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6-(Aryldiazenyl)pyrazolo[1,5-*a*]pyrimidines as Strategic Intermediates for the Synthesis of Pyrazolo[5,1-*b*]purines

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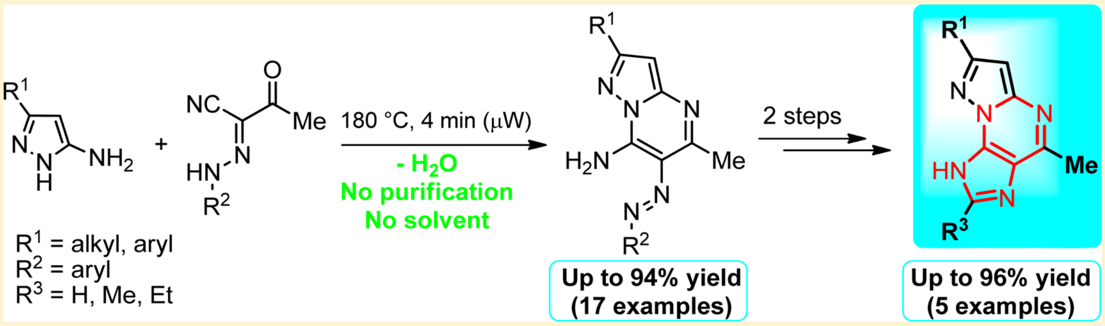
Supporting Information



ABSTRACT: A microwave-assisted approach for the regioselective synthesis of functionalized 6-(aryldiazenyl)pyrazolo[1,5-*a*]pyrimidin-7-amines from the cyclization of 3-oxo-2-(2-arylhydrazinylidene)butanenitriles with 5-amino-1*H*-pyrazoles under solvent-free conditions has been developed. This methodology was distinguished by its broad substrate scope, operational simplicity, high atom economy, and high-yielding without requiring chromatographic purification. In addition, an efficient and versatile palladium-catalyzed reductive azo cleavage is disclosed for the synthesis of diverse heteroaromatic 1,2-diamines, a valuable synthetic building block to develop new fused heteroaromatic systems. As synthetic example, several substituted pyrazolo[5,1-*b*]purines were synthesized in yields up to 96% by using microwave irradiation in the cyclocondensation of these 1,2-diamines with orthoesters.

■ INTRODUCTION

Analysis of database of U.S. FDA approved drugs reveals that 59% of unique small-molecule drugs contain a nitrogen heterocycle.[1] In recent years, purine-fused tricyclic and polycyclic derivatives have attracted considerable attention because of their valuable biological activities, medicinal properties, and special conjugated structures.[2] Although great endeavors have been devoted to the synthesis of purine-fused polycyclic derivatives and imidazo[2,1-*b*]purines, the development of new routes for the preparation of structurally diverse pyrazolo[5,1-*b*]purines still remains as an important and challenging goal for the chemists, due to few existing reports of its synthesis involving several reaction steps (Figure 1).

On the other hand, heterocyclic-fused pyrimidine represents one of the most prominent classes of privileged scaffolds in the field of drugs and pharmaceutical.[3] During the past decade, the synthesis of pyrazolo[1,5-*a*]pyrimidine derivatives and the investigation of their chemical and biological behavior have gained more importance due to pharmaceutical reasons.[4] For example, the hypnotic drug Zaleplon (**I**), the anticancer agent Dinaciclib (**II**), and the fungicide Pyrazophos (**III**) have this structural motif of pyrazolo[1,5-*a*]pyrimidine (examples highlighted in blue, Figure 2).[5]

In parallel to medicinal chemistry, recent discoveries in material sciences have proved that pyrazolo[1,5-*a*]pyrimidines containing an arylazo or hetarylazo group are useful synthetic intermediates in the dyestuff industry.[6] Consequently, synthetic methodologies for synthesis of novel pyrazolo[1,5-*a*]pyrimidine derivatives are of particular interest to organic and medicinal chemists. The importance of pyrazolo[1,5-*a*]pyrimidine scaffold has led to the development of various methods for its synthesis. Most of them involve the condensation reaction between aminopyrazoles and 1,3-bis-electrophilic reagents, such as 1,2-allenic ketones,[7] enaminones,[8] enaminonitriles,[9] β-ketonitriles,[10] 1,3-dicarbonyl compounds,[11] and α,β-unsaturated carbonyl compounds.[12] Therefore, further research is required to develop event more efficient methods to access to diversely functionalized pyrazolo[1,5-*a*]pyrimidines.

Currently, microwave-assisted organic synthesis (MAOS) and transformations using greener reaction media for the synthesis of drugs and biologically active molecules has proved to be efficient and environmentally benign due to its simplicity in operation, short reaction times, and clean product formation leading to better yields, selectivities, and easier workup.[13,14] An

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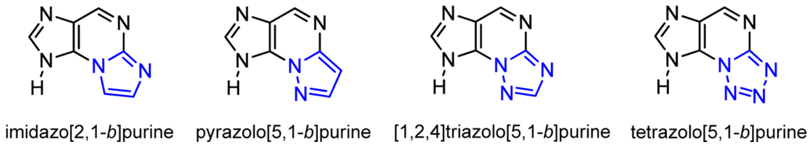


Figure 1. Most common type of azolo[*b*]purines.

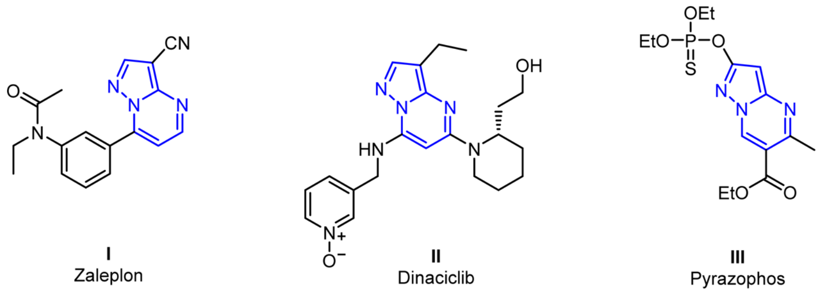
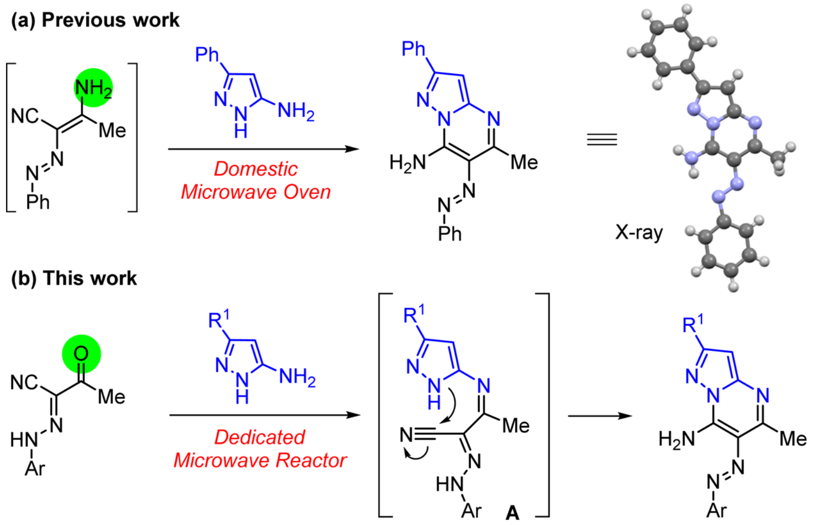
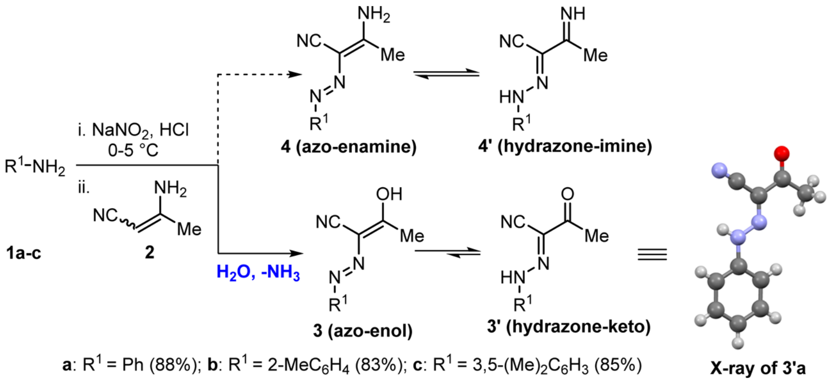


Figure 2. Examples of pyrazolo[1,5-*a*]pyrimidine drugs.

