JOC The Journal of Organic Chemistry

Article

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One-Step Synthesis of Fully Functionalized Pyrazolo[3,4-*b*]pyridines via Isobenzofuranone Ring Opening

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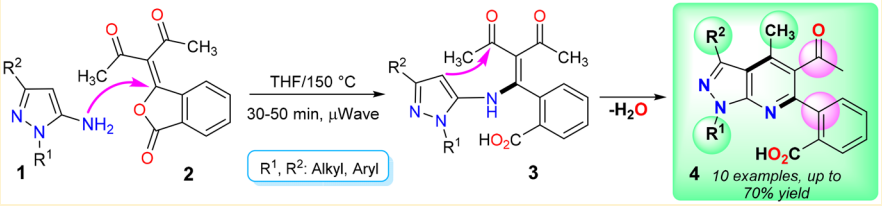
Supporting Information



ABSTRACT: A novel series of fully substituted pyrazolo[3,4-*b*]pyridines **4** has been prepared in a regioselective manner by the microwave-assisted reaction between *N*-substituted 5-aminopyrazoles **1** and 3-(3-oxo-2-benzofuran-1(3*H*)-ylidene)pentane-2,4-dione (**2**). This is the second reported example of a cyclocondensation reaction using substrate **2** as a 1,3-bis-electrophilic reagent. Remarkably, this synthesis offers functionalized products with acetyl and carboxyl groups in one step, in good yields, and with short reaction times. Additionally, the cyclization intermediate **3** was isolated, allowing us to postulate a mechanism for this reaction, which is initiated via isobenzofuranone ring opening of **2** in a Michael-type reaction. The structures of the products and regioselectivity of the reactions were determined on the basis of NMR measurements and X-ray diffraction. For this new reaction using substrate **2**, the optimal reaction conditions and its scope were investigated.

INTRODUCTION

The development of efficient procedures for the synthesis of highly functionalized *N*-heterocycles is an important area of research in organic and medicinal chemistry[1] because the functional groups may increase the scope and applicability of such compounds.[2] Pyrazolo[3,4-*b*]pyridine derivatives are fused *N*-heterocycles of biomedical importance and have been extensively studied for their broad spectrum of biological activities.[2] For example, the anxiolytic drug Tracazolate (**I**), amide derivative (**II**) (a potent inhibitor of glycogen synthase kinase-3 (GSK-3)), and analgesic *N*-acylhydrazone (**III**) have this structural motif, as well as diverse functional groups (Figure 1).[3−5]

Likewise, *N*-heterocyclic compounds containing acetyl or benzoic acid moieties are of special interest in both organic synthetic transformations and medicinal chemistry.[6] These groups can be converted into heterocyclic chalcones, hydrazones, amides, alcohols, and esters among other important functional groups. Therefore, the biological effect of such postfunctionalized compounds, as well as other possible applications, would be enhanced.[7]

Many different approaches have been described for the synthesis of pyrazolo[3,4-*b*]pyridine derivatives.[8] Among the reported methods, the reaction between *N*-substituted 5-aminopyrazoles and 1,3-bis-electrophilic compounds has been widely used for the preparation of these compounds.[8d−h] However, there are also some examples where the synthesis was carried out in a regioselective manner using aminopyrazoles without substituents on the ring-nitrogen atom but with α,β-unsaturated carbonyl compounds such as 1,3-bis-electrophile generated in situ.[8a−c] Notably, these three-component reactions usually provide dihydroderivatives of pyrazolo[3,4-*b*]pyridines. However, it is important to note that there are very few reports addressing the direct synthesis of functionalized pyrazolo[3,4-*b*]pyridines.[9] The existing methods used to obtain these conveniently functionalized heterocycles have several limitations, such as the use of multistep syntheses and therefore moderate global yields, poor availability of starting materials, tedious workup, long reaction times, and specialized reaction conditions (catalysts, additives, etc.).[9] These facts, along with our interest in the development of efficient protocols for the synthesis of novel nitrogen-containing heterocyclics,[10] have inspired us to develop a metal-free microwave-assisted method to synthesize a series of functionalized pyrazolo[3,4-*b*]pyridines **4** (Scheme 1b, right). For example, in a previous work, we carried out the regioselective synthesis of novel polyfunctionally substituted pyrazolo[1,5-*a*]pyrimidines **6** under solvent-free conditions, using 3-(3-oxo-2-benzofuran-1(3*H*)-ylidene)-pentane-2,4-dione (**2**) and 5-aminopyrazoles **5** that lack substituents on the ring nitrogen (*NH*-3-aminopyrazoles) as 1,3-bis-nucleophiles. This is the first report of cyclocondensation reactions using **2** as the substrate (Scheme 1a, left).[11]

Received: September 29, 2017
Published: November 10, 2017

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DOI: 10.1021/acs.joc.7b02471
J. Org. Chem. 2017, 82, 12674−12681

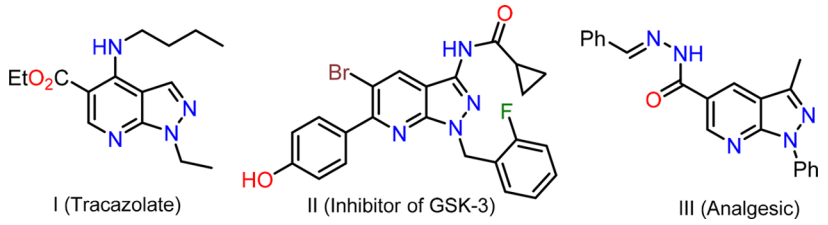
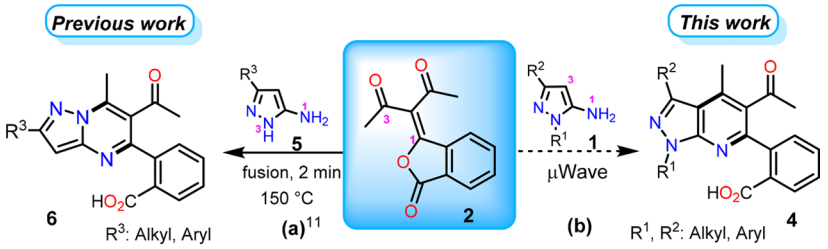


Figure 1. Drugs based on functionalized pyrazolo[3,4-*b*]pyridines.

