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Synthesis of Functionalized Pyrazolo[1,5-*a*]pyridines: [3+2] Cycloaddition of *N*-Aminopyridines and α,β-Unsaturated Carbonyl Compounds/Alkenes at Room Temperature

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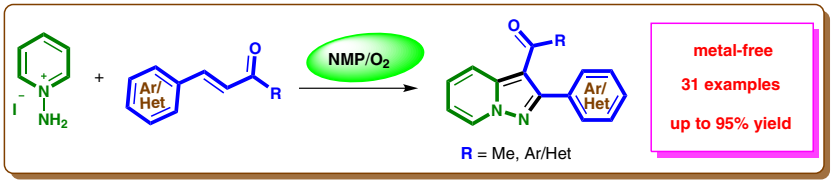

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Abstract The synthesis of functionalized pyrazolo[1,5-*a*]pyridines through oxidative [3+2] cycloaddition of *N*-aminopyridines with α,β-unsaturated carbonyl compounds or electron-withdrawing olefins is described. The reactions proceed in *N*-methylpyrrolidone as the solvent under metal-free conditions at room temperature.

Key words *N*-methylpyrrolidone, chalcones, metal-free, drug intermediates, [3+2] cycloaddition

Pyridine derivatives play significant roles in the synthesis of fused nitrogen-based heterocycles.[1] Heterocycles derived from pyridine including imidazo[1,2-*a*]pyridines, imidazo[1,5-*a*]pyridines, imidazo[1,2-*a*]pyrazines, indolizines, imidazo[2,1-*a*]isoquinolines and pyrazolo[1,5-*a*]pyridines are important intermediates in both medicinal chemistry and drug development.[2] In particular, pyrazolo[1,5-*a*]pyridines (Figure 1) exhibit a wide spectrum of biological activity; examples include 5HT3-adenosine antagonists,[3] p38 kinase inhibitors,[4] dopamine D3/D4 antagonists, 2,4-antiherpetic agents,[5] and potent treatments for cardiac arrhythmias.[6] Moreover, some pyrazole scaffolds are very useful moieties in supramolecular and polymer chemistry as well as in food and pharmaceutical industries.[2] The pyrazolo[1,5-*a*]pyridine structure has been proposed as a stable bioisosteres of the indole nucleus to circumvent problems arising from the metabolic instability of indoles.[7]

Due to the importance of these pyrazolo[1,5-*a*]pyridines, many methods for their synthesis have been developed from pyridinium ylides[8] through 1,3-dipolar cycloaddition and intramolecular 1,5-cyclization using different transition-metal catalysts such as copper,[9] palladium,[10] gold,[11] silver,[12] etc. In most of these cases, the reactions involve sequential regioselective [3+2] cycloaddition of *N*-

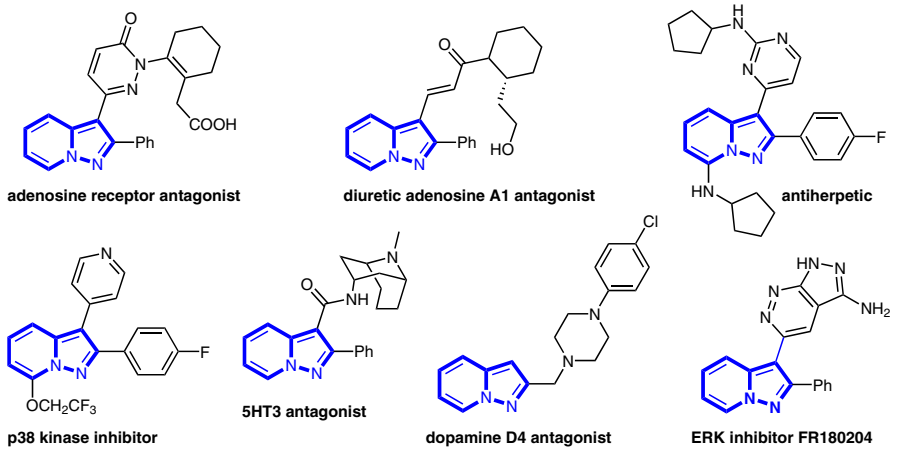
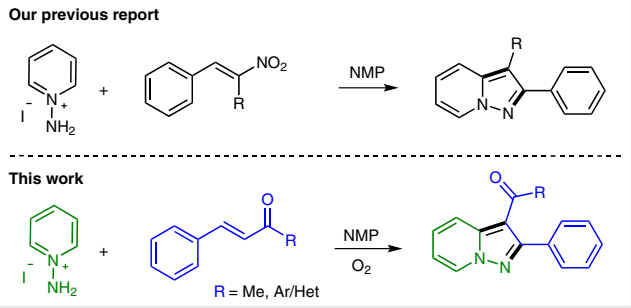