Scheme 1. Strategy for the Synthesis of Pyrazolo[1,5-*a*]pyrimidin-7-amines



Scheme 2. Tautomeric Forms of Arylazo-Dyes: Azo-enol and Hydrazone-keto



a: R^1 = Ph (88%); **b**: R^1 = 2-MeC_6H_4 (83%); **c**: R^1 = 3,5-$(Me)_2C_6H_3$ (85%)

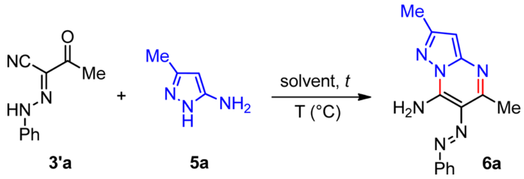
example of such methodology can be found in our recently reported imination/intramolecular nucleophilic addition work toward the synthesis of 6-(phenyldiazenyl)pyrazolo[1,5-*a*]-pyrimidin-7-amine from '3-amino-2-phenyldiazenylbut-2-enenitrile' with 5-amino-3-phenyl-1*H*-pyrazole as 1,3-*N*,*N*-bis-nucleophile (Scheme 1a).[15] Unambiguous proof of structure and regioselectivity was achieved by single-crystal X-ray diffraction analysis. In that report, we used a domestic microwave oven to obtain an efficient conversion to the desired product. However, most major scientific journals not longer accept manuscripts wherein domestic ovens have been described as heating sources, since there are many scientific arguments to be made for using dedicated microwave reactors instead of domestic ovens such as possibility of stirring, continuous power output, excellent parameter control, possibility of convenient solvent superheating, and safety under high-pressure/-temperature conditions. Inspired by these earlier studies, and our continuing interest in the synthesis of N-heterocycles,[12,16] we envisioned that microwave-assisted reaction of 2-arylhydrazinylidene-3-oxobutanenitrile with 5-amino-1*H*-pyrazole might generate an imine intermediate **A**, which could undergo intramolecular cyclization with pyrazole moiety. In consequence, leading to the formation of 6-(aryldiazenyl)pyrazolo[1,5-*a*]pyrimidin-7-amine by using a microwave reactor instead of the domestic oven (Scheme 1b).

RESULTS AND DISCUSSION

At the beginning, aniline derivatives **1a−c** were diazotised to give the corresponding aromatic diazonium salts which underwent a coupling reaction with 3-aminobut-2-enenitrile (**2**) to afford the arylazo-dyes in good yields (Scheme 2). Several decades before Elnagdi et al. reported that these derivatives exist mainly in the hydrazone-imine form **4′** using analysis of their IR, UV, and polarographic data.[15,17] However, we have confirmed by accurate mass measurements that the enamine group of these azo dyes was completely hydrolyzed under those diazotization conditions. Consequently, the structure of these dyes should have the tautomeric forms enol-keto **3**/**3′** instead of enamine-imine **4**/**4′**, suggesting that future papers should be reported according to our new results (see Supporting Information for details). The IR, HRMS and NMR spectroscopical data for all the arylazo-dyes **3**/**3′** are presented in the Experimental Section. ^{1}H NMR spectra of dyes **3**/**3′** recorded at 25 °C in $CDCl_3$ show a double set of signals, confirming that these dyes were obtained as mixtures of their corresponding azo-enol **3** and hydrazone-keto **3′** tautomers (Scheme 2). In general, the tautomeric enol (=CH−OH) and hydrazone (=N−NH−) protons appear as a broad singlet signal at 14.69−14.97 ppm and 9.20−9.44 ppm, respectively. In all cases, the azo-enol form **3** was the major tautomer in solution with the following ratios **3**/**3′a** (69:31), **3**/**3′b** (83:17), and **3**/**3′c** (71:29) (see Supporting Information for details). Notably, the IR data reveal the absence of the azo group band at 1454 cm^{-1}, which indicated that these dyes could exist in the hydrazone-keto form in the solid state. The structure of compound **3′a** was solved by single-crystal X-ray diffraction analysis,[18] showing that in the solid state, the dyes exist in the hydrazone-keto form **3′** and *E* configuration as the only stereochemical isomer. It is well-known that the applications of azo-dyes depend on the optical and physical properties of their tautomeric forms, azo, or hydrazone.[19] For example, the hydrazone form is often commercially preferred because it was found to be rendered higher photoconductivity to dual-layer photoreceptors.[20]

To continue our exploratory study, 3-oxo-2-(2-phenylhydrazinylidene)butanenitrile (**3′a**) and 5-amino-3-methyl-1*H*-pyrazole (**5a**) were prepared and probed as model substrates for cyclization reactions (Table 1). Initially, we performed the optimization by varying the solvent and testing the effect of conventional heating versus microwave irradiation. Heating to reflux an equimolar mixture of **3′a** and **5a** in anhydrous ethanol or toluene for 24 h did not lead to the desired product **6a** (Table 1, entries 1−2). To our delight, the use of high boiling solvents such as DMSO gave **6a** in 39% isolated yield as the only detectable regioisomer (Table 1, entry 3). A slightly higher yield of **6a** (43%) was achieved when DMF was used as solvent (Table 1, entry 4). Interestingly, we found out that higher temperatures favor the formation of pyrazolo[1,5-*a*]pyrimidin-7-amine **6a**, similarly to our previous work on the solvent-free synthesis of cyclopentapyrazolo[1,5-*a*]pyrimidines.[11d] The use of microwave irradiation to reach higher temperature (180 °C) under solvent-free conditions was performed with a 1:1 mixture of **3a′** and **5a**, and after 4 min of reaction in a sealed tube, we were pleased to find that the pyrazolo[1,5-*a*]pyrimidin-7-amine **6a** was obtained with high purity and nearly quantitative yield by simple collection with cold ethanol (Table 1, entry 5). The overall eco-compatibility of the process is highlighted. Reaction times below 4 min led to lesser yields of desired compound **6a** (Table 1, entries 6−7). Alternatively, we also carry out the reaction under conventional heating in fusion with acceptable results (Table 1, entries 8−9) and also under microwave irradiation using solvent. The formation of product **6a** was observed with ethanol in poor yield, whereas with DMF, the reaction proceeded in good isolated yield (Table 1 entries 10−12). For the reaction with ethanol, it was not possible to increase the temperature above 140 °C due to system overpressure. Finally, in the reactions with DMF, there is a complete conversion of the reactants, however, the crude must be isolated by a liquid−liquid extraction.

Table 1. Optimization of the Reaction Conditions for the Preparation of Pyrazolo[1,5-*a*]pyrimidine[a]

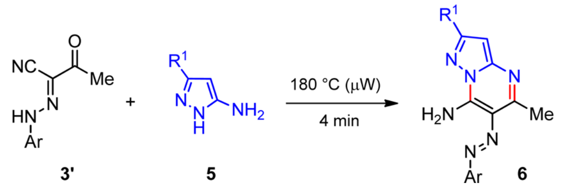


entry	solvent	*T* (°C)	time	yield (%)[b]
1	EtOH	80[c]	24 h	–
2	PhMe	110[c]	24 h	–
3	DMSO	140[c]	24 h	39
4	DMF	140[c]	24 h	43
5[d]	–	180	4 min	91
6[d]	–	180	3 min	77
7[d]	–	180	2 min	60
8[e]	–	180	10 min	55
9[e]	–	180	20 min	52
10[f]	EtOH	150	4 min	8
11[f]	DMF	180	4 min	61
12[f]	DMF	180	10 min	63

[a]Reaction conditions: **3′a** (0.50 mmol) and **5a** (0.50 mmol). [b]Isolated yield. [c]Conventional heating. [d]Run in 10 mL sealed tubes at a power of 300 W in the absence of solvent. [e]Conventional heating with a sand bath without solvent (fusion procedure). [f]Run in 10 mL sealed tubes at a power of 300 W in anhydrous solvent (2 mL).

With these optimized conditions, we set to explore the substrate scope using 2-arylhydrazinyliden-3-oxobutanenitriles (**3′a−c**) and a variety of 5-amino-1*H*-pyrazoles (**5a−h**). The results are reported in Table 2. A wide variety of pyrazolo[1,5-*a*]pyrimidines **6a−q** were obtained in good to excellent yields in a regioselective manner, without requiring chromatographic purification. In general, the reaction of 2-arylhydrazinyliden-3-oxobutanenitriles (**3′**) with 5-amino-1*H*-pyrazoles (**5**) containing diverse substituents attached to the carbon atom of the pyrazole ring proceeded efficiently to give the cyclized products **6** in up to 94% yield, which clearly indicated the low electronic influence of the substituents on the reactivity. Notably, this

Table 2. Microwave-Assisted Synthesis of Densely Substituted Pyrazolo[1,5-*a*]pyrimidines[a]



entry	3′ (Ar)	5 (R^1)	product	yield (%)[b]
1	Ph	Me	**6a**	86
2	Ph	*t*-Bu	**6b**	94
3	Ph	Ph	**6c**	85
4	Ph	4-$MeOC_6H_4$	**6d**	78
5	Ph	4-MeC_6H_4	**6e**	79
6	Ph	4-ClC_6H_4	**6f**	80
7	Ph	4-$O_2NC_6H_4$	**6g**	87
8	2-MeC_6H_4	Me	**6h**	91
9	2-MeC_6H_4	*t*-Bu	**6i**	85
10	2-MeC_6H_4	4-$MeOC_6H_4$	**6j**	76
11	2-MeC_6H_4	4-MeC_6H_4	**6k**	83
12	2-MeC_6H_4	4-ClC_6H_4	**6l**	78
13	2-MeC_6H_4	4-BrC_6H_4	**6m**	72
14	3,5-$(Me)_2C_6H_3$	Me	**6n**	92
15	3,5-$(Me)_2C_6H_3$	4-$MeOC_6H_4$	**6o**	70
16	3,5-$(Me)_2C_6H_3$	4-MeC_6H_4	**6p**	88
17	3,5-$(Me)_2C_6H_3$	4-ClC_6H_4	**6q**	91

[a] The reactions were carried out with 0.5 mmol of each reaction partner at 180 °C in sealed tubes under microwave irradiation; see Experimental Section for details. [b] Isolated yield.

method allows the preparation of a polyfunctional pyrazolo[1,5-*a*]pyrimidine scaffold containing the amino and aryldiazenyl groups. Therefore, these hetarylazo derivatives could be used as intermediates for the synthesis of biologically active N-fused heteroaromatic compounds. The structures of the novel synthesized compounds **6a−q** were determined by NMR, and these results correlate with our previous work in the synthesis and characterization of **6c**, by both NMR and X-ray crystallography.[15] In this synthetic work, we have placed a strong emphasis on sustainable chemistry which resulted in a protocol where (a) no purification is required, (b) water is produced as unique byproduct, (c) the reaction time is very short, and in general (d) the process is highly efficient.