Scheme 1. Synthesis of Pyrazolo[1,5-*a*]pyrimidines 6 and Pyrazolo[3,4-*b*]pyridines 4



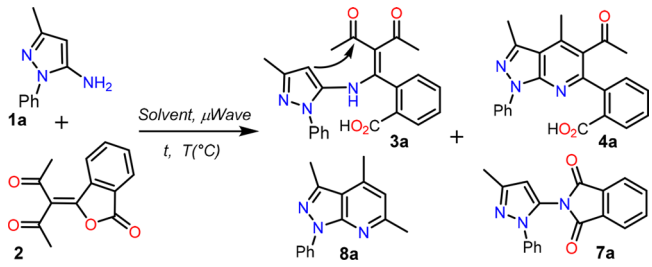
RESULTS AND DISCUSSION

Given our previous results regarding the synthesis of pyrazolo-[1,5-*a*]pyrimidines **6**, we sought to expand the scope of reaction using different *N*-substituted 5-aminopyrazoles **1** since our previous work was based on the good reactivity of *NH*-3-aminopyrazoles **5** toward alkoxymethylene-*β*-dicarbonyl compounds.[11,12] Therefore, we envisaged that the reaction between **1** and substrate **2** could be used to synthesize fully functionalized pyrazolo[3,4-*b*]pyridines **4** (Scheme 1b, right). It is important to note that heteroaryl amines **1** are less reactive than **5** toward alkoxymethylene-*β*-dicarbonyl compounds.[12,13] However, both heteroaryl amines **1** and **5** have proved to be very successful substrates for cyclocondensation reactions with *α*,*β*-unsaturated carbonyl compounds for the synthesis of pyrazolo[3,4-*b*]pyridines.[8a,b,14] In this context, we proposed to use microwave-assisted organic synthesis (MAOS) via a specialized reactor to control the relationship between reaction conditions and the fusion procedure. In addition, MAOS has been recognized as a valuable tool to ease some of the bottlenecks in the drug discovery process and the development of other valuable products due to its proven operational efficiency.[15]

Consequently, we started our work by examining the reaction of 5-amino-3-methyl-1-phenylpyrazole (**1a**, 0.50 mmol) with an equimolar amount of substrate **2** to optimize this chemical transformation (see Table 1). Initially, we observed that the reactions under conventional heating did not lead to the expected pyrazolo[3,4-*b*]pyridine **4a**. In the fusion procedure, decomposition was observed when the reaction mixture was heated at 150 °C for 2 min, and when the reaction was heated to reflux in different solvents (THF, EDC, EtOH, H_2O, toluene, or DMF) for 4 h, the reaction did not proceed. Subsequently, the use of microwave irradiation at 100 °C for 2 min under solvent-free conditions led to the expected product **4a** in 27% yield; however, *N*-pyrazolylphthalimide **7a** was isolated as a byproduct, and at higher temperatures, a complex mixture of products was observed by TLC analysis (Table 1, entries 1 and 2).

We continue our study using microwave irradiation and solvents such as THF, EDC, EtOH, H_2O, toluene, DMF, and HOAc at temperatures between 90 and 150 °C for 30 min

Table 1. Optimization of the Synthesis of the Pyrazolo[3,4-*b*]pyridine 4a[a]



entry	solvents or additives	*T* (°C)	time (min)	yields (%) 3a	4a	7a	8a
1		100	2		27	18	
2		150	2				
3	THF	90	30	72			
4	THF	120	30	45	28		
5	THF	150	30		62	10	12
6	EDC	150	30	25			
7	EtOH	150	30	31			
8	H_2O	150	30		25		11
9	toluene	150	30		27	17	
10	DMF	150	30		21		15
11	HOAc	150	30		41	22	18
12	THF/$FeCl_3$[b]	150	30		58		
13	THF/$CuCl_2$[b]	150	30		55		
14	THF/$InCl_3$[b]	150	30		60		
15	silica gel[c]	80	60		43	14	
16	THF/Et_3N[d]	150	30		28		
17	THF/KOH[d]	150	30		47		
18	THF/K_2CO_3[d]	150	30		52		

[a]Reaction conditions: **1** (0.5 mmol) and **2** (0.5 mmol) in 1.0 mL of a solvent under microwave irradiation. [b]$FeCl_2$, $CuCl_2$, and $InCl_3$ were used as Lewis acid catalysts (10 wt %). [c]Silica gel (0.1 g, 70−230 mesh) was used as a solid support and catalyst. [d]Et_3N, KOH, and K_2CO_3 were used as catalysts (10 wt %).

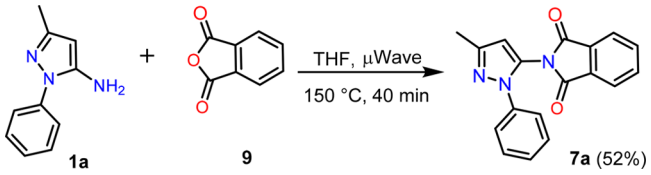
(Table 1, entries 3−11). Interestingly, the reaction at 90 °C in THF provided cyclization intermediate **3a** in good yields, and while at 120 °C, the desired product **4a** was obtained along

DOI: 10.1021/acs.joc.7b02471
J. Org. Chem. 2017, 82, 12674−12681

with **3a** but in poor yield (Table 1, entries 3 and 4). When the reaction was run at 150 °C in THF, intermediate **3a** was not isolated, and the desired product **4a** was obtained in good yield together with the byproducts **7a** and **8a** (Table 1, entry 5). In addition, reactions in other solvents with higher boiling points and different polarities afforded worse results than in tetrahydrofuran (Table 1, entries 6–11). In fact, we tested the reaction using iron, copper, and indium salts as Lewis catalysts, and even silica gel as a solid support and catalyst, but there was no improvement under these acidic conditions (Table 1, entries 12–15). Similarly, when basic catalysis was used (Et_3N, KOH, or K_2CO_3), the results did not improve in any way (Table 1, entries 16–18). In general, these results showed that higher temperatures tend to favor the formation of the desired product **4a** along with a mixture of the byproducts **7a** and **8a**. Likewise, using THF as a solvent in the absence of a catalyst provided the best results. The byproducts **7a** and **8a** were obtained from the reaction between aminopyrazole **1a** with the products (phthalic anhydride and acetylacetone) of the hydrolysis of substrate **2**.

It is important to mention that the *N*-pyrazolylphthalimide **7a** was also obtained from the reaction between 5-amino-3-methyl-1-phenylpyrazole (**1a**) and phthalic anhydride (**9**), under conditions analogous to those previously optimized for the synthesis of **4a** (Scheme 2). These results are important

Scheme 2. Synthesis of 2-(3-Methyl-1-phenyl-1*H*-pyrazol-5-yl)isoindoline-1,3-dione (7a)[a]



[a]Reaction conditions: **1a** (1.00 mmol) and **9** (1.00 mmol) in THF (2.0 mL).

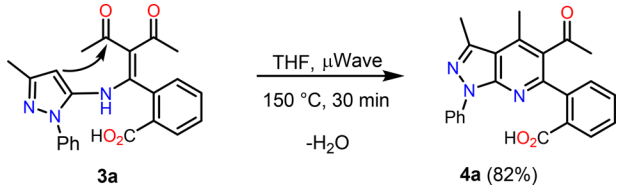
because they allowed us to corroborate the hydrolysis of substrate **2** and to obtain the *N*-hetarylphthalimide **7a**, which has been isolated by other less efficient procedures.[16] Notably, phthalimides are suitable protective groups to primary amines.[17] Structures of **3a**, **4a**, **7a**, and **8a** were confirmed by ^{1}H NMR, ^{13}C NMR, and mass spectroscopy.

