.4, 53.2, 15.2 ppm; HRMS (ESI-TOF), m/z, [M + H]$^+$: calcd mass for $C_{13}H_{10}BrIN_3^+$: 413.9097; found: 413.9112.

*3-Iodo-2-methyl-7-(3-nitrophenyl)pyrazolo[1,5-a]-pyrimidine (**3ag**).* Yellow solid, (**GP 1A**: 57 mg, 75%. **GP 2**: 61 mg, 80%); Mp = 148−150 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.84 (s, 1H), 8.53 (d, J = 4.0 Hz, 1H), 8.35−8.32 (m, 2H), 7.70 (t, J = 8.0 Hz, 1H), 6.89 (d, J = 4.0 Hz, 1H), 2.46 (s, 3H) ppm; ^{13}C{H}NMR ($CDCl_3$, 100 MHz): δ 157.0, 149.8, 149.5, 148.3, 144.1, 135.1, 131.9, 129.9, 125.8, 124.4, 107.8, 53.8, 15.2 ppm; HRMS (ESI-TOF), m/z, [M + H]$^+$: calcd mass for $C_{13}H_{10}IN_4O_2^+$: 380.9843; found: 381.2985.

*3-Iodo-2-methyl-7-(naphthalen-1-yl)pyrazolo[1,5-a]-pyrimidine (**3ah**).* Pale yellow crystalline solid, (**GP 1A**: 67 mg, 87%. **GP 2**: 71 mg, 92%); Mp = 120−122 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.49 (d, J = 2.8 Hz, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 6.4 Hz, 1H), 7.49−7.47 (m, 1H), 7.43−7.39 (m, 1H), 7.32−7.25 (m, 2H), 6.75 (d, J = 2.8 Hz, 1H), 2.3 (s, 3H) ppm; ^{13}C{H}NMR ($CDCl_3$, 100 MHz): δ 156.7, 149.7, 149.3, 146.8, 133.5, 131.3, 130.5, 128.7, 128.3, 128.0, 127.1, 126.6, 125.2, 124.9, 110.1, 53.1, 15.2 ppm; HRMS (ESI-TOF), m/z, [M + H]$^+$: calcd mass for $C_{17}H_{13}IN_3^+$: 386.0149; found: 386.0156.

*3-Iodo-2-methyl-7-(naphthalen-2-yl)pyrazolo[1,5-a]-pyrimidine (**3ai**).* Pale yellow crystalline solid, (**GP 1A**: 65 mg, 84%); Mp = 140−142 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.49 (d, J = 4.4 Hz, 2H), 7.97−7.94 (m, 1H), 7.92−7.87 (m, 2H), 7.82 (d, J = 7.6 Hz, 1H), 7.52−7.48 (m, 2H), 6.89 (d, J = 4 Hz, 1H), 2.46 (s, 3H) ppm; ^{13}C{H}NMR ($CDCl_3$, 100 MHz): δ 156.5, 149.9, 149.6, 146.9, 134.5, 132.8, 129.9, 128.9, 128.4, 127.9, 127.8, 127.7, 126.8, 125.5, 107.9, 53.0, 15.3 ppm; HRMS (ESI-TOF), m/z, [M + H]$^+$: calcd mass for $C_{17}H_{13}IN_3^+$: 386.0149; found: 385.2921.

*3-Iodo-2-methyl-7-(pyridin-2-yl)pyrazolo[1,5-a]-pyrimidine (**3aj**).* Yellow solid, (**GP 1A**: 42 mg, 63%. **GP 2**: 51 mg, 75%); Mp = 103−105 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.96 (d, J = 8.0 Hz, 1H), 8.74 (d, J = 4.8 Hz, 1H), 8.57 (d, J = 4.4 Hz, 1H), 7.89−7.85 (m, 1H), 7.61 (d, J = 4.4 Hz, 1H), 7.41−7.38 (m, 1H), 2.51 (s, 3H) ppm; ^{13}C{H}NMR ($CDCl_3$, 100 MHz): δ 156.3, 150.1, 150.0, 149.9, 147.8, 144.3, 136.7, 126.1, 125.5, 108.2, 53.2, 15.2 ppm; HRMS (ESI-TOF), m/z, [M + H]$^+$: calcd mass for $C_{12}H_{10}IN_4^+$: 336.9945; found: 336.9951.