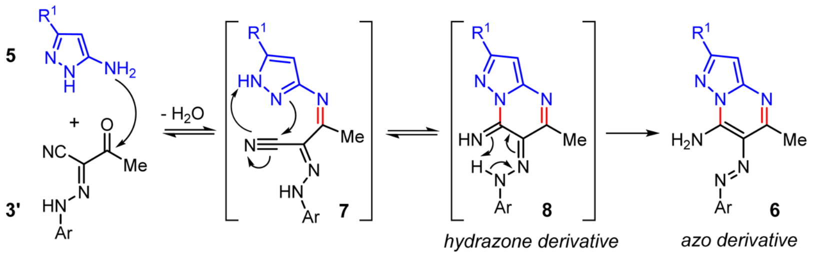
On the basis of the aforementioned results and literature precedents,[9,10] a plausible mechanism was proposed for the generation of the pyrazolo[1,5-*a*]pyrimidin-7-amines, as depicted in Scheme 3. It starts with the condensation of *β*-ketonitrile **3′** with exocyclic amino group of the pyrazole **5** to form the imine intermediate **7**. An intramolecular nucleophilic attack by the NH group of the pyrazole on the nitrile carbon atom occurs to form the cyclized intermediate **8**. Finally, the tautomerization of the hydrazone-imine intermediate **8** to the stable azo-enamine tautomer would explain the formation of **6** as the only product.

Recently, pyridone and pyrimidine derivatives have attracted considerable interest as N-heterocyclic intermediates for the preparation of hetarylazo dyes.[6,19c] Moreover, the applications of azo-dyes are strongly dependent on the photophysical properties of azo-hydrazone tautomerism (i.e., as structures **6** or **8** respectively, see Scheme 3). The above observations have motivated us to carry out a preliminary studies of the solvatochromic properties for all azo-dyes **6a−q** in various organic solvents with different dipole moment parameters (see Supporting Information, Table 1). The absorption spectra of those 6-(aryldiazenyl)pyrazolo[1,5-*a*]pyrimidin-7-amines **6a−q** were studied in the range of 200−800 nm, in organic solvents with different dipole moment parameters (ε_r) such as polar-aprotic: DMF (36.7); polar-protic: EtOH (24.5); and nonpolar: CH_2Cl_2 (8.93). We found that the absorption spectra of these hetarylazo dyes indicated a regular variation with the polarity of solvents. In general, the red-shifting (bathochromic shift) of λ_{max} ocurrs with the increase of dipole moment parameters (ε_r) of the solvents. Nevertheless, the phenomenon is different in the case of dichloromethane, which can be explained by interactions between the chlorine atoms and the hetarylazo dyes.[19c]

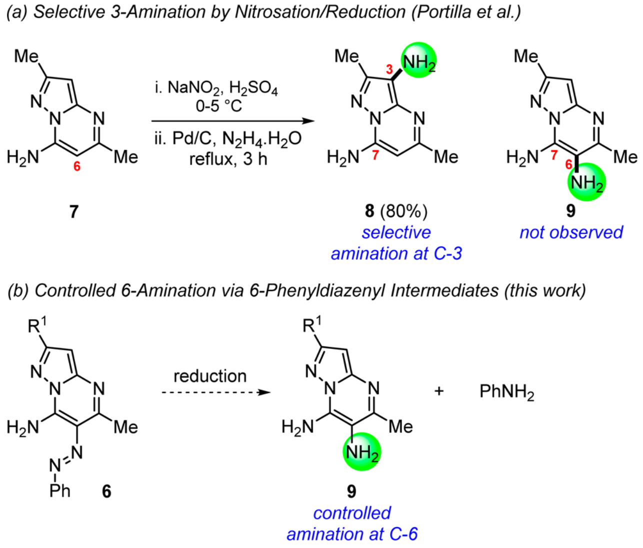
Once 7-amino-6-(aryldiazenyl)pyrazolo[1,5-*a*]pyrimidines **6** were obtained and due to the importance of 1,2-diamines as synthetic intermediate of pharmacologically active heterocyclic compounds, we developed an operationally simple method to convert the 6-aryldiazenyl group of **6** in an 6-amino group in order to generate the 1,2-diamine functionality. To justify the use of derivatives **6** as strategic intermediates to 6,7-diamino derivatives **9**, we refer to our previous work where the nitrosation of 2,5-dimethylpyrazolo[1,5-*a*]pyrimidin-7-amine **7** and subsequent reduction of the nitroso group produced the undesired 3,7-diamine **8** instead of the 6,7-diamine **9** (Scheme 4a).[21] Those results can be explained by the better nucleophilicity at the C-3 position due to the high electronic density of the *π*-excedent pyrazole ring. Therefore, we planned the palladium-catalyzed reductive cleavage of azocompounds **6** in order to reach the desire heteroaromatic 1,2-diamine scaffold (Scheme 4b).

Gratifyingly, we found that the reductive azo bond cleavage was achieved at 60 °C under an H_2 atmosphere at ambient pressure using Pd/C as catalyst in ethanol, giving the expected heteroaromatic 1,2-diamine **9a** in 90% yield with the full recovery of aniline (Scheme 5). Pleasingly, the overall synthesis of pyrazolo[1,5-*a*]pyrimidine-6,7-diamines (**9**) was shown to be efficient in the presence of various substituents such as methyl, *t*-butyl, and phenyl groups at pyrazole ring (**9a−c**, Scheme 5).

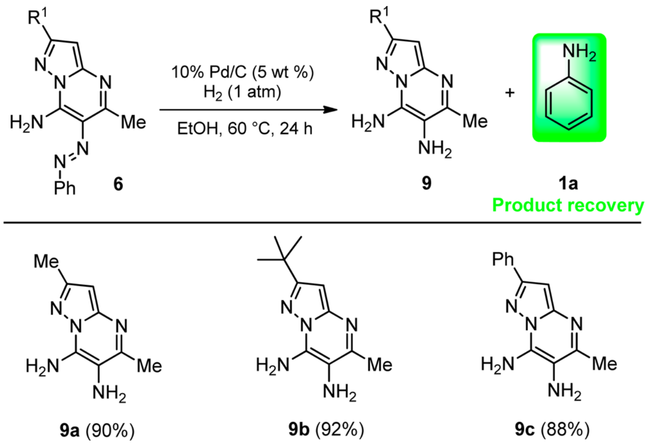
Scheme 3. Plausible Mechanism for the Formation of Pyrazolo[1,5-*a*]pyrimidin-7-amines **6**



Scheme 4. Selective Amination in 7-Aminopyrazolo[1,5-*a*]pyrimidines



Scheme 5. Reductive Cleavage of Azocompounds into Heteroaromatic 1,2-Diamines by Pd/C–H_2 System[a]



[a] Reaction conditions: hetarylazo dye **6** (2.0 mmol) and 10% Pd/C (5 wt %) under an H_2 atmosphere at ambient pressure in EtOH (10 mL) at 60 °C for 24 h.

It is important to emphasize that aniline is recovered as the unique byproduct, as the reaction is carried out in relatively low temperatures and in the absence of acids. Therefore, this method is attractive and advantageous in organic synthesis to obtain 1,2-diamines. In addition, this is a new methodology not reported up to now that allows the efficient access to these heteroaromatic building blocks.

Subsequently, we examined the synthesis of bioactive N-heterocycles from those heteroaromatic 1,2-diamines **9**. Although great endeavors have been devoted to the synthesis of purine-fused polycyclic derivatives, the structural diversity of azolo derivatives is still very limited.[22] Given the need for developing efficient and expeditious methods to prepare structurally diverse purine-fused tricyclic derivatives, the synthesis of multisubstituted pyrazolo[5,1-*b*]purines was tried. As shown in the Scheme 6, the microwave-assisted cyclocondensation of pyrazolo[1,5-*a*]pyrimidine-6,7-diamines **9** with various orthoesters **10** provided the desired products **11a**–**e** in good to excellent yields (81–96%). To further evaluate the scope of this methodology, additional studies are currently underway to expand the range of 5-amino-1*H*-azoles containing triazole, imidazole, and pyrrole ring as well as to study the synthesis of 1,4-diazepine derivatives via the cyclocondensation of pyrazolo[1,5-*a*]pyrimidine-6,7-diamines **9** with 1,3-bis-electrophiles.