Figure 1 Biologically active pyrazolo[1,5-*a*]pyridines

aminopyridine with benzyne intermediates and alkynes bearing electron-withdrawing groups,[13] domino direct alkynylation,[13b,14] direct oxidative annulation of *N*-iminopyridinium ylides with terminal alkynes,[15] nitrene insertion,[16] denitrogenation[17a] rearrangements of pyridine derivatives[17b] and other methods.[18] Therefore, the development of more facile methods employing mild reaction conditions to access these molecules is still challenging and deserves further investigation.[7,19,20]

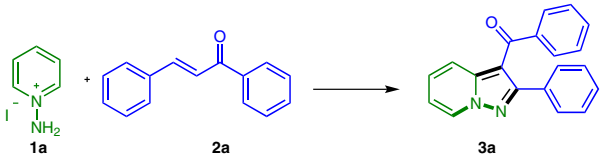
Within our program on the synthesis of *N*-heterocycles,[21] we have developed a strategy for the synthesis of functionalized pyrazolo[1,5-*a*]pyridines under metal-free conditions from a commercially available *N*-aminopyridine and α,β-unsaturated carbonyl compounds (Scheme 1). Some of these molecules are key intermediates for the synthesis of the ERK inhibitor, FR180204, and an adenosine A1 receptor.[22]



Scheme 1 Cyclization of 1-aminopyridinium iodide

Initially, we focused on the optimization of the reaction conditions for the annulation reaction of *N*-aminopyridine **1a** and (*E*)-chalcone (**2a**) as starting substrates, as both of these are commercially available. *N*-Aminopyridine and (*E*)-chalcone have not been previously reported for the construction of pyrazolo[1,5-*a*] pyridines. Firstly, we performed the reaction of 1-aminopyridinium iodide (**1a**) (0.3 mmol), (*E*)-chalcone (**2a**) (0.25 mmol), and CuI (0.025 mmol) as the catalyst at 110 °C in toluene under O_2 (balloon), which resulted in the formation of a trace amount of phenyl(2-phenylpyrazolo[1,5-*a*]pyridin-3-yl)methanone (**3a**) (Table 1, entry 1). The reaction with iron salts such as $FeCl_3$ and $FeCl_2$ was examined, but only a trace and 10% yield of **3a** were isolated, respectively (Table 1, entries 2 and 3). A further reaction with $FeCl_2$ to which I_2 (20 mol%) had been added resulted in an increased yield (33%) of **3a** (Table 1, entry 4). Next, we turned our attention to a system utilizing I_2 (0.05 mmol) and di-*tert*-butyl peroxide (DTBP) (0.5 mmol), and screened different solvents including toluene, 1,2-dichlorobenzene (DCB) and DMSO; under these conditions, 42%, 41% and 30% yields of **3a**, respectively, were obtained (Table 1, entries 5–7). Further, we screened various inorganic and organic bases such as KOH, Cs_2CO_3, DBU, pyrrolidine, piperidine and *N*-methylpyrrolidone (NMP), but only NMP was reactive compared to the other bases, giving a 35% yield of **3a** (Table 1, entries 8–13). Along with NMP, other solvents such as DMSO, DMF and water were tested; in these cases, **3a** was isolated in 24%, 29% and 51% yield,

Table 1 Optimization of the Conditions for the Synthesis of **3a**[a]