At this stage of our study, we carried out the cyclo-condensation reaction of the isolated intermediate **3a** (Table 1, entry 3) under conditions similar to those of the direct synthesis of **4a** starting from reagents **1a** and **2** (Table 1, entry 5). In that reaction, microwave irradiation of compound **3a** for 30 min at 150 °C in THF, led to the formation of the expected pyrazolo[3,4-*b*]pyridine **4a** in a high yield (Scheme 3). This result confirmed that the reaction proceeds through **3** as an intermediate with the subsequent loss of a water molecule.

With the optimized reaction conditions in hand (Table 1, entry 5), we then examined the scope of the reaction with a variety of *N*-substituted 5-aminopyrazoles (**1a–j**). The results are summarized in Scheme 4.

In general, the microwave-assisted reaction of substrate **2a** with a wide range of substituted 5-aminopyrazoles **1a–j** chemoselectively and regioselectively afforded pyrazolo[3,4-*b*]pyridines **4a–j** in moderate to good yields. Almost no loss of efficiency was observed when the hetarylamines were tested, which indicated that the electronic demands of the substituents

Scheme 3. Synthesis of the Product 4a Starting from Intermediate 3a[a]



[a]Reaction conditions: **3a** (0.25 mmol) in THF (0.6 mL).

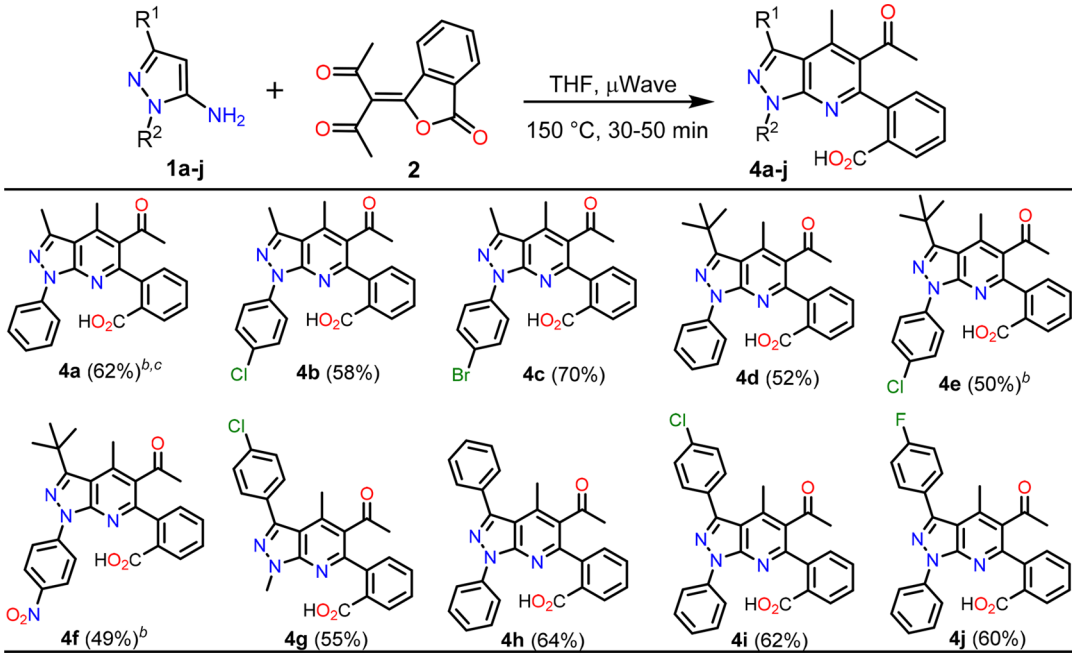
had little influence on the reactivity. Although, it should be noted that, when 3-*tert*-butyl-5-aminopyrazoles **1d–f** were used, the reaction afforded the lowest yields toward the formation of the corresponding pyrazolo[3,4-*b*]pyridines **4d–f** (49–52% yields). We hypothesized that steric effect was responsible for this observation, which could be explained by a reaction mechanism involving an intermediate analogous to **3a** (see Table 1 and Scheme 3). Therefore, we decided to carry out the reaction between 3-*tert*-butyl-5-aminopyrazole (**1d**) and the freshly synthesized substrate **11**[11a] to determine the importance of the steric effects. 1,3-Bis-electrophile **11** possesses greater steric hindrance due to the presence of aromatic rings instead of methyl groups. Remarkably, the reaction at 160 °C for 50 min in THF provided intermediate **12** instead of the expected pyrazolo[3,4-*b*]pyridine **13**; even under higher reaction temperatures (180–220 °C), no cyclization was achieved (Scheme 5).

Additionally, when 3-aminopyrazole **5a**, which is not substituted at the ring-nitrogen, was reacted with substrate **2** under conditions similar to those used for the synthesis of **4a**, another interesting result was observed. The expected pyrazolo[1,5-*a*]pyridine **6a**[11] was isolated in a better yield and after a shorter reaction time than what was seen for the synthesis of products **4a–j**. In addition, the formation of byproducts was not observed, and the reaction proceeded with better control of the conditions relative to our previous work[11] (Scheme 6). Therefore, these findings allowed us to confirm that *N*-substituted 5-aminopyrazoles **1** are less reactive than *NH*-3-aminopyrazoles **5** toward substrate **2** and analogous systems.[11−13]

Gratifyingly, the structures of pyrazolo[3,4-*b*]pyridines **4a**, **4b**, **4g**, and **4j**, as well as the structure of the isolated intermediate **3a**, were solved by single-crystal X-ray diffraction analysis.[18] (See the Supporting Information for details of structural and supramolecular information.) Structures were solved using an iterative algorithm, subsequently completed by difference Fourier map, and refined using the program SHELXL2014.[19a,b] From the analysis of the crystallographic results, we can conclude that the crystal structure of the compounds **4a**, **4b**, **4g**, and **4f** shows that the pyrazolo[3,4-*b*]pyridine moiety is distorted in all cases, leaving its constituent atoms in a nearly but not completely planar conformation. The least-squares planes that contain the respective pyrazole and pyridine moieties have dihedral angles between them of 2.51(15)°, 2.33(19)°, 3.49(12)°, and 4.52(16)° for each compound. Considering the different substituents on the fused ring and the fact that, in some of the compounds (**4a**, **4b**, and **4f**), the solvent molecules crystallized in the asymmetric unit, the distortion might be influenced by packing effects. In the supramolecular assembly of these compounds, including the isolated intermediate **3a**, similar hydrogen

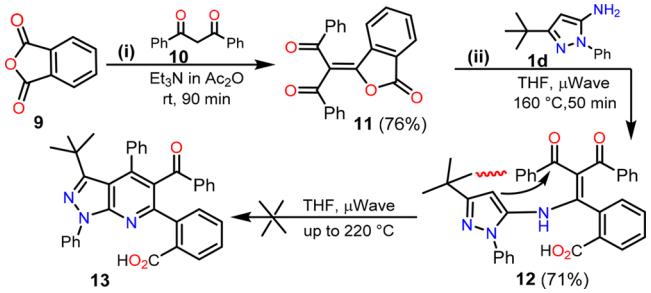
DOI: 10.1021/acs.joc.7b02471
J. Org. Chem. 2017, 82, 12674−12681