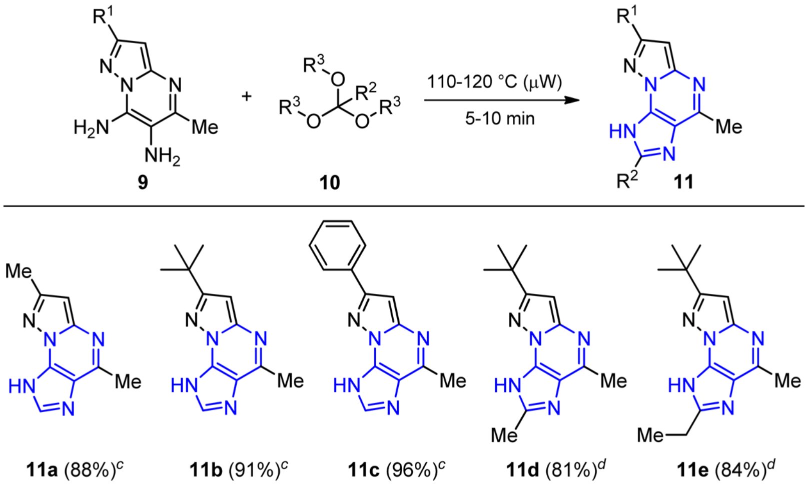
■ CONCLUSIONS

In summary, the 1,3-bis-electrophiles α-arylhydrazinylidene-β-ketonitriles were characterized by spectroscopic analysis and single-crystal X-ray diffraction analysis, which evidence the hydrazone-keto tautomer **3′** as the predominant form in the solid state, whereas in solution the azo-enol tautomer **3** is the major form. Notably, we have developed a regioselective solvent-free microwave-assisted reaction to prepare functionalized pyrazolo[1,5-*a*]pyrimidin-7-amines containing an aryldiazenyl group in good to excellent yields with the formation of two new C–N bonds in one step, by reacting 5-amino-1*H*-pyrazoles and 2-(2-arylhydrazinylidene)-3-oxobutanenitriles. In addition, it is important to mention that this reaction is environmentally sustainable and highly atom economical, producing water as the unique byproduct under solvent-free conditions. Furthermore, we have successfully developed a palladium-catalyzed reductive cleavage method at ambient pressure of hetarylazo compounds, affording pyrazolo[1,5-*a*]pyrimidine-6,7-diamines in good yields. Pleasingly, the pyrazolo[1,5-*a*]pyrimidine-6,7-diamine products readily engage in cyclocondensation reactions with various orthoesters for the synthesis of structurally diverse pyrazolo[5,1-*b*]purines in yields up to 96% by using microwave irradiation. Notably, these tricyclic derivatives were obtained in four reaction steps (diazotization/cyclization/reduction/cyclization) starting from aniline in 60–70% overall yield. This methodology constitutes a new approach to generate tricyclic heteroaromatic systems, and we expect that postmodification strategies could be useful in medicinal chemistry toward the synthesis of novel drug candidates.

■ EXPERIMENTAL SECTION

General Information. All reagents were purchased from commercial sources and used without further purification, unless otherwise noted. All starting materials were weighed and handled in air at room temperature. The reactions were monitored by TLC visualized by UV lamp (254 or 365 nm) and/or with *p*-anisaldehyde and H_2SO_4 in EtOH. Column chromatography was performed on silica gel (70–230 mesh). Reactions under microwave irradiation were performed in oven-dried 10.0 mL sealable Pyrex tubes equipped with a Teflon coated stirring bar (obtained from CEM). All reactions under microwave irradiation (ν = 2.45 GHz) were performed in a CEM Discover 1-300W system equipped with a built-in pressure measurement sensor. NMR spectra were recorded at 400 MHz (^{1}H) and 100 MHz (^{13}C) at 298 K using tetramethylsilane (0 ppm) as the internal reference. NMR spectroscopic data were recorded in $CDCl_3$ or [D_6]DMSO using as internal standards the residual nondeuteriated signal for ^{1}H NMR and the deuteriated solvent signal for ^{13}C NMR spectroscopy. DEPT spectra were used for the assignment of carbon signals. Chemical shifts (δ) are given in ppm, and coupling constants (*J*) are given in Hz. The following abbreviations are used for multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, and m = multiplet. Melting points were collected using a capillary melting point apparatus and are uncorrected. IR spectra were recorded on a FT-IR spectrophotometer using KBr discs. Spectra are reported in frequency of absorption in cm^{-1}, and only selected resonances are reported. Mass spectra were recorded with a spectrometer (with a direct inlet probe) operating at 70 eV. High-

Scheme 6. Novel Approach to Substituted Pyrazolo[5,1-*b*]purines[a,b]



[a]Reaction conditions: heteroaromatic 1,2-diamine **9** (0.5 mmol) and orthoester **10** (0.6 mmol); see Supporting Information for detail. [b]Isolated yields are shown. [c]Reaction performed at 110 °C for 5 min. [d]Reaction performed at 120 °C for 10 min.

resolution mass spectra (HRMS) were recorded using a Q-TOF spectrometer via electrospray ionization (ESI). UV−vis absorption spectra were recorded in 1 cm cuvettes. Crystallographic data were recorded on a diffractometer using graphite-monochromated Mo Kα radiation (λ= 0.71073 Å). Structures were solved by direct methods in SHELXS-97.[24] Compounds **3**/**3′** and **5** were prepared by protocols reported in the literature.[11b,23]

General Procedure for the Synthesis of 2-(2-Arylhydrazinylidene)-3-oxo-butanenitrile 3′. A solution of the aniline derivate **1a**−**c** (20.0 mmol) was cooled at 0−5 °C, and concentrated hydrochloric acid (20.0 mL) was slowly added. An aqueous solution of sodium nitrite (20.0 mmol in 10.0 mL of water) was added slowly into the cooled stirred aniline-hydrochloride solution. 3-Aminobut-2-enenitrile (**2**, 20.0 mmol) and sodium acetate (4.0 g, 48.0 mmol) were dissolved in 10.0 mL of 50% aqueous ethanol. The solution was placed in an ice bath to cool it to 0−5 °C. To this solution, the diazotized solution was added slowly with constant stirring for 30 min. The pH of the mixture was maintained at 5−6 by adding an aqueous solution of sodium acetate (4%). A bright yellow color precipitation started to appear. The reaction mixture was stirred at room temperature for additional 2 h. The resulting precipitate was filtered, washed with cold water, dried, and recrystallized from ethanol−water to give the pure compound as a mixture of the tautomeric forms **3**/**3′**.

3-Oxo-2-(2-phenylhydrazinylidene)butanenitrile ***3′a***. Following the general procedure, the reaction of aniline (**1a**, 1.82 mL, 20.0 mmol) and 3-aminobut-2-enenitrile (**2**, 1642 mg, 20.0 mmol) afforded the desired product as a yellow solid (3292 mg, 88%) and as mixtures of azo-enol and hydrazone-keto tautomers (69:31 ratio) after silica gel purification. Mp 159−161 °C (amorphous) (Lit. 168 °C).[17] Recrystallization of **3′a** from methanol afforded crystalline yellow prisms suitable for X-ray diffraction analysis.[18] FTIR: ν = 3229 (N−H), 3060, 2213 (C≡N), 1644 (C═O), 1540 (N═C) cm^{-1}. Azo-enol tautomer **3a**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.50 (s, 3H), 7.21−7.45 (m, 5H), 14.75 (br s, 1H, O−H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ = 28.1 (CH_3), 112.0 (C), 116.5 (CH), 117.1 (C), 126.9 (CH), 129.7 (CH), 140.5 (C), 194.1 (C) ppm. Hydrazone-keto tautomer **3′a**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.50 (s, 3H), 7.21−7.45 (m, 5H), 9.44 (br s, 1H, N−H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ = 24.5 (CH_3), 109.7 (C), 115.7 (CH), 117.1 (C), 125.8 (CH), 129.8 (CH), 140.3 (C), 191.8 (C) ppm. HRMS (ESI+): calcd for $C_{10}H_{10}N_3O^+$ 188.0824 [M + H]$^+$; found 188.0824. These NMR data matched previously reported data.[17]

3-Oxo-2-(ortho-tolylhydrazinylidene)butanenitrile ***3′b***. Following the general procedure, the reaction of *ortho*-methylaniline (**1b**, 2.14 mL, 20.0 mmol) and 3-aminobut-2-enenitrile (**2**, 1642 mg, 20.0 mmol) afforded the desired product as an orange solid (3338 mg, 83%) and as mixtures of azo-enol and hydrazone-keto tautomers (83:17 ratio) after silica gel purification. Mp 112−114 °C (amorphous) (Lit. 151 °C).[17] FTIR: ν = 3242 (N−H), 3075, 2217 (C≡N), 1640 (C═O), 1533 (N═C) cm^{-1}. Azo-enol tautomer **3b**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.38 (s, 3H), 2.52 (s, 3H), 7.12−7.32 (m, 3H), 7.74 (d, *J* = 7.5 Hz, 1H), 14.97 (br s, 1H, O−H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ = 16.7 (CH_3), 28.0 (CH_3), 112.6 (C), 115.5 (CH), 117.2 (C), 125.6 (C), 126.8 (CH), 127.7 (CH), 131.0 (CH), 138.8 (C), 194.1 (C) ppm. Hydrazone-keto tautomer **3′b**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.41 (s, 3H), 2.50 (s, 3H), 7.12−7.32 (m, 3H), 7.55 (d, *J* = 7.5 Hz, 1H), 9.20 (br s, 1H, N−H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ = 16.6 (CH_3), 24.5 (CH_3), 109.6 (C), 115.6 (CH), 116.7 (C), 124.3 (C), 125.6 (CH), 127.7 (CH), 131.4 (CH), 138.7 (C), 191.7 (C) ppm. HRMS (ESI+): calcd for $C_{11}H_{12}N_3O^+$ 202.0980 [M + H]$^+$; found 202.0988. These NMR data matched previously reported data.[17]

3-Oxo-2-(2,6-dimethylphenylhydrazinylidene)butanenitrile ***3′c***. Following the general procedure, the reaction of 3,5-dimethylaniline (**1c**, 2.49 mL, 20.0 mmol) and 3-aminobut-2-enenitrile (**2**, 1642 mg, 20.0 mmol) afforded the desired compound as an orange solid (3657 mg, 85%) and as mixtures of azo-enol and hydrazone-keto tautomers (71:29 ratio) after silica gel purification. Mp 153−156 °C (amorphous). FTIR: ν = 3215 (N−H), 3066, 2215 (C≡N), 1651 (C═O), 1528 (N═C) cm^{-1}. Azo-enol tautomer **3c**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.33 (s, 6H), 2.48 (s, 3H), 6.88 (s, 1H), 7.02 (s, 2H), 14.69 (br s, 1H, O−H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ = 21.2 (CH_3), 28.0 (CH_3), 111.6 (C), 114.3 (CH), 117.3 (C), 128.9 (CH), 139.7 (C), 140.4 (C), 194.0 (C) ppm. Hydrazone-keto tautomer **3′c**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.35 (s, 6H), 2.50 (s, 3H), 6.85 (s, 1H), 6.95 (s, 2H), 9.40 (br s, 1H, N−H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ = 21.3 (CH_3), 24.6 (CH_3), 113.1 (C), 113.6 (CH), 115.3 (C), 127.7 (CH), 139.8 (C), 140.5 (C), 192.0 (C) ppm. HRMS (ESI+): calcd for $C_{12}H_{14}N_3O^+$ 216.1137 [M + H]$^+$; found 216.1145.