Entry	Cat. (mol%)	Base (mmol)	Solvent	Temp (°C)	Yield (%)[b]
1	CuI (10)	–	toluene	110	trace
2	$FeCl_3$ (10)	–	toluene	110	trace
3	$FeCl_2$ (10)	–	toluene	110	10
4[c]	$FeCl_2$ (10)	–	toluene	110	33
5[d]	I_2 (20)	–	toluene	110	42
6[d]	I_2 (20)	–	DCB	110	41
7[d]	I_2 (20)	–	DMSO	110	30
8	–	KOH (0.5)	toluene	110	nr
9	–	Cs_2CO_3 (0.5)	toluene	110	trace
10	–	DBU (0.5)	toluene	110	nr
11	–	pyrrolidine (0.5)	toluene	110	nr
12	–	piperidine (0.5)	toluene	110	nr
13	–	NMP (0.5)	toluene	110	35
14	–	NMP (0.5)	DMSO	110	24
15	–	NMP (0.5)	DMF	110	29
16	–	NMP (0.5)	H_2O	110	51
17	–	NMP (0.5)	–	110	47
18	–	NMP (1.25)	–	110	55
19	–	–	NMP	r.t.	84
20	–	–	NMP[e]	r.t.	81
21	–	–	NMP	60	83
22[f]	–	–	NMP	r.t.	72
23[g]	–	–	NMP	r.t.	62
24[h]	–	–	NMP	r.t.	18
25	–	–	DMSO	r.t.	nr
26	–	–	toluene	r.t.	nr
27	–	–	DMF	r.t.	nr

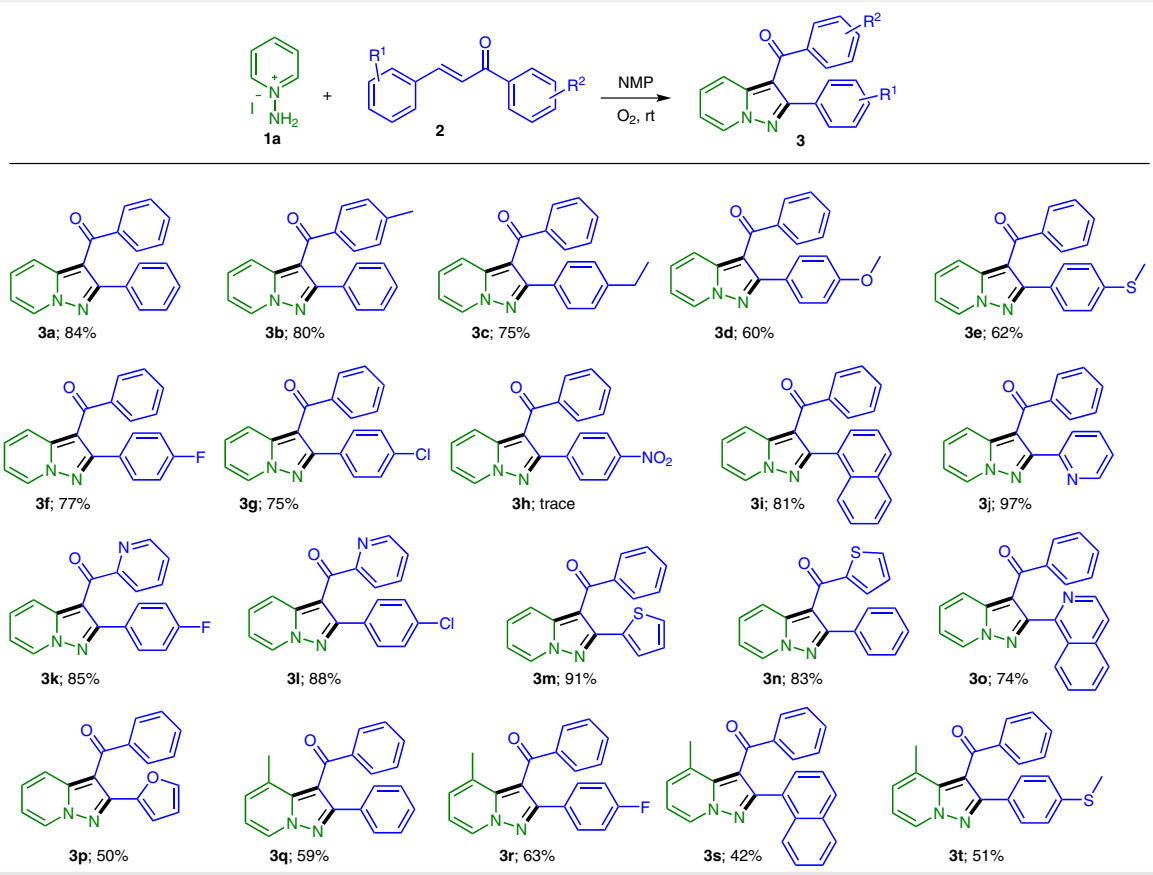
[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.25 mmol), solvent (1 mL), O_2 (balloon), 24 h.
[b] Yield of isolated product; nr = no reaction.
[c] I_2 (0.05 mmol) was also added.
[d] Di-*tert*-butyl peroxide (DTBP) (0.5 mmol) was added.
[e] NMP (2 mL) was used.
[f] Reaction time = 12 h.
[g] Reaction performed open to air.
[h] Reaction performed under argon (balloon).