Scheme 4. Microwave-Assisted Synthesis of Pyrazolo[3,4-*b*]pyridines 4a–j[a,b,c]



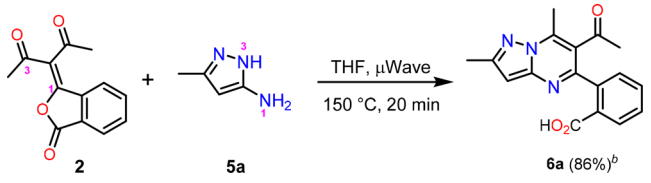
[a]Reaction conditions: **1** (0.50 mmol) and **2** (0.50 mmol) in THF (1.0 mL). [b]Phthalimides **7a**, **7e**, and **7f** were isolated as byproducts at 10%, 16%, and 15% yields, respectively. [c]Pyrazolo[3,4-*b*]pyridine **8a** was isolated as a byproduct in 12% yield. (See the Experimental Section for details.)

Scheme 5. Synthesis of Intermediate 12[a]



[a]Reaction conditions: (i) **9** (2.50 mmol) and **10** (2.50 mmol), Et_3N (0.7 mL, 5.02 mmol) in Ac_2O (1.5 mL, 15.87 mmol) and (ii) **11** (0.50 mmol) and **1d** (0.50 mmol) in THF (1 mL).

Scheme 6. Synthesis of the Pyrazolo[1,5-*a*]pyrimidine 6a[a]



[a]Reaction conditions: **2** (0.50 mmol) and **5a** (0.50 mmol) in THF (1.0 mL).

interactions control the three-dimensional array: O—H···O, C—H··· (O, N), and C—H···π, for instance. In general, it is possible that molecules that tend to have less distortion and that substituents with least-squares planes that form small dihedral angles with the main plane of the fused-ring core tend to crystallize with high symmetry. (See Tables S1–S10 and Figures S1–S5.)

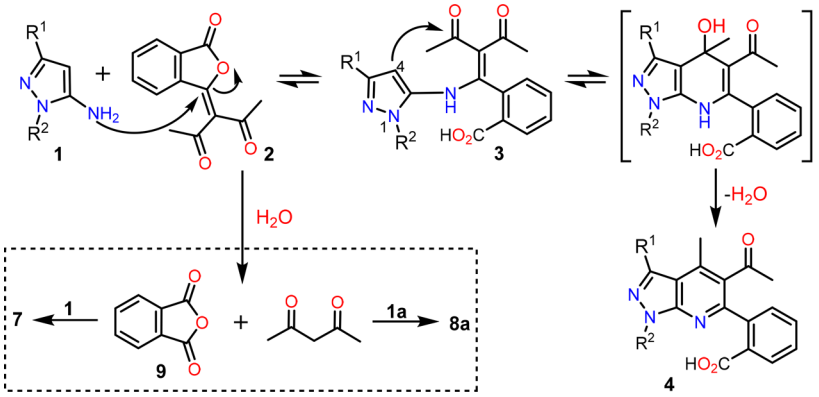
On the basis of the aforementioned results, a plausible mechanism was proposed for the generation of pyrazolo[3,4-*b*]pyridines **4a–j**, and it is depicted in Scheme 7. It starts with a Michael-type nucleophilic addition of the NH_2 group on the pyrazole moiety of **1** to the C=C bond of substrate **2** with intramolecular ring opening of the furanone moiety to regioselectively form the isolated intermediate **3**. Subsequently, an intramolecular nucleophilic attack by the carbon atom at position 4 of the pyrazolic moiety to a carbonyl group afforded a dihydropyridine intermediate; this was followed by an elimination of a water molecule to form the desired compounds **4**. The formation of the byproducts **7** and **8a** involves the hydrolysis of substrate **2** under the optimized reaction conditions.

CONCLUSIONS

In summary, we have developed a novel regioselective protocol for preparing a series of fully substituted and biologically promising pyrazolo[3,4-*b*]pyridines **4** in 49–70% yields. Remarkably, short reaction times were observed under microwave conditions using tetrahydrofuran as the solvent in all reactions. It is worth noting that intermediate **3a** and its structural analogue **12** were isolated in good yields, which corroborated that the reaction proceeds through these *β*-enaminones. The results obtained allowed us to establish that the steric effect in the reagents and the temperature are important factors in determining the course of the reaction. All synthesized compounds were characterized by spectroscopic analysis, and the structures of some products (**4a**, **4b**, **4g**, and **4j**) and intermediate **3a** were confirmed by single-crystal X-ray diffraction analysis. This methodology is the second example of cyclization using the valuable substrate **2**, and it could be used to synthesize other polyfunctionally substituted heterocyclic compounds starting from other hetarylamines or even arylamines. Therefore, we expect to extend the use of this methodology by exploring the reactions with other heterocyclic amines.

DOI: 10.1021/acs.joc.7b02471
J. Org. Chem. 2017, 82, 12674–12681

Scheme 7. Plausible Mechanism for the Formation of Pyrazolo[3,4-*b*]pyrimidines 4



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 using a UV lamp (254 or 365 nm) and/or with *p*-anisaldehyde and H_2SO_4 in EtOH. Flash chromatography was performed on silica gel (230−400 mesh). All reactions under microwave irradiation were performed using a sealed reaction vessel (10 mL, max pressure = 300 psi) containing a Teflon-coated stir bar (obtained from CEM). Microwave-assisted reactions were performed in a CEM Discover SP focused microwave (ν = 2.45 GHz) reactor equipped with a built-in pressure measurement sensor and a vertically focused IR temperature sensor. Controlled temperature, power, and time settings were used for all reactions. 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 DMSO-d_6 using the residual nondeuterated signal as the internal standard for ^{1}H NMR and the deuterated solvent signal as the internal standard for ^{13}C NMR spectroscopy. DEPT spectra were used to assign the carbon signals. Chemical shifts (δ) were given in ppm, and coupling constants (J) were given in Hz. The following abbreviations were used for multiplicities: s = singlet, d = doublet, t = triplet, and m = multiplet. Melting points were determined using a capillary melting point apparatus and were uncorrected. High-resolution mass spectra (HRMS) were recorded using a Q-TOF spectrometer via electrospray ionization (ESI). Crystallographic data were recorded on a diffractometer using graphite-monochromated Mo Kα radiation (λ = 0.710 73 Å). Structures were solved using an iterative algorithm,[19a] subsequently completed by a difference Fourier map, and refined using the program SHELXL2014,[19b] and the graphic material was prepared using the Mercury 3.8 software.[19c] *N*-Substituted 5-aminopyrazoles **1a−j**[20] and 3-(3-oxo-2-benzofuran-1(3*H*)-ylidene)pentane-2,4-dione (**2**)[11a] were prepared using known procedures.