General Procedure for the Synthesis of 2-Substituted-7-amino-6-(aryldiazenyl)-5-methylpyrazolo[1,5-*a*]pyrimidines 6a−s. A mixture of 2-(2-arylhydrazinylidene)-3-oxo-butanenitrile (**3′a**−**c**, 0.5 mmol) and 5-amino-1*H*-pirazole (**5a**−**j**, 0.5 mmol) was irradiated with microwaves at 180−220 °C for 4 min in a sealed tube containing a Teflon-coated magnetic stirring bar. The resulting reaction mixture was cooled to 55 °C, and the precipitated product formed upon the addition of cold ethanol (2.0 mL) was filtered off, washed, and dried to give the pure product **6**.

(E)-7-Amino-2,5-dimethyl-6-(phenyldiazenyl)pyrazolo[1,5-a]-pyrimidine ***6a***. The general procedure at 180 °C for 4 min with **3′a** (94 mg, 0.50 mmol) and **5a** (49 mg, 0.50 mmol) afforded product **6a**

as a yellow solid (114 mg, 86%). Mp 231–233 °C (amorphous). FTIR (KBr): ν = 3274 (N–H), 1623 (C=N), 1454 (N=N) cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 2.41 (s, 3H), 2.73 (s, 3H), 6.24 (s, 1H), 7.41 (t, J = 7.3 Hz,1H), 7.52 (t, J = 7.5 Hz, 2H), 7.83 (d, J = 7.5 Hz, 2H), 9.11 (br s, 1H), 10.25 (br s, 1H) ppm. ^{13}C{^{1}H} NMR (100 MHz, [D$_6$]DMSO): δ = 13.7 (CH$_3$), 21.1 (CH$_3$), 95.3 (CH), 116.3 (C), 120.7 (CH), 128.6 (CH), 128.6 (CH), 138.9 (C), 147.6 (C), 152.1 (C), 155.4 (C), 160.0 (C) ppm. HRMS (ESI+): calcd for $C_{14}H_{15}N_6^+$ 267.1358 [M + H]$^+$; found 267.1387.

(E)-7-Amino-2-tert-butyl-5-methyl-6-(phenyldiazenyl)pyrazolo-[1,5-a]pyrimidine ***6b***. The general procedure at 180 °C for 4 min with **3′a** (100 mg, 0.53 mmol) and **5b** (74 mg, 0.53 mmol) afforded product **6b** as a yellow solid (154 mg, 94%). Mp 152–154 °C (amorphous). FTIR (KBr): ν = 3229 (N–H), 1616 (C=N), 1485 (N=N) cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.38 (s, 9H), 2.75 (s, 3H), 6.35 (s, 1H), 7.42 (t, J = 7.5 Hz, 1H), 7.54 (t, J = 7.5 Hz, 2H), 7.84 (d, J = 7.7 Hz, 2H), 8.70 (br s, 1H), 10.23 (br s, 1H) ppm. ^{13}C{^{1}H} NMR (100 MHz, [D$_6$]DMSO): δ = 21.1 (CH$_3$), 29.4 (CH$_3$), 32.1 (C), 92.2 (CH), 115.9 (C), 120.7 (CH), 128.5 (CH), 128.6 (CH), 138.9 (C), 147.3 (C), 152.1 (C), 159.8 (C), 168.3 (C) ppm. HRMS (ESI+): calcd for $C_{17}H_{21}N_6^+$ 309.1828 [M + H]$^+$; found 309.1846.

(E)-7-Amino-5-methyl-2-phenyl-6-(phenyldiazenyl)pyrazolo[1,5-a]pyrimidine ***6c***. The general procedure at 180 °C for 4 min with **3′a** (97 mg, 0.52 mmol) and **5c** (83 mg, 0.52 mmol) afforded product **6c** as a yellow-orange solid (145 mg, 85%). Mp 152–154 °C (amorphous). Recrystallization of this material from *N*,*N*-dimethylformamide afforded orange crystals suitable for X-ray diffraction analysis.[15] FTIR (KBr): ν = 3381 (N–H), 1618 (C=N), 1457 (N=N) cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 2.78 (s, 3H), 6.93 (s, 1H), 7.41–7.56 (m, 6H), 7.86 (d, J = 7.5 Hz, 2H), 8.08 (d, J = 7.5 Hz, 2H), 9.00 (br s, 1H), 10.28 (br s, 1H) ppm. ^{13}C{^{1}H} NMR (100 MHz, [D$_6$]DMSO): δ = 21.2 (CH$_3$), 92.7 (CH), 116.8 (C), 120.8 (CH), 125.8 (CH), 128.0 (CH), 128.5 (CH), 128.6 (CH), 128.7 (CH), 132.0 (C), 139.0 (C), 148.0 (C), 152.1 (C), 156.2 (C), 160.4 (C) ppm. HRMS (ESI+): calcd for $C_{19}H_{17}N_6^+$ 329.1515 [M + H]$^+$; found 329.1540.

(E)-7-Amino-2-(4-methoxyphenyl)-5-methyl-6-(phenyldiazenyl)-pyrazolo[1,5-a]pyrimidine ***6d***. The general procedure at 180 °C for 4 min with **3′a** (95 mg, 0.51 mmol) and **5d** (94 mg, 0.50 mmol) afforded product **6d** as a yellow solid (140 mg, 78%). Mp 250–252 °C (amorphous). FTIR (KBr): ν = 3442 (N–H), 1619 (C=N), 1453 (N=N) cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 2.78 (s, 3H), 3.83 (s, 3H), 6.72 (s, 1H), 7.03 (d, J = 8.1 Hz, 2H), 7.40 (t, J = 7.4 Hz, 1H), 7.51 (t, J = 7.4 Hz, 2H), 7.80 (d, J = 7.5 Hz, 2H), 7.95 (d, J = 8.1 Hz, 2H), 9.22 (br s, 2H) ppm. ^{13}C{^{1}H} NMR (100 MHz, [D$_6$]DMSO): δ = 21.0 (CH$_3$), 54.7 (OCH$_3$), 92.1 (CH), 113.8 (CH), 116.7 (C), 120.7 (CH), 124.6 (C), 127.1 (CH), 128.4 (CH), 128.6 (CH), 138.9 (C), 147.9 (C), 152.1 (C), 156.1 (C), 159.9 (C), 160.1 (C) ppm. MS (70 eV, EI): m/z (%) = 358 (100) [M]$^+$, 341 (10), 226 (16). HRMS: calcd for $C_{20}H_{18}N_6O^+$ 358.1542 [M]$^+$; found 358.1548.

(E)-7-Amino-5-methyl-2-(4-methylphenyl)-6-(phenyldiazenyl)-pyrazolo[1,5-a]pyrimidine ***6e***. The general procedure at 180 °C for 4 min with **3′a** (90 mg, 0.48 mmol) and **5e** (83 mg, 0.48 mmol) afforded product **6e** as a yellow solid (130 mg, 79%). Mp 214–216 °C (amorphous). FTIR (KBr): ν = 3391 (N–H), 1617 (C=N), 1451 (N=N) cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 2.37 (s, 3H), 2.77 (s, 3H), 6.89 (s, 1H), 7.31 (d, J = 8.0 Hz, 2H), 7.43 (t, J = 7.2 Hz, 1H), 7.54 (t, J = 7.2 Hz, 2H), 7.87 (d, J = 7.3 Hz, 2H), 7.98 (d, J = 8.0 Hz, 2H), 9.02 (br s, 1H), 10.27 (br s, 1H) ppm. ^{13}C{^{1}H} NMR (100 MHz, [D$_6$]DMSO): δ = 20.9 (CH$_3$), 22.0 (CH$_3$), 93.0 (CH), 116.9 (C), 121.4 (CH), 126.2 (CH), 129.2 (CH x 2), 129.3 (CH), 129.4 (C), 138.7 (C), 139.4 (C), 148.3 (C), 152.3 (C), 156.4 (C), 160.9 (C) ppm. MS (70 eV, EI): m/z (%) = 342 (100) [M]$^+$, 237 (18), 210 (13), 77 (11). HRMS: calcd for $C_{20}H_{18}N_6^+$ 342.1593 [M]$^+$; found 342.1591.

(E)-7-Amino-2-(4-chlorophenyl)-5-methyl-6-(phenyldiazenyl)-pyrazolo[1,5-a]pyrimidine ***6f***. The general procedure at 180 °C for 4 min with **3′a** (98 mg, 0.52 mmol) and **5f** (100 mg, 0.52 mmol) afforded product **6f** as a yellow-orange solid (151 mg, 80%). Mp 259–260 °C (amorphous). FTIR (KBr): ν = 3437 (N–H), 1616 (C=N), 1448 (N=N) cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 2.79 (s, 3H), 6.81 (s, 1H), 7.41 (t, J = 7.4 Hz, 1H), 7.48–7.53 (m, 4H), 7.81 (d, J = 7.4 Hz, 2H), 8.03 (d, J = 8.0 Hz, 2H), 9.27 (br s, 2H) ppm. ^{13}C{^{1}H} NMR (100 MHz, [D$_6$]DMSO): δ = 21.0 (CH$_3$), 92.7 (CH), 116.8 (C), 120.7 (CH), 127.3 (CH), 128.0 (CH), 128.4 (CH), 128.5 (CH), 130.9 (C), 133.3 (C), 138.8 (C), 148.0 (C), 152.1 (C), 154.9 (C), 160.4 (C) ppm. MS (70 eV, EI): m/z (%) = 364/362 (32/100) [M]$^+$, 259/257 (8/22), 232/230 (8/23), 77 (11). HRMS: calcd for $C_{19}H_{15}ClN_6^+$ 362.1047 [M]$^+$; found 362.1050.