respectively (Table 1, entries 14–16). In the reactions without any solvent, but with 0.5 mmol or 1.25 mmol of NMP, the yield was increased to 47% and 55%, respectively (Table 1, entries 17 and 18). Surprisingly, in the reaction in NMP (1.0 mL) without any co-solvent at room temperature, the yield of **3a** was increased to 84% (Table 1, entry19). A further increase in the amount of NMP to 2 mL, and raising the temperature to 60 °C led to diminished yields (Table 1, entries 20 and 21). By reducing the reaction time and performing the reaction in air or argon atmospheres, the yield of **3a** was further decreased (Table 1, entries 22–24). When NMP was replaced with DMSO, toluene or DMF as the solvent (1.0 mL), no reaction was observed (Table 1, entries 25–27). The best yield of the desired product was observed in NMP as the solvent at room temperature, hence the conditions shown in entry 19 (Table 1) were deemed as optimum.

Generally, the insertion of acyl/benzoyl groups on azaheterocycles is a difficult task and often requires forcible reaction conditions. To overcome these difficulties, we took on the challenge to obtain directly acylated/benzoylated pyrazolo[1,5-*a*]pyridines from *N*-aminopyridines under metal-free conditions. Gratifyingly, good yields of the desired products were obtained using the optimized conditions (Schemes 2 and 3).

Having established the optimized conditions, the reactions of 1-aminopyridinium iodide (**1a**) with chalcones **2** (containing a substituent on one of either of the two phenyl groups) were examined (Scheme 2). It was found that the majority of the reactions proceeded with chalcones **2** possessing electron-donating (such as methyl, ethyl, methoxy and thiomethyl) or electron-withdrawing (fluoro and chloro) substituents on the phenyl rings, and afforded the corresponding products **3b–g** in good yields (60–80%). The structure of **3g** was also confirmed by single crystal XRD analysis (Figure 2).

In the case of a strong electron-withdrawing (nitro) chalcone, only a trace amount of the desired product was observed **3h**. The reaction of **1a** with (*Z*)-3-(naphthalen-1-yl)-1-phenylprop-2-en-1-one gave the desired product **3i** in 81% yield. This reaction indicates the steric hindrance due to the presence of the naphthalene group did not affect the outcome. Furthermore, heteroarylated chalcones (such as 2-pyridyl, 2-thiophene and 1-isoquinoline) were well



Scheme 2 Substrate scope of benzoylated pyrazolo[1,5-*a*]pyridines. *Reagents and conditions*: **1a** (0.3 mmol), **2** (0.25 mmol), NMP (1.0 mL), 24 h, r.t., O_2 (balloon). Yields are those of isolated products.