Synthesis and Characterization. *General Procedure for the Synthesis of 2-(5-Acetyl-1,3,4-triR-1H-pyrazolo[3,4-b]pyridin-6-yl)-benzoic Acids **4a−j**.* An equimolar mixture (0.50 mmol) of the corresponding *N*-substituted 5-aminopyrazole **1** and 3-(3-oxo-2-benzofuran-1(3*H*)-ylidene)pentane-2,4-dione (**2**, 115 mg, 0.50 mmol) in THF (1.0 mL) was subjected to microwave irradiation at 150 °C (160 W, monitored by an IR temperature sensor) and maintained at this temperature for 30−50 min in a sealed tube containing a Teflon-coated magnetic stir bar. The resulting reaction mixture was cooled to 55 °C by airflow and concentrated under reduced pressure, and the residue was directly purified by flash chromatography on silica gel (eluent = CH_2Cl_2/CH_3OH 40:1) to afford pure product **4**. Recrystallization of **4** from *N*,*N*-dimethylformamide afforded monocrystals suitable for X-ray diffraction analysis of **4a**, **4b**, **4g**, and **4j**.

*2-(5-Acetyl-3,4-dimethyl-1-phenyl-1H-pyrazolo[3,4-b]pyridin-6-yl)benzoic Acid (**4a**).* By following the general procedure at 150 °C and by maintaining that temperature for 30 min in the reaction with 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**1a**, 87 mg, 0.50 mmol), pyrazolopyridine **4a** was obtained as a white solid (119 mg, 62%). Mp 267−268 °C. Recrystallization of **4a** from DMF afforded crystalline colorless prisms suitable for X-ray diffraction analysis. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.06 (s, 3H), 2.68 (s, 3H), 2.78 (s, 3H), 7.26−7.30 (m, 2H), 7.49 (t, J = 8.7 Hz, 2H), 7.58−764 (m, 2H), 7.91 (m, 1H), 8.17 (d, J = 8.7 Hz, 2H), 12.9 (br s, 1H) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 15.3 (CH_3), 15.7 (CH_3), 32.0 (CH_3), 114.5 (C), 120.2 (CH), 125.6 (CH), 129.0 (CH), 129.1 (CH), 129.8 (CH), 130.5 (CH), 130.9 (CH), 131.6 (C), 132.7 (C), 138.8 (C), 139.6 (C), 140.5 (C), 143.9 (C), 148.8 (C), 155.6 (C), 168.6 (C), 204.6 (C) ppm. HRMS (ESI+): calcd for $C_{23}H_{20}N_3O_3^+$, 386.1505 [M + H]$^+$; found, 386.1507.

*2-(5-Acetyl-1-(4-chlorophenyl)-3,4-dimethyl-1H-pyrazolo[3,4-b]-pyridin-6-yl)benzoic Acid (**4b**).* By following the general procedure at 150 °C and by maintaining that temperature for 40 min in the reaction with 1-(4-chlorophenyl)-3-methyl-1*H*-pyrazol-5-amine (**1b**, 104 mg, 0.50 mmol), pyrazolopyridine **4b** was obtained as a white solid (122 mg, 58%). Mp 281−282 °C. Recrystallization of **4b** from DMF afforded crystalline colorless prisms suitable for X-ray diffraction analysis. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.05 (s, 3H), 2.67 (s, 3H), 2.77 (s, 3H), 7.28 (m, 1H), 7.55 (d, J = 9.0 Hz, 2H), 7.62 (m, 2H), 7.91 (m, 1H), 8.22 (d, J = 9.0 Hz, 2H) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 15.5 (CH_3), 15.9 (CH_3), 32.1 (CH_3), 114.8 (C), 121.5 (CH), 129.2 (CH), 129.4 (CH), 129.9 (CH), 130.6 (CH), 131.1 (CH), 132.0 (C), 132.9 (C), 134.1 (C), 137.7 (C), 139.5 (C), 140.9 (C), 144.6 (C), 148.9 (C), 155.7 (C), 168.7 (C), 204.7 (C) ppm. HRMS (ESI+): calcd for $C_{23}H_{19}ClN_3O_3^+$, 420.1115 [M + H]$^+$; found, 420.1123.

*2-(5-Acetyl-1-(4-bromophenyl)-3,4-dimethyl-1H-pyrazolo[3,4-b]-pyridin-6-yl)benzoic Acid (**4c**).* By following the general procedure at 150 °C and by maintaining that temperature for 40 min in the reaction with 1-(4-bromophenyl)-3-methyl-1*H*-pyrazol-5-amine (**1c**, 126 mg, 0.50 mmol), pyrazolopyridine **4c** was obtained as a white solid (92 mg, 70%). Mp 267−268 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.05 (s, 3H), 2.67 (s, 3H), 2.77 (s, 3H), 7.28 (m, 1H), 7.61 (m, 2H), 7.67 (d, J = 9.0 Hz, 2H), 7.91 (m, 1H), 8.16 (d, J = 9.0 Hz, 2H), 12.93 (br s, 1H) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 15.3 (CH_3), 15.7 (CH_3), 32.0 (CH_3), 114.8 (C), 117.6 (C), 121.7 (CH), 129.2 (CH), 129.7 (CH), 130.5 (CH), 130.9 (CH), 131.8 (C), 131.9 (CH), 132.7 (C), 138.1 (C), 139.4 (C), 140.7 (C), 144.4 (C), 148.8 (C), 155.7 (C), 168.5 (C), 204.4 (C) ppm. HRMS (ESI+): calcd for $C_{23}H_{19}BrN_3O_3^+$, 464.0610 [M + H]$^+$; found, 464.0619.

*2-(5-Acetyl-3-(tert-butyl)-4-methyl-1-phenyl-1H-pyrazolo[3,4-b]-pyridin-6-yl)benzoic Acid (**4d**).* By following the general procedure at 150 °C and by maintaining that temperature for 40 min in the reaction with 3-(*tert*-butyl)-1-phenyl-1*H*-pyrazol-5-amine (**1d**, 108 mg, 0.50 mmol), pyrazolopyridine **4d** was obtained as a white solid (111 mg, 52%). Mp 229−230 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.63 (s, 9H), 2.08 (s, 3H), 2.82 (s, 3H), 7.15 (t, J = 7.5 Hz, 1H), 7.32 (d, J = 7.1 Hz, 1H), 7.37 (t, J = 7.6 Hz, 2H), 7.48 (m, 2H), 7.88 (d, J = 7.1 Hz, 1H),

DOI: 10.1021/acs.joc.7b02471
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8.17 (d, J = 7.7 Hz, 2H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 20.4 (CH_3), 30.8 ((CH_3)$_3$), 32.5 (CH_3), 34.1 (C), 114.4 (C), 121.2 (CH), 125.6 (CH), 128.8 (CH), 128.9 (CH), 130.7 (CH), 130.9 (C), 131.4 (CH), 131.7 (CH), 132.2 (C), 139.3 (C), 139.4 (C), 140.2 (C), 150.1 (C), 153.6 (C), 154.2 (C), 172.2 (C), 206.8 (C) ppm. HRMS (ESI+): calcd for $C_{26}H_{26}N_3O_3^+$, 428.1974 [M + H]$^+$; found, 428.1971.