3-Iodo-2-methyl-5,7-diphenylpyrazolo[1,5-a]-pyrimidine[15c] *(**7aa**).* Yellow crystalline solid, (**GP 1B**: 49 mg, 60%. **GP 2**: 66 mg, 80%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.11 (d, J = 6.8 Hz, 2H), 7.97−7.96 (m, 2H), 7.50−7.48 (m, 3H), 7.43−7.41 (m, 3H), 7.22 (s, 1H), 2.45 (s, 3H) ppm; ^{13}C{H}NMR ($CDCl_3$, 100 MHz): δ 156.8, 149.5, 146.8, 137.1, 131.2, 130.9, 130.5, 129.3, 128.9, 128.7, 127.4, 105.2, 53.3, 15.4 ppm.

3-Iodo-2,5,7-triphenylpyrazolo[1,5-a]pyrimidine[15c] *(**7ba**).* Yellow crystalline solid, (**GP 1B**: 60 mg, 63%. **GP 2**: 78 mg, 82%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.14 (d, J = 6.8 Hz, 2H), 8.06−8.05 (m, 2H), 8.01 (d, J = 7.2 Hz, 2H), 7.49−7.48 (m, 3H), 7.45−7.35 (m, 6H), 7.32 (s, 1H) ppm; ^{13}C{H}NMR ($CDCl_3$, 100 MHz): δ 157.0, 156.0, 150.3, 146.9, 137.0, 132.9, 131.2, 130.7, 130.6, 129.5, 129.1, 129.0, 128.9, 128.7, 128.3, 127.4, 105.9, 50.7 ppm.

3-Iodo-5,7-diphenylpyrazolo[1,5-a]pyrimidine[15c] *(**7ca**).* Yellow crystalline solid, (**GP 1B**: 48 mg, 60%. **GP 2**: 57 mg, 72%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.23−8.19 (m, 3H), 8.04 (brs, 2H), 7.62 (brs, 3H), 7.54 (brs, 3H), 7.40 (s, 1H)

https://doi.org/10.1021/acsomega.3c02270
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ppm; $^{13}C\{H\}$NMR ($CDCl_3$, 100 MHz): δ 157.2, 149.2, 148.8, 147.4, 136.9, 131.2, 130.8, 130.7, 129.3, 128.9, 128.8, 127.5, 105.7, 50.2 ppm.

3-Iodo-2,5,7-trimethylpyrazolo[1,5-a]pyrimidine[15c] (**7ab**). Brownish white crystalline solid, (**GP 2**: 43 mg, 75%); ^1H NMR ($CDCl_3$, 400 MHz): δ 6.46 (s, 1H), 2.63 (s, 3H), 2.52 (s, 3H), 2.44 (s, 3H) ppm; $^{13}C\{H\}$NMR ($CDCl_3$, 100 MHz): δ 159.8, 155.8, 148.5, 145.3, 108.8, 51.2, 24.8, 16.6, 15.1 ppm.

3-Bromo-2-methyl-7-phenylpyrazolo[1,5-a]pyrimidine[15b] (**4aa**). Pale yellow crystalline solid, (**GP 1A**: 47 mg, 81%. **GP 2**: 55 mg, 95%); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.46 (d, J = 4.4 Hz, 1H), 7.95−7.93 (m, 2H), 7.49−7.48 (m, 3H), 6.79 (d, J = 4.4 Hz, 1H), 2.44 (s, 3H) ppm; $^{13}C\{H\}$NMR ($CDCl_3$, 100 MHz): δ 153.3, 149.6, 146.8, 146.7, 131.3, 130.3, 129.3, 128.7, 107.5, 85.1, 13.4 ppm.

3-Bromo-7-(4-fluorophenyl)-2-methylpyrazolo[1,5-a]-pyrimidine[15b] (**4ad**). Yellow crystalline solid, (**GP 1A**: 44 mg, 72%. **GP 2**: 51 mg, 84%); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.45 (d, J = 4.4 Hz, 1H), 8.01−7.97 (m, 2H), 7.17 (t, J = 8.4 Hz, 2H), 6.77 (d, J = 4.4 Hz, 1H), 2.44 (s, 3H) ppm; $^{13}C\{H\}$NMR ($CDCl_3$, 100 MHz): δ 164.4 ($J_{C\text{-}F}$ = 251 Hz), 153.4, 149.6, 146.8, 145.6, 131.6 ($J_{C\text{-}F}$ = 8 Hz), 126.4 ($J_{C\text{-}F}$ = 3 Hz), 116.0 ($J_{C\text{-}F}$ = 22 Hz), 107.2, 85.2, 13.4 ppm.

3-Bromo-7-(4-chlorophenyl)-2-methylpyrazolo[1,5-a]-pyrimidine[15a] (**4ae**). Yellow crystalline solid, (**GP 1A**: 48 mg, 75%. **GP 2**: 61 mg, 95%); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.46 (d, J = 4.4 Hz, 1H), 7.92 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H), 6.78 (d, J = 4 Hz, 1H), 2.44 (s, 3H) ppm; $^{13}C\{H\}$NMR ($CDCl_3$, 100 MHz): δ 153.4, 149.6, 146.8, 145.5, 137.5, 130.6, 129.1, 128.7, 107.3, 85.3, 13.4 ppm.