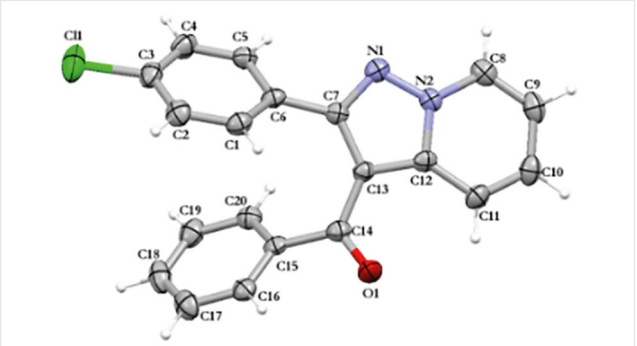


Figure 2 ORTEP diagram of **3g** (CCDC 1496245)

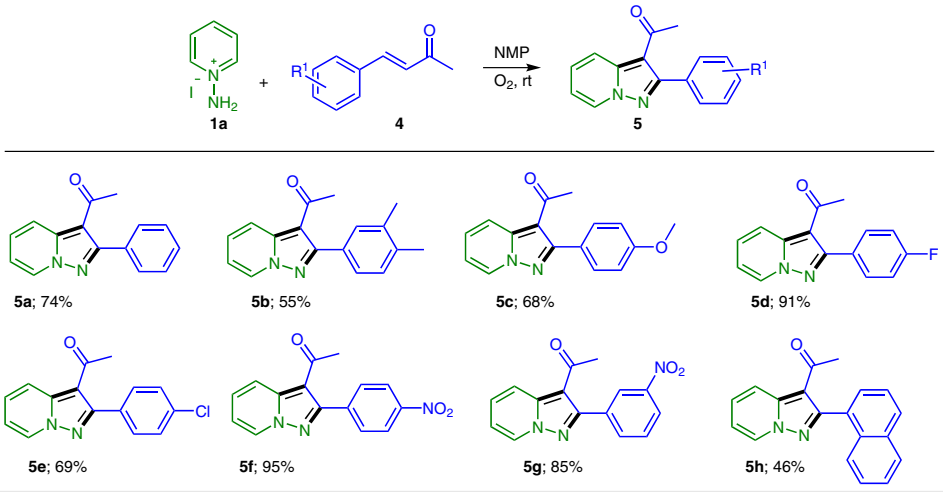
tolerated under these metal-free conditions and gave excellent yields (74–97%) of the corresponding heteroarylated pyrazolo[1,5-*a*]pyridines **3j–o**. These heteropyrazolo[1,5-*a*]pyridines are known to exhibit better biological activities than those of simple pyrazolo[1,5-*a*]pyridines.[4] Also, the 2-furylchalcone derivative gave a moderate yield (50%) of the desired product **3p**. We also subjected a substituted aminopyridinium iodide (1-amino-2-methylpyridin-1-ium iodide) to this reaction with different chalcones, and obtained the corresponding products **3q–t** in moderate to good yields.

To expand the scope of the methodology, a variety of benzylideneacetones **4** were reacted with 1-aminopyridinium iodide (**1a**) to afford the acylated pyrazolo[1,5-*a*]pyridines **5** (Scheme 3). The reaction of **1a** with **4a** under the optimized conditions gave the desired acylated pyrazolo[1,5-*a*]pyridine derivative **5a** in 74% yield. These acylated pyrazolo[1,5-*a*]pyridines are highly useful intermediates in the total synthesis of various drugs. In particular, **5a** is a key intermediate for the synthesis of the ERK inhibitor, FR180204.[22]

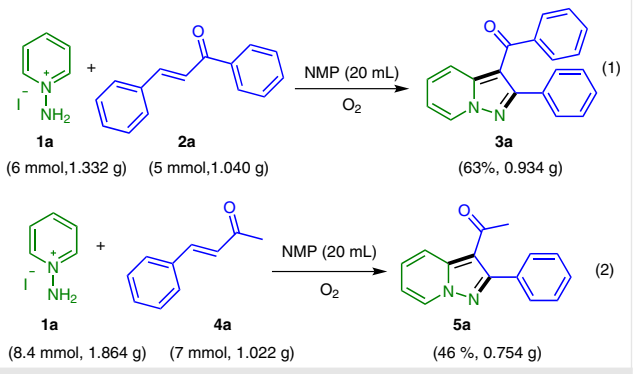
Due to their efficacy in the syntheses of a variety of drugs, further studies were undertaken. The presence of electron-donating or electron-withdrawing substituents on the phenyl ring of benzylideneacetones **4** provided the corresponding products **5b–g** in good to excellent yields (55–95%). Under the same conditions, a 46% yield of 1-[2-(naphthalen-1-yl)pyrazolo[1,5-*a*]pyridin-3-yl]ethan-1-one (**5h**) was isolated from the corresponding naphthalene derivative **4**.