*2-(5-Acetyl-3-(tert-butyl)-1-(4-chlorophenyl)-4-methyl-1H-pyrazolo[3,4-b]pyridin-6-yl)benzoic Acid (**4e**).* By following the general procedure at 150 °C and by maintaining that temperature for 40 min in the reaction with 3-(*tert*-butyl)-1-(4-chlorophenyl)-1*H*-pyrazol-5-amine (**1e**, 125 mg, 0.50 mmol), pyrazolopyridine **4e** was obtained as a yellow solid (115 mg, 50%). Mp 190−191 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 1.61 (s, 9H), 2.12 (s, 3H), 2.82 (s, 3H), 7.32 (m, 3H), 7.52 (m, 2H), 7.87 (m, 1H), 8.14 (d, J = 8.9 Hz, 2H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 20.4 (CH_3), 30.6 ((CH_3)$_3$), 32.6 (CH_3), 34.1 (C), 114.5 (C), 122.0 (CH), 128.8 (CH), 129.1 (CH), 130.6 (CH), 131.4 (CH), 131.7 (CH), 132.2 (C), 136.6 (C), 137.8 (C), 139.7 (C), 139.9 (C), 143.8 (C), 145.8 (C), 149.9 (C), 153.6 (C), 154.5 (C), 172.4 (C), 206.8 (C) ppm. HRMS (ESI+): calcd for $C_{26}H_{25}ClN_3O_3^+$, 462.1584 [M + H]$^+$; found, 462.1592.

*2-(5-Acetyl-3-(tert-butyl)-4-methyl-1-(4-nitrophenyl)-1H-pyrazolo[3,4-b]pyridin-6-yl)benzoic Acid (**4f**).* By following the general procedure at 150 °C and by maintaining that temperature for 50 min in the reaction with 3-(*tert*-butyl)-1-(4-nitrophenyl)-1*H*-pyrazol-5-amine (**1f**, 130 mg, 0.50 mmol), pyrazolopyridine **4f** was obtained as a yellow solid (116 mg, 49%). Mp 253−254 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 1.64 (s, 9H), 2.12 (s, 3H), 2.83 (s, 3H), 7.36 (d, J = 7.3 Hz, 1H), 7.55 (m, 2H), 7.92 (d, J = 7.2 Hz, 1H), 8.22 (d, J = 9.2 Hz, 2H), 8.54 (d, J = 9.2 Hz, 2H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 20.4 (CH_3), 30.5 ((CH_3)$_3$), 32.4 (CH_3), 34.3 (C), 115.5 (C), 119.9 (CH), 124.7 (CH), 129.3 (CH), 130.6 (C), 130.7 (CH), 131.4 (CH), 132.0 (CH), 132.6 (C), 133.2 (C), 139.9 (C), 144.2 (C), 144.4 (C), 150.9 (C), 154.0 (C), 156.2 (C), 171.3 (C), 206.2 (C) ppm. HRMS (ESI+): calcd for $C_{26}H_{25}N_4O_5^+$, 473.1825 [M + H]$^+$; found, 473.1838.

*2-(5-Acetyl-3-(4-chlorophenyl)-1,4-dimethyl-1H-pyrazolo[3,4-b]-pyridin-6-yl)benzoic Acid (**4g**).* By following the general procedure at 150 °C and by maintaining that temperature for 30 min in the reaction with 3-(4-chlorophenyl)-1-methyl-1*H*-pyrazol-5-amine (**1g**, 104 mg, 0.50 mmol), pyrazolopyridine **4g** was obtained as a yellow solid (115 mg, 55%). Mp 261−262 °C. Recrystallization of **4g** from DMF afforded crystalline yellow prisms suitable for X-ray diffraction analysis. ^1H NMR (400 MHz, $CDCl_3$): δ 2.03 (s, 3H), 2.36 (s, 3H), 4.11 (s, 3H), 7.37 (d, J = 7.4 Hz, 12H), 7.46 (d, J = 8.4 Hz, 2H), 7.52−7.61 (m, 4H), 8.02 (d, J = 8.4 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 17.2 (CH_3), 32.2 (CH_3), 34.0 (CH_3), 112.7 (C), 128.6 (CH), 129.1 (CH), 130.5 (C), 131.0 (CH), 131.2 (CH), 131.3 (CH), 132.0 (C), 132.1 (CH), 132.3 (C), 134.8 (C), 140.2 (C), 140.5 (C), 144.2 (C), 149.6 (C), 155.4 (C), 170.6 (C), 205.6 (C) ppm. HRMS (ESI+): calcd for $C_{23}H_{19}ClN_3O_3^+$, 420.1115 [M + H]$^+$; found, 420.1124.

*2-(5-Acetyl-4-methyl-1,3-diphenyl-1H-pyrazolo[3,4-b]pyridin-6-yl)benzoic Acid (**4h**).* By following the general procedure at 150 °C and by maintaining that temperature for 50 min in the reaction with 1,3-diphenyl-1*H*-pyrazol-5-amine (**1h**, 118 mg, 0.50 mmol), pyrazolopyridine **4h** was obtained as a white solid (143 mg, 64%). Mp 239−240 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 2.08 (s, 3H), 2.39 (s, 3H), 7.17 (t, J = 7.3 Hz, 1H), 7.37 (m, 3H), 7.50−7.56 (m, 5H), 7.70 (m, 2H), 7.92 (d, J = 7.3 Hz, 1H), 8.18 (d, J = 7.9 Hz, 2H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 17.2 (CH_3), 32.3 (CH_3), 114.5 (C), 121.4 (CH), 128.4 (CH), 128.8 (CH), 128.9 (CH), 129.1 (CH), 130.0 (CH), 130.7 (CH), 130.9 (C), 131.4 (CH), 131.8 (CH), 132.4 (C), 133.5 (C), 139.0 (C), 140.4 (C), 141.1 (C), 147.1 (C), 149.1 (C), 155.1 (C), 172.4 (C), 205.6 ppm. HRMS (ESI+): calcd for $C_{28}H_{22}N_3O_3^+$, 448.1661 [M + H]$^+$; found, 448.1669.