3-Bromo-7-(4-bromophenyl)-2-methylpyrazolo[1,5-a]-pyrimidine[15b] (**4af**). Yellow crystalline solid, (**GP 1A**: 54 mg, 74%. **GP 2**: 62 mg, 85%); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.55 (d, J = 4.4 Hz, 1H), 7.94 (d, J = 8.4 Hz, 2H), 7.71 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 4.4 Hz, 1H), 2.53 (s, 3H) ppm; $^{13}C\{H\}$NMR ($CDCl_3$, 100 MHz): δ 153.4, 149.6, 146.8, 145.5, 132.0, 130.8, 129.1, 125.9, 107.2, 85.4, 13.4 ppm.

3-Bromo-7-(furan-2-yl)-2-methylpyrazolo[1,5-a]-pyrimidine[15a] (**4ak**). Brownish yellow crystalline solid, (**GP 1A**: 35 mg, 63%. **GP 2**: 53 mg, 96%); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.44 (d, J = 4.4 Hz, 1H), 8.13 (d, J = 3.2 Hz, 1H), 7.62 (d, J = 1.2 Hz), 7.20 (d, J = 4.4 Hz, 1H), 6.63 (dd, J_1 = 3.6 Hz, J_2 = 1.6 Hz, 1H), 2.48 (s. 3H) ppm; $^{13}C\{H\}$NMR ($CDCl_3$, 100 MHz): δ 153.2, 148.7, 146.6, 145.8, 143.5, 135.6, 120, 113.1, 102.6, 85.0, 13.5 ppm.

3-Chloro-2-methyl-7-phenylpyrazolo[1,5-a]pyrimidine (**5aa**). Yellowish white crystalline solid, (**GP 1A**: 28 mg, 57%. **GP 2**: 44 mg, 90%); Mp = 135−137 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.52 (d, J = 4.0 Hz, 1H), 8.03−8.01 (m, 2H), 7.57−7.55 (m, 3H), 6.86 (d, J = 4.0 Hz, 1H), 2.51 (s, 3H) ppm; $^{13}C\{H\}$NMR ($CDCl_3$, 100 MHz): δ 151.7, 149.3, 146.6, 145.4, 131.3, 130.3, 129.3, 128.8, 107.3, 99.1, 12.4 ppm; HRMS (ESI-TOF), m/z, $[M + H]^+$: calcd mass for $C_{13}H_{11}ClN_3^+$: 244.0642; found: 244.0643.

3-Chloro-7-(4-chlorophenyl)-2-methylpyrazolo[1,5-a]-pyrimidine[15a] (**5ae**). Yellowish white crystalline solid, (**GP 2**: 49 mg, 89%); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.44 (d, J = 3.2 Hz, 1H), 7.92 (d, J = 8 Hz, 2H), 7.46 (d, J = 8 Hz, 2H), 6.77 (d, J = 2.8 Hz, 1H), 2.43 (s, 3H) ppm; $^{13}C\{H\}$NMR ($CDCl_3$, 100 MHz): δ 151.9, 149.2, 145.4, 137.5, 130.6, 129.1, 128.6, 107.1, 99.4, 12.4 ppm.

Large-Scale Synthesis of 3-Iodo-2-methyl-7-phenylpyrazolo[1,5-a]pyrimidine (**3aa**). In a RB, 5-methyl-1*H*-pyrazol-3-amine (**1a**, 3 mmol, 0.29 g) and (*E*)-3-(dimethylamino)-1-phenylprop-2-en-1-one (**2a**, 3 mmol, 0.53 g) were taken, and 12 mL of H_2O was added. Then, NaI (1.2 equiv, 0.54 g) and $K_2S_2O_8$ (1.5 equiv, 1.2 g) were added into the RB. The reaction mixture was then stirred in air at 80 °C. After the completion of the reaction (monitored by TLC), the reaction mixture was extracted with DCM−water and dried over anhydrous sodium sulfate (Na_2SO_4). The DCM was then evaporated to get the crude product, which was purified by column chromatography employing a mixture of ethyl acetate and hexane as eluent.