(E)-7-Amino-5-methyl-2-(4-nitrophenyl)-6-(phenyldiazenyl)-pyrazolo[1,5-a]pyrimidine ***6g***. The general procedure at 180 °C for 4 min with **3′a** (100 mg, 0.53 mmol) and **5g** (106 mg, 0.52 mmol) afforded product **6g** as a yellow solid (169 mg, 87%). Mp 288–290 °C (amorphous). FTIR (KBr): ν = 3419 (N–H), 1617 (C=N), 1534 (NO$_2$), 1453 (N=N), 1353 (NO$_2$) cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 2.80 (s, 3H), 6.95 (s, 1H), 7.42 (t, J = 7.5 Hz, 1H), 7.52 (t, J = 7.3 Hz, 2H), 7.82 (d, J = 7.3 Hz, 2H), 8.23–8.32 (m, 4H), 9.34 (br s, 2H) ppm. ^{13}C{^{1}H} NMR (100 MHz, [D$_6$]DMSO): δ = 21.0 (CH$_3$), 93.6 (CH), 115.8 (C), 120.8 (CH), 123.0 (CH), 126.6 (CH), 128.4 (CH), 128.7 (CH), 138.0 (C), 138.8 (C), 147.3 (C), 148.1 (C), 152.1 (C), 153.6 (C), 160.7 (C) ppm. MS (70 eV, EI): m/z (%) = 373 (100) [M]$^+$, 356 (15), 241 (21), 77 (29). HRMS: calcd for $C_{19}H_{15}N_7O_2^+$ 373.1287 [M]$^+$; found 373.1279.

(E)-7-Amino-2,5-dimethyl-6-(2-methylphenyldiazenyl)pyrazolo-[1,5-a]pyrimidine ***6h***. The general procedure at 180 °C for 4 min with **3′b** (100 mg, 0.50 mmol) and **5a** (49 mg, 0.50 mmol) afforded product **6h** as a yellow solid (127 mg, 91%). Mp 189–190 °C (amorphous). FTIR (KBr): ν = 3421 (N–H), 1599 (C=N), 1436 (N=N) cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 2.39 (s, 3H), 2.54 (s, 3H), 2.73 (s, 3H), 6.23 (s, 1H), 7.29–7.31 (m, 2H), 7.36–7.38 (m, 1H), 7.61–7.63 (m, 1H), 9.26 (br s, 1H), 10.17 (br s, 1H) ppm. ^{13}C{^{1}H} NMR (100 MHz, [D$_6$]DMSO): δ = 14.4 (CH$_3$), 17.8 (CH$_3$), 21.8 (CH$_3$), 95.9 (CH), 114.9 (CH), 117.2 (C), 126.7 (CH), 129.0 (C), 131.1 (CH), 134.4 (CH), 139.4 (C), 147.8 (C), 150.2 (C), 155.9 (C), 160.5 (C) ppm. MS (70 eV, EI): m/z (%) = 280 (100) [M]$^+$, 175 (21), 148 (31), 91 (49). HRMS (ESI+): calcd for $C_{15}H_{17}N_6^+$ 281.1515 [M + H]$^+$; found 281.1514.

(E)-7-Amino-2-tert-butyl-5-methyl-6-(2-methylphenyldiazenyl)-pyrazolo[1,5-a]pyrimidine ***6i***. The general procedure at 180 °C for 4 min with **3′b** (104 mg, 0.52 mmol) and **5b** (72 mg, 0.52 mmol) afforded product **6i** as a yellow-orange solid (142 mg, 85%). Mp 86–88 °C (amorphous). FTIR (KBr): ν = 3435 (N–H), 1612 (C=N), 1523 (N=N) cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.39 (s, 9H), 2.62 (s, 3H), 2.93 (s, 3H), 6.34 (s, 1H), 7.24–7.34 (m, 4H), 7.69–7.71 (m, 1H), 10.41 (br s, 1H) ppm. ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ = 18.4 (CH$_3$), 21.7 (CH$_3$), 30.1 (CH$_3$), 33.1 (C), 93.2 (CH), 115.4 (CH), 117.8 (C), 126.8 (CH), 129.5 (CH), 131.1 (CH), 134.9 (C), 139.2 (C), 139.7 (C), 150.7 (C), 161.3 (C), 169.8 (C) ppm. MS (70 eV, EI): m/z (%) = 322 (100) [M]$^+$, 307 (30), 265 (18), 203 (43), 91 (38). HRMS (ESI+): calcd for $C_{18}H_{23}N_6^+$ 323.1984 [M + H]$^+$; found 323.2004.

(E)-7-Amino-2-(4-methoxyphenyl)-5-methyl-6-(2-methylphenyldiazenyl)pyrazolo[1,5-a]pyrimidine ***6j***. The general procedure at 180 °C for 4 min with **3′b** (100 mg, 0.50 mmol) and **5d** (95 mg, 0.50 mmol) afforded product **6j** as a yellow solid (141 mg, 76%). Mp 251–252 °C (amorphous). FTIR (KBr): ν = 3395 (N–H), 1606 (C=N), 1456 (N=N) cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]-DMSO): δ = 2.60 (s, 3H), 2.80 (s, 3H), 3.84 (s, 3H), 6.72 (s, 1H), 7.04 (d, J = 8.0 Hz, 2H), 7.29–7.38 (m, 3H), 7.61–7.63 (m, 1H), 7.95 (d, J = 8.0 Hz, 2H), 9.28 (br s, 2H) ppm. ^{13}C{^{1}H} NMR (100 MHz, [D$_6$]DMSO): δ = 16.9 (CH$_3$), 21.0 (CH$_3$), 54.7 (CH$_3$), 92.1 (CH), 113.7 (CH), 115.0 (CH), 117.3 (C), 124.6 (C), 125.9 (CH), 127.1 (CH), 128.3 (CH), 130.3 (CH), 133.5 (C), 138.9 (C), 147.9 (C), 150.3 (C), 156.1 (C), 159.8 (C), 160.0 (C) ppm. MS (70 eV, EI): m/z (%) = 372 (100) [M]$^+$, 357 (20), 355 (18), 253 (23), 226 (22), 91 (11). HRMS (ESI+): calcd for $C_{21}H_{21}N_6O^+$ 373.1777 [M + H]$^+$; found 373.1795.

(E)-7-Amino-5-methyl-2-(4-methylphenyl)-6-(2-methylphenyldiazenyl)pyrazolo[1,5-a]pyrimidine ***6k***. The general

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procedure at 180 °C for 4 min with **3′b** (110 mg, 0.55 mmol) and **5e** (95 mg, 0.55 mmol) afforded product **6k** as a yellow-orange solid (162 mg, 83%). Mp 242−244 °C (amorphous). FTIR (KBr): ν = 3421 (N−H), 1613 (C=N), 1456 (N=N) cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 2.38 (s, 3H), 2.61 (s, 3H), 2.80 (s, 3H), 6.77 (s, 1H), 7.27−7.38 (m, 5H), 7.61−7.64 (m, 1H), 7.92 (d, J = 8.0 Hz, 2H), 9.31 (br s, 2H) ppm. ^{13}C{^{1}H} NMR (100 MHz, [D$_6$]DMSO): δ = 16.9 (CH$_3$), 20.0 (CH$_3$), 21.0 (CH$_3$), 92.4 (CH), 115.0 (CH), 117.3 (C), 125.6 (CH), 125.9 (CH), 128.3 (CH), 128.5 (CH), 129.4 (C), 130.4 (CH), 133.6 (C), 138.0 (C), 139.0 (C), 147.9 (C), 150.3 (C), 156.3 (C), 160.1 (C) ppm. MS (70 eV, EI): m/z (%) = 356 (100) [M]$^+$, 341 (21), 237 (27), 210 (20), 91 (17). HRMS (ESI+): calcd for $C_{21}H_{21}N_6^+$ 357.1828 [M + H]$^+$; found 357.1836.

(E)-7-Amino-2-(4-chlorophenyl)-5-methyl-6-(2-methylphenyldiazenyl)pyrazolo[1,5-a]pyrimidine **6l**. The general procedure at 180 °C for 4 min with **3′b** (105 mg, 0.52 mmol) and **5f** (101 mg, 0.52 mmol) afforded product **6l** as a yellow-orange solid (152 mg, 78%). Mp 284−286 °C (amorphous). FTIR (KBr): ν = 3446 (N−H), 1610 (C=N), 1450 (N=N) cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 2.60 (s, 3H), 2.82 (s, 3H), 6.84 (s, 1H), 7.30−7.40 (m, 3H), 7.53 (d, J = 8.5 Hz, 2H), 7.61−7.65 (m, 1H), 8.05 (d, J = 8.5 Hz, 2H), 9.31 (br s, 2H) ppm. ^{13}C{^{1}H} NMR (100 MHz, [D$_6$]DMSO): δ = 16.9 (CH$_3$), 21.1 (CH$_3$), 92.7 (CH), 115.0 (CH), 117.7 (C), 126.0 (CH), 127.3 (CH), 128.0 (CH), 128.4 (CH), 128.9 (C), 130.4 (CH), 133.3 (C), 133.6 (C), 139.5 (C), 148.0 (C), 153.4 (C), 158.5 (C), 162.8 (C) ppm. MS (70 eV, EI): m/z (%) = 378/376 (33/100) [M]$^+$, 363/361 (8/25), 359 (16), 259/257 (9/20), 232/230 (9/24), 91 (18). HRMS (ESI+): calcd for $C_{20}H_{18}ClN_6^+$ 377.1281 [M + H]$^+$; found 377.1303.