Gram-scale reactions were also performed with *N*-aminopyridine **1a** and α,β-unsaturated carbonyl compounds **2a** and **4a** for the synthesis of intermediates **3a** and **5a** under the optimized conditions (Scheme 4). The reaction of **1a** (1.332 g, 6 mmol) and **2a** (1.04 g, 5 mmol) gave the desired product **3a** in 63% yield (0.934 g) (Scheme 4, eq 1) (with periodic bubbling of O_2). Similarly, the reaction of 1-aminopyridinium iodide (**1a**) (1.864 g, 8.4 mmol) and benzylideneacetone **4a** (1.022 g, 7 mmol) gave the key intermediate **5a** (used in the synthesis of the ERK inhibitor, FR180204) in 46% yield (0.754 g) (Scheme 4, eq 2). These experiments indicate the practical applicability of the present methodology for the synthesis of desirable key intermediates, which are required for drug design and synthesis.

Finally, we extended this strategy for the synthesis of functionally designed pyrazolo[1,5-*a*]pyridines (Scheme 5). Under the optimized conditions, acrylonitrile (**6a**) was reacted with **1a** to afford **7a** in a moderate 41% yield. Further, the regiochemistry of the product **7a**[23] was also confirmed by single crystal XRD analysis (Figure 3). Under the same conditions, the reaction of **1a** with substrates **6b–d** (ethyl acrylate, diethyl but-2-ynedioate, ethyl cinnamate) pro-



Scheme 3 Substrate scope of acylated pyrazolo[1,5-*a*]pyridines. *Reagents and conditions*: **1a** (0.3 mmol), **4** (0.25 mmol), NMP (1.0 mL), 24 h, r.t., O_2 (balloon). Yields are those of isolated products.



Scheme 4 Gram-scale syntheses of key intermediates **3a** and **5a**

ceeded smoothly and provided the corresponding functionalized products **7b–d** in 84%, 75% and 20% yields, respectively. However, simple styrene (**6e**) and stilbene (**6f**) did not give the desired products under the present conditions, indicating that an olefin bearing an electron-withdrawing group is necessary for the reaction to proceed.

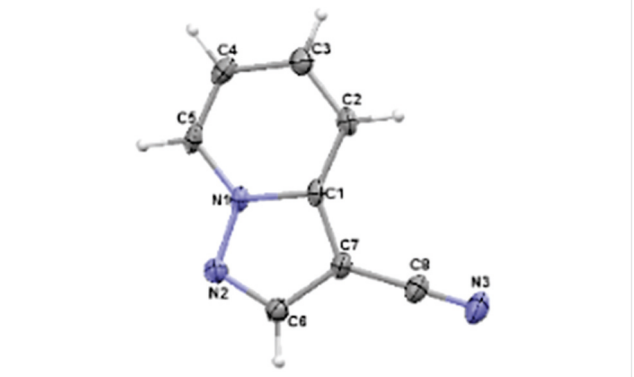
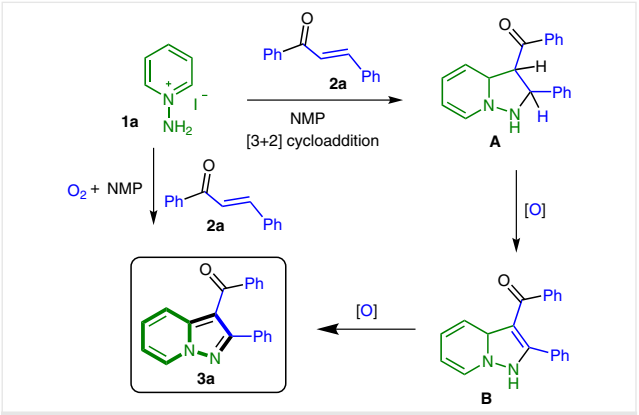