*2-(5-Acetyl-3-(4-chlorophenyl)-4-methyl-1-phenyl-1H-pyrazolo-[3,4-b]pyridin-6-yl)benzoic Acid (**4i**).* By following the general procedure at 150 °C and by maintaining that temperature for 50 min in the reaction with 3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-5-amine (**1i**, 135 mg, 0.50 mmol), pyrazolopyridine **4i** was obtained as a white solid (149 mg, 62%). Mp 166−167 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 2.09 (s, 3H), 2.38 (s, 3H), 7.15 (t, J = 7.3 Hz, 1H), 7.34 (m, 3H), 7.48−7.56 (m, 4H), 7.66 (d, J = 8.2 Hz, 2H), 7.92 (d, J = 7.3 Hz, 1H), 8.12 (d, J = 8.0 Hz, 2H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 17.3 (CH_3), 32.3 (CH_3), 114.3 (C), 121.4 (CH), 128.7 (CH), 128.9 (CH), 129.2 (CH), 130.6 (CH), 130.8 (C), 131.3 (CH), 131.4 (CH), 131.9 (CH), 132.0 (C), 132.5 (C), 133.2 (C), 138.8 (C), 140.3 (C), 140.8 (C), 145.8 (C), 149.1 (C), 155.2 (C), 172.4 (C), 205.4 ppm. HRMS (ESI+): calcd for $C_{28}H_{21}ClN_3O_3^+$, 482.1271 [M + H]$^+$; found, 482.1268.

*2-(5-Acetyl-3-(4-fluorophenyl)-4-methyl-1-phenyl-1H-pyrazolo-[3,4-b]pyridin-6-yl)benzoic Acid (**4j**).* By following the general procedure at 150 °C and by maintaining that temperature for 50 min in the reaction with 3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-5-amine (**1j**, 127 mg, 0.50 mmol), pyrazolopyridine **4j** was obtained as a white solid (140 mg, 60%). Mp 222−223 °C. Recrystallization of **4j** from DMF afforded crystalline colorless prisms suitable for X-ray diffraction analysis. ^1H NMR (400 MHz, $CDCl_3$): δ 2.08 (s, 3H), 2.37 (s, 3H), 7.14−7.24 (m, 3H), 7.35 (m, 3H), 7.49−7.56 (m, 2H), 7.69 (m, 2H), 7.92 (d, J = 7.0 Hz, 1H), 8.14 (d, J = 7.7 Hz, 2H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 17.2 (CH_3), 32.3 (CH_3), 114.3 (C), 115.4/115.6 (CH, d, J = 21.7 Hz), 121.4 (CH), 126.1 (CH), 128.9 (CH), 129.2 (CH), 129.5 (C, d, J = 3.6 Hz), 130.6 (CH), 130.9 (C), 131.4 (CH), 131.8 (CH), 131.9 (CH), 138.8 (C), 140.2 (C), 140.9 (C), 152.2 (C), 162.0/164.5 (C, d, J = 247.9 Hz), 172.5 (C), 205.6 ppm. HRMS (ESI+): calcd for $C_{28}H_{21}FN_3O_3^+$, 466.1567 [M + H]$^+$; found, 466.1574.

*Synthesis of 2-(2-Acetyl-1-((3-methyl-1-phenyl-1H-pyrazol-5-yl)-amino)-3-oxobut-1-en-1-yl)benzoic Acid (**3a**).* By following the general procedure at 90 °C (100 W, monitored by IR temperature sensor) and by maintaining that temperature for 30 min in the reaction with 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**1a**, 87 mg, 0.50 mmol), intermediate **3a** was obtained as a yellow solid (145 mg, 72%). Mp 207−208 °C. Recrystallization of **3a** from DMF afforded crystalline yellow prisms suitable for X-ray diffraction analysis. ^1H NMR (400 MHz, DMSO-d_6): δ 1.61 (s, 3H), 1.93 (s, 3H), 2.10 (s, 3H), 4.61 (s, 1H), 7.21 (m, 1H), 7.46 (m, 1H), 7.53 (m, 4H), 7.68 (m, 2H), 8.00 (m, 1H), 13.8 (br s, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ 13.6 (CH_3), 29.2 (CH_3), 31.8 (CH_3), 98.3 (CH), 116.5 (C), 124.4 (CH), 128.1 (CH), 129.5 (CH), 130.5 (CH), 130.7 (CH), 131.1 (CH), 132.9 (CH), 133.0 (C), 137.5 (C), 147.9 (C), 160.3 (C), 166.5 (C), 196.1 (C), 201.5 (C) ppm. HRMS (ESI+): calcd for $C_{23}H_{22}N_3O_4^+$, 404.1610 [M + H]$^+$; found, 404.1623.

*Isolation of 2-(1,3-DiR-1H-pyrazol-5-yl)isoindoline-1,3-diones **7a**, **7e**, and **7f**.* These compounds were obtained as byproducts in the synthesis of **4a**, **4e**, and **4f**, respectively. Additionally, pyrazolylphthalimide **7a** was also obtained from the direct reaction between phthalic anhydride (**9**, 148 mg, 1.00 mmol) and 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**1a**, 173 mg, 1.00 mmol) under the conditions optimized for the synthesis of **4a**−**j** (150 °C/160 W and by maintaining that temperature for 40 min) in THF (2.0 mL). The residue was purified by flash chromatography on silica gel (eluent = CH_2Cl_2, 158 mg, 52%).

*2-(3-Methyl-1-phenyl-1H-pyrazol-5-yl)isoindoline-1,3-dione (**7a**).* Yellow solid (15 mg, 10%, using the general procedure for the preparation of **4a**−**j**). Mp 124−125 °C (Lit. 124−126 °C).[16a] ^1H NMR (400 MHz, $CDCl_3$): δ 2.42 (s, 3H), 7.30 (m, 1H), 7.34 (m, 2H), 7.40 (m, 2H), 7.80 (m, 2H), 8.90 (m, 2H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 14.1 (CH_3), 106.4 (CH), 124.2 (CH), 124.3 (CH), 128.1 (CH), 129.2 (CH), 129.4 (C), 131.4 (C), 134.8 (CH), 138.3 (C), 149.6 (C), 166.2 (C) ppm. HRMS (ESI+): calcd for $C_{18}H_{14}N_3O_2^+$, 304.1086 [M + H]$^+$; found, 304.1088.

*2-(3-(tert-Butyl)-1-(4-chlorophenyl)-1H-pyrazol-5-yl)isoindoline-1,3-dione (**7e**).* White solid (31 mg, 16%). Mp 235−236 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 1.39 (s, 9H), 7.30 (d, J = 9.1 Hz, 2H), 7.34 (d, J = 9.1 Hz, 2H), 7.81 (m, 2H), 8.91 (m, 2H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 30.3 ((CH_3)$_3$), 32.6 (C), 103.6 (CH), 124.3 (CH), 125.5 (CH), 128.9 (C), 129.4 (CH), 131.3 (C), 133.7 (C), 134.9 (CH), 137.1 (C), 162.7 (C), 166.3 (C) ppm. HRMS (ESI+): calcd for $C_{21}H_{19}ClN_3O_2^+$, 380.1166 [M + H]$^+$; found, 380.1165.

DOI: 10.1021/acs.joc.7b02471
J. Org. Chem. 2017, 82, 12674−12681

2-(3-(tert-Butyl)-1-(4-nitrophenyl)-1H-pyrazol-5-yl)isoindoline-1,3-dione (7f). White solid (29 mg, 15%). Mp 260−261 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40 (s, 9H), 7.60 (d, J = 9.1 Hz, 2H), 7.84 (m, 2H), 8.94 (m, 2H), 8.22 (d, J = 9.1 Hz, 2H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 30.1 ((CH_3)$_3$), 32.7 (C), 105.0 (CH), 123.4 (CH), 124.5 (CH), 124.9 (CH), 129.4 (C), 131.2 (C), 135.2 (CH), 143.7 (CH), 146.2 (C), 163.9 (C), 166.0 (C) ppm. HRMS (ESI+): calcd for $C_{21}H_{19}N_4O_4^+$, 391.1406 [M + H]$^+$; found, 391.1404.