Procedure for Suzuki Coupling with **7ca**. In an oven-dried seal tube, a mixture of $Pd(OAc)_2$ (1 mg, 2 mol %), Na_2CO_3 (42 mg, 2 equiv), PEG 400 (0.6 mL), and water (0.5 mL) were heated at 60 °C with stirring. Then, 3-iodo-5,7-diphenylpyrazolo[1,5-*a*]pyrimidine (80 mg, 0.2 mmol, **7ca**) and phenylboronic acid (36 mg, 0.3 mmol, **8**) were added to the reaction mixture and heated at 60 °C for 7 h. After the completion of the reaction (monitored by TLC), the resulting mixture was extracted with diethyl ether and dried over anhydrous Na_2SO_4. Afterward, diethyl ether was evaporated, and a crude product was obtained. Further, the crude product was purified by column chromatography employing 100−200 mesh silica gel with a mixture of ethyl acetate and petroleum ether (1:15) as eluent.

3,5,7-Triphenylpyrazolo[1,5-a]pyrimidine (**9**).[12e] Yellow solid (63 mg, 90%). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.48 (s, 1H), 8.24−8.21 (m, 4H), 8.07−8.04 (m, 2H), 7.61−7.58 (m, 3H), 7.54−7.47 (m, 5H), 7.38 (s, 1H), 7.29 (t, J = 7.4 Hz, 1H) ppm; $^{13}C\{H\}$NMR ($CDCl_3$, 100 MHz): δ 155.9, 147.0, 145.9, 142.9, 137.3, 132.4, 131.5, 131.0, 130.4, 129.3, 128.9, 128.8, 128.7, 127.3, 126.3, 126.1, 110.7, 105.1 ppm.

Procedure for Sonogashira Coupling with **3aa**. In an oven-dried seal tube, a mixture of 3-iodo-2-methyl-7-phenylpyrazolo[1,5-*a*]pyrimidine (67 mg, 0.2 mmol, **3aa**), phenylacetylene (22 μL, 0.2 mmol, **10**), $Pd(OAc)_2$ (1 mg, 2 mol %), DABCO (66 mg, 0.6 mmol), and CH_3CN (1 mL) were heated at 80 °C with stirring for 12 h. After the completion of the reaction (monitored by TLC), the resulting mixture was extracted with dichloro methane and dried over anhydrous Na_2SO_4. Afterward, dichloro methane was evaporated, and a crude product was obtained. Further, the crude product was purified by column chromatography employing 100−200 mesh silica gel with a mixture of ethyl acetate and petroleum ether (1:10) as eluent.

2-Methyl-7-phenyl-3-(phenylethynyl)pyrazolo[1,5-a]-pyrimidine (**11**).[15a] Brown gummy mass, (41 mg, 66%). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.56 (d, J = 4.4 Hz, 1H), 8.05−8.03 (m, 2H), 7.62−7.60 (m, 2H), 7.57−7.56 (m, 3H), 7.37−7.30 (m, 3H), 6.88 (d, J = 4.4 Hz, 1H), 2.63 (s, 3H) ppm; $^{13}C\{H\}$NMR ($CDCl_3$, 100 MHz): δ 157.3, 150.2, 149.8, 146.9, 131.5, 131.3, 130.6, 129.3, 128.7, 128.2, 127.8, 123.8, 107.8, 94.8, 93.4, 79.7, 13.7 ppm.

Control Experiments. In an oven dried seal tube, enaminone (**2a**, 0.2 mmol, 35 mg) and amino pyrazole (**1a**, 0.2 mmol, 20 mg) were taken and 1 mL of H_2O was added. Then, NaI (1.2 equiv, 36 mg) and $K_2S_2O_8$ (1.5 equiv, 81 mg) were added into the seal tube. After that, TEMPO or DPE (1.5 equiv) was added to the reaction mixture, and the reaction mixture was stirred in air at 80 °C for 2 h. The reaction mixture was extracted with DCM−water and dried over

https://doi.org/10.1021/acsomega.3c02270
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anhydrous sodium sulfate (Na_2SO_4). The DCM was then evaporated to get the crude product, which was purified by column chromatography employing a mixture of ethyl acetate and hexane as eluent.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c02270.

Primary NMR FID files for compounds **3**, **4**, **5**, **7**, **9**, and **11**; synthetic procedures for large-scale reaction, control experiments, and ^1H, ^{13}C NMR spectra and HRMS (only for unknown compounds) of the synthesized compounds **3**, **4**, **5**, **7**, **9**, and **11** (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

A.K.B. acknowledges the financial support from the SERB, DST (file no. EEQ/2018/000498). A.K.B. also acknowledges the University of Kalyani (PRG) for financial support. P.S. acknowledges financial support from SVMCM for her fellowship. T.C. (URS) acknowledges the University of Kalyani for his fellowship. S.P. (CSIR-JRF) and S.D. (UGC-JRF) acknowledge the CSIR-New Delhi and UGC-New Delhi for their fellowships.

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https://doi.org/10.1021/acsomega.3c02270
ACS Omega 2023, 8, 23851−23859