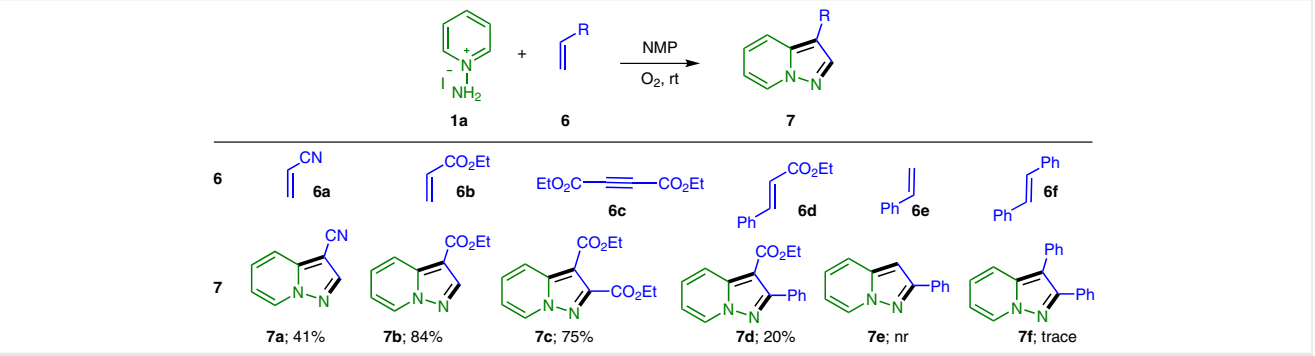
Figure 3 ORTEP diagram of **7a** (CCDC 1498880)

Based on our present observations and previous reports,[13] a plausible reaction mechanism has been proposed (Scheme 6). Initially, the [3+2] cycloaddition of **1a** and **2a** in NMP generates the intermediate **A**. In the presence of O_2, **A** is transformed into intermediate **B**. Finally, oxidation of intermediate **B** followed by aromatization yields the desired product **3a**.



Scheme 6 A plausible reaction mechanism

In summary, we have developed a new protocol for the synthesis of functionalized (acylated/benzoylated) pyrazolo[1,5-*a*]pyridines including the key intermediate for the ERK inhibitor, FR180204, through the selective [3+2] cycloaddition of *N*-aminopyridines with α,β-unsaturated carbonyl compounds under metal-free conditions at room temperature. This methodology is also applicable for electron-withdrawing olefins, which afford good to excellent yields of the corresponding pyrazolo[1,5-*a*]pyridines under mild reaction conditions. The feasibility of the method for scale-up studies has been demonstrated by the synthesis of the two key drug intermediates, **3a** and **5a**.



Scheme 5 Synthesis of functionalized pyrazolo[1,5-*a*]pyridines. *Reagents and conditions*: **1a** (0.3 mmol), **6** (0.25 mmol), NMP (1.0 mL), 24 h, r.t., O_2 (balloon). Yields are those of isolated products.

All commercially available chemicals and reagents were used without any further purification unless otherwise indicated. The progress of the reactions was monitored by thin-layer chromatography (TLC) using Merck TLC silica gel 60 F_{254} plates. All products were purified through column chromatography using SDFCL silica gel (100–200 mesh size) and 20% EtOAc/hexane as the eluent. Melting points were recorded using a Mettler Toledo Mel-Temp melting point apparatus. ^{1}H and ^{13}C NMR spectra were recorded at 500 MHz and 125 MHz, respectively using a Bruker Avance II 500 spectrometer, and at 600 MHz and 125 MHz, respectively, using a Jeol Resonance EC 600R spectrometer. The spectra were recorded in $CDCl_3$ as the solvent. The multiplicities are indicated as follows: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet), and coupling constants (*J*) are given in Hz. Chemical shifts are reported in ppm relative to TMS as an internal standard. The signals around δ values of 7.2 (^{1}H NMR) and 77.0 (^{13}C NMR) correspond to the residual non-deuterated solvent. Mass spectra were obtained using a Micromass Q-TOF, Waters 2487 spectrometer and applying the electron impact (EI) ionization method.