Synthesis of 3,4,6-Trimethyl-1-phenyl-1H-pyrazolo[3,4-b]pyridine (8a). This compound was obtained as a byproduct in the synthesis of **4a**. Yellow solid (14 mg, 12%). Mp 128−130 °C (Lit. 129−131 °C).[21] ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.63 (s, 3H), 2.66 (s, 3H), 2.73 (s, 3H), 6.79 (s, 1H), 7.24 (t, J = 7.7 Hz, 1H), 7.48 (t, J = 7.7/8.3 Hz, 2H), 8.27 (d, J = 8.3 Hz, 2H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 15.3 (CH_3), 19.0 (CH_3), 24.9 (CH_3), 114.5 (C), 118.6 (CH), 120.9 (CH), 125.2 (CH), 128.9 (CH), 139.7 (C), 142.5 (C), 151.3 (CH), 158.8 (C) ppm. HRMS (ESI+): calcd for $C_{15}H_{16}N_3^+$, 238.1344 [M + H]$^+$; found, 238.1349.

Synthesis of 2-(2-Benzoyl-1-((3-(tert-butyl)-1-phenyl-1H-pyrazol-5-yl)amino)-3-oxo-3-phenylprop-1-en-1-yl)benzoic Acid (12). For the synthesis of **12**, it was necessary to prepare 2-(3-oxoisobenzofuran-1(3*H*)-ylidene)-1,3-diphenylpropane-1,3-dione (**11**) by a protocol analogous to that used for the synthesis of precursor **2**.[11a] To a solution of phthalic anhydride (**9**, 561 mg, 2.50 mmol) and 1,3-diphenylpropane-1,3-dione (**10**, 370 mg, 2.50 mmol) in acetic anhydride (1.5 mL) at room temperature was added triethylamine dropwise, and the mixture was stirred for 90 min. Later, the reaction was quenched by the addition of aqueous hydrochloric acid (10 mL of a 1 N solution), and the resulting mixture was partitioned between DCM and H_2O. The organic layer was washed with H_2O and then brine, dried over $MgSO_4$, and concentrated under reduced pressure. Then, the solid residue was treated with methanol, and the precipitated product was collected by filtration to give **10** as an orange solid (673 mg, 76%). Mp 159−160 °C (Lit. 156−158 °C).[22] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (m, 4H), 7.55−7.66 (m, 5H), 7.96 (d, J = 7.4 Hz, 1H), 8.06 (d, J = 7.8 Hz, 2H), 8.14 (d, J = 7.9 Hz, 2H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 121.7 (C), 124.7 (CH), 125.7 (C), 125.9 (CH), 128.7 (CH), 129.0 (CH), 130.1 (CH), 130.3 (CH), 132.2 (CH), 134.1 (CH), 134.6 (CH), 135.0 (CH), 136.3 (C), 136.4 (C), 136.6 (C), 149.3 (C), 164.6 (C), 189.8 (C), 191.4 (C) ppm. HRMS (ESI+): calcd for $C_{23}H_{15}O_4^+$, 355.0970 [M + H]$^+$; found, 355.0974. By following the general procedure (see the synthesis of **4a**−**j**) at 160 °C (170 W, monitored by an IR temperature sensor) and by maintaining that temperature for 50 min in the reaction with 3-(*tert*-butyl)-1-phenyl-1*H*-pyrazol-5-amine (**1d**, 108 mg, 0.50 mmol) and the corresponding substrate (**11**, 177 mg, 0.50 mmol), intermediate **12** was obtained as a yellow solid (202 mg, 71%). Mp 209−210 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.10 (s, 9H), 5.00 (s, 1H), 6.11 (br s, 1H), 7.02−7.09 (m, 5H), 7.15 (t, J = 7.5 Hz, 2H), 7.35 (m, 3H), 7.40−7.49 (m, 6H), 7.58 (t, J = 7.6 Hz, 2H), 7.90 (m, 1H), 13.8 (br s, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 30.0 (CH_3), 32.2 (C), 97.7 (CH), 112.5 (C), 124.7 (CH), 127.7 (CH), 127.8 (CH), 127.9 (CH), 127.9 (C), 128.0 (CH), 129.1 (CH), 129.4 (CH), 129.5 (CH), 129.8 (CH), 130.5 (CH), 130.6 (CH), 132.0 (CH), 132.4 (CH), 133.7 (C), 136.6 (C), 138.1 (C), 140.4 (C), 141.4 (C), 161.9 (C), 163.8 (C), 168.9 (C), 195.0 (C), 196.8 (C) ppm. HRMS (ESI+): calcd for $C_{36}H_{32}N_3O_4^+$, 570.2393 [M + H]$^+$; found, 570.2405.

Synthesis of 2-(6-Acetyl-2,7-dimethylpyrazolo[1,5-a]pyrimidin-5-yl)benzoic Acid (6a). By following the general procedure (see the synthesis of **4a**−**j**) at 150 °C (160 W, monitored by IR temperature sensor) and by maintaining that temperature for 20 min in the reaction with 3-methyl-1*H*-pyrazol-5-amine (**5a**, 49 mg, 0.50 mmol), product **6a** was obtained as a white solid (133 mg, 86%). Mp 152−153 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.02 (s, 3H), 2.53 (s, 3H), 2.80 (s, 3H), 6.49 (s, 1H), 7.31 (d, J = 7.3 Hz, 1H), 7.52−7.60 (m, 2H), 8.06 (d, J = 7.4 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 14.7 (CH_3), 14.9 (CH_3), 31.8 (CH_3), 97.1 (CH), 121.9 (C), 129.4 (CH), 130.1 (C), 130.4 (CH), 131.3 (CH), 132.2 (CH), 140.0 (C), 144.2 (C), 147.5 (C), 155.4 (C), 156.7 (C), 169.8 (C), 201.4 (C) ppm. HRMS (ESI+): calcd for $C_{17}H_{15}N_3O_3^+$, 309.1113 [M + H]$^+$; found, 309.1109.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b02471.

Copies of ^{1}H and $^{13}C\{^1H\}$ NMR spectra for all compounds (PDF)

CIFs for compounds **3a**, **4a**, **4b**, **4g**, and **4j** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Department of Chemistry and Vicerrectoría de Investigaciones at Universidad de los Andes for financial support. We are grateful to the Colombian Institute for Science and Research (COLCIENCIAS) for their financial support (project code: 120465843502) and for the research scholarship conferred to A.C.-M. (Con. 673). We also acknowledge Edwin Guevara for acquiring the high-resolution mass spectra.

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DOI: 10.1021/acs.joc.7b02471
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