(E)-7-Amino-2-(4-bromophenyl)-5-methyl-6-(2-methylphenyldiazenyl)pyrazolo[1,5-a]pyrimidine **6m**. The general procedure at 180 °C for 4 min with **3′b** (108 mg, 0.54 mmol) and **5h** (128 mg, 0.54 mmol) afforded product **6m** as a yellow-orange solid (163 mg, 72%). Mp 289−290 °C (amorphous). FTIR (KBr): ν = 3439 (N−H), 1619 (C=N), 1452 (N=N) cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 2.60 (s, 3H), 2.80 (s, 3H), 6.82 (s, 1H), 7.29−7.38 (m, 3H), 7.60−7.64 (m, 1H), 7.65 (d, J = 8.6 Hz, 2H), 7.96 (d, J = 8.6 Hz, 2H), 9.31 (br s, 2H) ppm. ^{13}C{^{1}H} NMR (100 MHz, [D$_6$]DMSO): δ = 16.9 (CH$_3$), 21.0 (CH$_3$), 92.7 (CH), 115.0 (CH), 117.4 (C), 121.7 (C), 126.0 (CH), 127.6 (CH), 128.4 (CH), 130.4 (CH), 130.9 (CH), 131.2 (C), 133.6 (C), 138.9 (C), 148.0 (C), 150.3 (C), 154.9 (C), 160.3 (C) ppm. MS (70 eV, EI): m/z (%) = 422/420 (94/100) [M]$^+$, 393/391 (12/13), 303/301 (26/27), 276/274 (19/21), 91 (21). HRMS (ESI+): calcd for $C_{20}H_{18}BrN_6^+$ 421.0776 [M + H]$^+$; found 421.0794.

(E)-7-Amino-2,5-dimethyl-6-(3,5-dimethylphenyldiazenyl)-pyrazolo[1,5-a]pyrimidine **6n**. The general procedure at 180 °C for 4 min with **3′c** (108 mg, 0.50 mmol) and **5a** (49 mg, 0.50 mmol) afforded product **6n** as a yellow solid (135 mg, 92%). Mp 265−267 °C (amorphous). FTIR (KBr): ν = 3308 (N−H), 1619, 8 (C=N), 1498 (N=N) cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.40 (s, 6H), 2.46 (s, 3H), 2.88 (s, 3H), 6.21 (s, 1H), 7.04 (br s, 2H), 7.40 (s, 2H), 10.44 (br s, 1H) ppm. ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ = 14.7 (CH$_3$), 21.3 (CH$_3$), 22.1 (CH$_3$), 96.3 (CH), 117.1 (C), 119.4 (CH), 131.2 (CH), 138.8 (C), 139.2 (C), 148.2 (C), 152.7 (C), 156.7 (C), 161.6 (C) ppm. MS (70 eV, EI): m/z (%) = 294 (100) [M]$^+$, 279 (25), 265 (28), 161 (38), 134 (19). HRMS: calcd for $C_{16}H_{18}N_6^+$ 294.1593 [M]$^+$; found 294.1591.

(E)-7-Amino-2-(4-methoxyphenyl)-5-methyl-6-(3,5-dimethylphenyldiazenyl)pyrazolo[1,5-a]pyrimidine **6o**. The general procedure at 180 °C for 4 min with **3′c** (110 mg, 0.51 mmol) and **5d** (96 mg, 0.51 mmol) afforded product **6o** as a yellow solid (138 mg, 70%). Mp 265−266 °C (amorphous). FTIR (KBr): ν = 3245 (N−H), 1617 (C=N), 1505 (N=N) cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]-DMSO): δ = 2.39 (s, 6H), 2.79 (s, 3H), 3.85 (s, 3H), 6.72 (s, 1H), 7.04−7.07 (m, 3H), 7.43 (s, 2H), 7.97 (d, J = 8.0 Hz, 2H), 9.20 (br s, 2H) ppm. ^{13}C{^{1}H} NMR (100 MHz, [D$_6$]DMSO): δ = 20.0 (CH$_3$), 20.9 (CH$_3$), 54.7 (OCH$_3$), 92.0 (CH), 113.8 (CH), 116.6 (C), 118.5 (CH), 124.6 (C), 127.1 (CH), 130.0 (CH), 137.7 (C), 138.9 (C), 148.2 (C), 152.3 (C), 156.1 (C), 159.9 (C), 160.0 (C) ppm. MS (70 eV, EI): m/z (%) = 386 (100) [M]$^+$, 371 (25), 105 (72), 77 (52). HRMS (ESI+): calcd for $C_{22}H_{23}N_6O^+$ 387.1933 [M + H]$^+$; found 387.1950.

(E)-7-Amino-5-methyl-2-(4-methylphenyl)-6-(3,5-dimethylphenyldiazenyl)pyrazolo[1,5-a]pyrimidine **6p**. The general procedure at 180 °C for 4 min with **3′c** (118 mg, 0.55 mmol) and **5e** (95 mg, 0.55 mmol) afforded product **6p** as a yellow-orange solid (179 mg, 88%). Mp 227−229 °C (amorphous). FTIR (KBr): ν = 3301 (N−H), 1614 (C=N), 1497 (N=N) cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 2.40 (s, 9H), 2.81 (s, 3H), 6.71 (s, 1H), 7.08 (s, 1H), 7.30 (d, J = 7.6 Hz, 2H), 7.42 (s, 2H), 7.90 (d, J = 7.6 Hz, 2H), 9.03 (br s, 2H) ppm. ^{13}C{^{1}H} NMR (100 MHz, [D$_6$]DMSO): δ = 19.6 (CH$_3$), 20.6 (CH$_3$), 21.5 (CH$_3$), 92.1 (CH), 116.6 (C), 118.2 (CH), 125.5 (CH), 128.2 (CH), 129.7 (CH), 130.8 (C), 137.5 (C), 137.8 (C), 138.7 (C), 148.4 (C), 152.3 (C), 156.2 (C), 159.8 (C) ppm. HRMS (ESI+): calcd for $C_{22}H_{23}N_6^+$ 371.1984 [M + H]$^+$; found 371.1995.

(E)-7-Amino-2-(4-chlorophenyl)-5-methyl-6-(3,5-dimethylphenyldiazenyl)pyrazolo[1,5-a]pyrimidine **6q**. The general procedure at 180 °C for 4 min with **3′c** (114 mg, 0.53 mmol) and **5f** (103 mg, 0.53 mmol) afforded product **6q** as a yellow solid (188 mg, 91%). Mp 254−256 °C (amorphous). FTIR (KBr): ν = 3301 (N−H), 1610 (C=N), 1502 (N=N) cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]-DMSO): δ = 2.39 (s, 6H), 2.81 (s, 3H), 6.78 (s, 1H), 7.08 (s, 1H), 7.43 (s, 2H), 7.51 (d, J = 8.5 Hz, 2H), 8.03 (d, J = 8.5 Hz, 2H), 9.11 (br s, 2H) ppm. ^{13}C{^{1}H} NMR (100 MHz, [D$_6$]DMSO): δ = 19.8 (CH$_3$), 20.7 (CH$_3$), 92.4 (CH), 116.7 (C), 118.3 (CH), 127.2 (CH), 127.8 (CH), 129.9 (CH), 130.8 (C), 133.2 (C), 137.6 (C), 138.7 (C), 147.9 (C), 152.2 (C), 154.8 (C), 160.1 (C) ppm. MS (70 eV, EI): m/z (%) = 391/389 (27/63) [M]$^+$, 376/374 (14/35), 105 (100), 77 (89). HRMS (ESI+): calcd for $C_{21}H_{20}ClN_6^+$ 391.1438 [M + H]$^+$; found 391.1457.

General Procedure for the Synthesis of 2-Substituted-5-methylpyrazolo[1,5-*a*]pyrimidine-6,7-diamines 9. A solution of 6-(aryldiazenyl)pyrazolo[1,5-*a*]pyrimidin-7-amine (6, 2.0 mmol) in EtOH (10.0 mL) was treated with 10% Pd/C (5 wt % of substrate). The reaction mixture was vigorously stirred and heated at 60 °C under an H$_2$ atmosphere at ambient pressure for 24 h. After the reaction was cooled to room temperature, the reaction mixture was filtered through a Celite pad and washed with EtOH (2 × 5.0 mL). The filtrate was evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: CH$_2$Cl$_2$/MeOH = 15:1−20:1) to give the desired heteroaromatic 1,2-diamine 9.

2,5-Dimethylpyrazolo[1,5-a]pyrimidine-6,7-diamine **9a**. Following the general procedure, the reaction of (*E*)-2,5-dimethyl-6-(phenyldiazenyl)pyrazolo[1,5-*a*]pyrimidin-7-amine (**6a**, 700 mg, 2.6 mmol) and 10% Pd/C (35 mg) in 10.0 mL of EtOH at 60 °C for 24 h afforded compound **9a** as a white solid (419 mg, 90%) after silica gel purification (CH$_2$Cl$_2$/MeOH = 20:1). Mp 165−166 °C (amorphous). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.44 (br s, 2H), 2.45 (s, 3H), 2.50 (s, 3H), 5.80 (br s, 2H), 6.13 (s, 1H) ppm. ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ = 14.5 (CH$_3$), 21.5 (CH$_3$), 93.3 (CH), 105.7 (C), 142.6 (C), 147.1 (C), 154.0 (C), 154.2 (C) ppm. HRMS (ESI+): calcd for $C_8H_{12}N_5^+$ 178.1093 [M + H]$^+$; found 178.1087.

2-(tert-Butyl)-5-methylpyrazolo[1,5-a]pyrimidine-6,7-diamine **9b**. Following the general procedure, the reaction of (*E*)-2-(*tert*-butyl)-5-methyl-6-(phenyldiazenyl)pyrazolo[1,5-*a*]pyrimidin-7-amine (**6b**, 620 mg, 2.0 mmol) and 10% Pd/C (31 mg) in 10.0 mL of EtOH at 60 °C for 24 h afforded compound **9b** as a white solid (405 mg, 92%) after silica gel purification (CH$_2$Cl$_2$/MeOH = 20:1). Mp 215−217 °C (amorphous). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.37 (s, 9H), 2.48 (s, 3H), 3.03 (br s, 2H), 6.00 (br s, 2H), 6.17 (s, 1H) ppm. ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ = 21.1 (CH$_3$), 30.4 (CH$_3$), 32.8 (C), 89.7 (CH), 105.7 (C), 142.7 (C), 146.2 (C), 153.1 (C), 167.3 (C) ppm. HRMS (ESI+): calcd for $C_{11}H_{18}N_5^+$ 220.1562 [M + H]$^+$; found 220.1580.

5-Methyl-2-phenylpyrazolo[1,5-a]pyrimidine-6,7-diamine **9c**. Following the general procedure, the reaction of (*E*)-5-methyl-2-phenyl-6-(phenyldiazenyl)pyrazolo[1,5-*a*]pyrimidin-7-amine (**6c**, 700 mg, 2.1 mmol) and 10% Pd/C (35 mg) in 10.0 mL of EtOH at 60 °C for 24 h afforded compound **9c** as a white solid (448 mg, 88%) after silica gel purification (CH_2Cl_2/MeOH = 15:1). Mp 158−159 °C (amorphous). ^1H NMR (400 MHz, [D_6]DMSO): δ = 2.38 (s, 3H), 3.85 (br s, 2H), 6.63 (s, 1H), 7.10 (br s, 2H), 7.35 (t, J = 7.5 Hz, 1H), 7.45 (t, J = 7.7 Hz, 2H), 8.01 (d, J = 7.5 Hz, 2H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, [D_6]DMSO): δ = 21.0 (CH_3), 88.6 (CH), 110.6 (C), 125.7 (CH), 128.0 (CH), 128.4 (CH), 133.5 (C), 136.8 (C), 144.9 (C), 148.2 (C), 152.4 (C) ppm. HRMS (ESI+): calcd for $C_{13}H_{14}N_5^+$ 240.1249 [M + H]$^+$; found 240.1258.

General Procedure for the Synthesis of Substituted Pyrazolo[5,1-*b*]purines 11. A mixture of heteroaromatic 1,2-diamine **9** (0.5 mmol) and orthoester **10** (0.6 mmol) was irradiated with microwaves at 110−120 °C for 5−10 min in a sealed tube containing a Teflon-coated magnetic stirring bar. The resulting reaction mixture was cooled to 55 °C by airflow and directly purified by column chromatography on silica gel (eluent: CH_2Cl_2/MeOH = 15:1−25:1) to give the pure product **11**.

*4,7-Dimethyl-1H-pyrazolo[5,1-b]purine **11a**.* Following the general procedure at 110 °C for 5 min for the reaction with 2,5-dimethylpyrazolo[1,5-*a*]pyrimidine-6,7-diamine (**9a**, 90 mg, 0.51 mmol) and trimethyl orthoformate (**10a**, 112 μL, 1.02 mmol), compound **11a** was obtained as a white solid (84 mg, 88%) after silica gel purification (CH_2Cl_2/MeOH = 15:1). Mp > 300 °C (amorphous). ^1H NMR (400 MHz, [D_6]DMSO): δ = 2.44 (s, 3H), 2.70 (s, 3H), 6.34 (s, 1H), 8.18 (s, 1H), 13.10 (br s, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, [D_6]DMSO): δ = 13.3 (CH_3), 19.6 (CH_3), 94.1 (CH), 116.8 (C), 139.5 (CH), 141.8 (C), 146.2 (C), 147.0 (C), 150.7 (C) ppm. HRMS (ESI+): calcd for $C_9H_{10}N_5^+$ 188.0936 [M + H]$^+$; found 188.0934.

*7-(tert-Butyl)-4-methyl-1H-pyrazolo[5,1-b]purine **11b**.* Following the general procedure at 110 °C for 5 min for the reaction with 2-(*tert*-butyl)-5-methylpyrazolo[1,5-*a*]pyrimidine-6,7-diamine (**9b**, 110 mg, 0.50 mmol) and trimethyl orthoformate (**10a**, 114 μL, 1.04 mmol), compound **11b** was obtained as a white solid (104 mg, 91%) after silica gel purification (CH_2Cl_2/MeOH = 20:1). Mp > 300 °C (amorphous). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.35 (s, 9H), 2.79 (s, 3H), 6.52 (s, 1H), 8.28 (s, 1H), 14.71 (br s, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 21.2 (CH_3), 30.6 (CH_3), 32.8 (C), 92.9 (CH), 117.2 (C), 140.4 (CH), 142.2 (C), 147.4 (C), 147.6 (C), 166.2 (C) ppm. HRMS (ESI+): calcd for $C_{12}H_{16}N_5^+$ 230.1406 [M + H]$^+$; found 230.1414.

*4-Methyl-7-phenyl-1H-pyrazolo[5,1-b]purine **11c**.* Following the general procedure at 110 °C for 5 min for the reaction with 5-methyl-2-phenylpyrazolo[1,5-*a*]pyrimidine-6,7-diamine (**9c**, 120 mg, 0.50 mmol) and trimethyl orthoformate (**10a**, 107 μL, 0.98 mmol), compound **11c** was obtained as a white solid (120 mg, 96%) after silica gel purification (CH_2Cl_2/MeOH = 25:1). Mp 297−298 °C (amorphous). ^1H NMR (400 MHz, [D_6]DMSO): δ = 2.72 (s, 3H), 7.10 (s, 1H), 7.38 (t, J = 7.5 Hz, 1H), 7.48 (t, J = 7.7 Hz, 2H), 8.05 (d, J = 7.5 Hz, 2H), 8.44 (s, 1H), 13.78 (br s, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, [D_6]DMSO): δ = 20.7 (CH_3), 92.7 (CH), 117.0 (C), 125.8 (CH), 128.2 (CH), 128.7 (CH), 133.2 (C), 141.3 (CH), 142.0 (C), 147.4 (C), 147.7 (C), 152.7 (C) ppm. HRMS (ESI+): calcd for $C_{14}H_{12}N_5^+$ 250.1093 [M + H]$^+$; found 250.1100.

*7-(tert-Butyl)-2,4-dimethyl-1H-pyrazolo[5,1-b]purine **11d**.* Following the general procedure at 120 °C for 10 min for the reaction with 2-(*tert*-butyl)-5-methylpyrazolo[1,5-*a*]pyrimidine-6,7-diamine (**9b**, 110 mg, 0.50 mmol) and triethyl orthoacetate (**10b**, 111 μL, 0.61 mmol), compound **11d** was obtained as a white solid (98 mg, 81%) after silica gel purification (CH_2Cl_2/MeOH = 25:1). Mp 118−119 °C (amorphous). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.34 (s, 9H), 2.56 (s, 3H), 2.70 (s, 3H), 6.45 (s, 1H) ppm, NH is absent. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 15.1 (CH_3), 20.7 (CH_3), 30.5 (CH_3), 32.8 (C), 91.9 (CH), 117.4 (C), 143.0 (C), 146.2 (C), 146.9 (C), 152.2 (C), 166.3 (C) ppm. HRMS (ESI+): calcd for $C_{13}H_{18}N_5^+$ 244.1562 [M + H]$^+$; found 244.1590.

*7-(tert-Butyl)-2-ethyl-4-methyl-1H-pyrazolo[5,1-b]purine **11e**.* Following the general procedure at 120 °C for 10 min for the reaction with 2-(*tert*-butyl)-5-methylpyrazolo[1,5-*a*]pyrimidine-6,7-diamine (**9b**, 100 mg, 0.46 mmol) and triethyl orthopropionate (**10c**, 111 μL, 0.55 mmol), compound **11e** was obtained as a white solid (99 mg, 84%) after silica gel purification (CH_2Cl_2/MeOH = 25:1). Mp 113−114 °C (amorphous). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.19 (t, J = 7.1 Hz, 3H), 1.32 (s, 9H), 2.69 (s, 3H), 2.89 (q, J = 7.1 Hz, 2H), 6.44 (s, 1H) ppm, NH is absent $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 11.9 (CH_3), 20.7 (CH_3), 22.6 (CH_2), 30.5 (CH_3), 32.8 (C), 91.8 (CH), 117.1 (C), 143.2 (C), 146.4 (C), 146.7 (C), 157.4 (C), 166.2 (C) ppm. HRMS (ESI+): calcd for $C_{14}H_{20}N_5^+$ 258.1719 [M + H]$^+$; found 258.1730.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02431.

Crystallographic data for compound **3′a** (CIF)
Copies of ^1H and $^{13}C\{^1H\}$ NMR spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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