Phenyl(2-phenylpyrazolo[1,5-*a*]pyridin-3-yl)methanone (3a); Typical Procedure

A clean, washed boiling tube equipped with a magnetic stir bar was charged with 1-aminopyridinium iodide (**1a**) (0.0665 g, 0.3 mmol), (*E*)-chalcone (**2a**) (0.0520 g, 0.25 mmol) and NMP (1 mL). The mixture was stirred for 24 h at r.t. under O_2 (balloon). After completion of the reaction, the mixture was poured into hypo solution (10 mL). The mixture was extracted with EtOAc (3 × 10 mL), dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure. The residue was purified through column chromatography using silica gel (20% EtOAc/hexane) to afford **3a**.

Yield: 62.5 mg (84%); white solid; mp 103 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.48 (d, *J* = 7.0 Hz, 1 H), 7.94 (d, *J* = 8.5 Hz, 1 H), 7.49 (d, *J* = 7.0 Hz, 2 H), 7.34 (t, *J* = 6.0 Hz, 3 H), 7.30 (t, *J* = 7.0 Hz, 1 H), 7.22 (t, *J* = 7.5 Hz, 1 H), 7.12–7.04 (m, 4 H), 6.89 (q, *J* = 7.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 191.1, 156.3, 143.0, 139.0, 132.2, 131.6, 129.6, 129.3, 128.6, 128.3, 127.7, 127.4, 119.2, 114.2, 109.4.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{15}N_2O$: 299.1184; found: 299.1196.

(2-Phenylpyrazolo[1,5-a]pyridin-3-yl)(*p*-tolyl)methanone (3b)

Yield: 62.5 mg (80%); white solid; mp 109 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.56 (d, *J* = 7.0 Hz, 1 H), 7.94 (d, *J* = 8.5 Hz, 1 H), 7.53 (d, *J* = 8.5 Hz, 2 H), 7.47 (t, *J* = 6.0 Hz, 2 H), 7.34 (t, *J* = 7.5 Hz, 1 H), 7.21 (t, *J* = 6.0 Hz, 3 H), 6.99–6.93 (m, 3 H), 2.27 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 190.7, 156.0, 142.8, 142.3, 136.3, 132.3, 129.5, 128.5, 128.4, 128.2, 127.8, 127.0, 119.0, 114.0, 109.5, 21.4.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{17}N_2O$: 313.1341; found: 313.1333.

[2-(4-Ethylphenyl)pyrazolo[1,5-*a*]pyridin-3-yl](phenyl)methanone (3c)

Yield: 61.4 mg (75%); colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.57 (d, *J* = 7.0 Hz, 1 H), 8.00 (d, *J* = 9.0 Hz, 1 H), 7.53 (d, *J* = 8.0 Hz, 2 H), 7.45 (d, *J* = 7.5 Hz, 2 H), 7.36 (t, *J* = 7.5 Hz, 1 H), 7.20 (q, *J* = 6.0 Hz, 3 H), 7.00–6.95 (m, 3 H), 2.58 (q, *J* = 7.5 Hz, 2 H), 1.14 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 190.8, 156.1, 148.5, 142.7, 136.5, 132.3, 129.5, 128.5, 128.2, 127.8, 127.2, 127.1, 119.0, 114.0, 109.5, 28.7, 15.2.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{19}N_2O$: 327.1497; found: 327.1512.

[2-(4-Methoxyphenyl)pyrazolo[1,5-*a*]pyridin-3-yl](phenyl)methanone (3d)

Yield: 49.6 mg (60%); white solid; mp 144.7 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.56 (d, *J* = 7.0 Hz, 1 H), 7.98 (d, *J* = 8.5 Hz, 1 H), 7.60 (d, *J* = 7.5 Hz, 2 H), 7.40–7.32 (m, 4 H), 7.19 (t, *J* = 7.5 Hz, 2 H), 6.97 (t, *J* = 7.0 Hz, 1 H), 6.72 (d, *J* = 7.5 Hz, 2 H), 3.74 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 191.1, 159.7, 156.0, 143.0, 139.0, 131.6, 130.9, 129.3, 128.5, 127.7, 127.3, 124.6, 119.0, 114.0, 113.4, 109.1, 55.1.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{17}N_2O_2$: 329.1290; found: 329.1291.

{2-[4-(Methylthio)phenyl]pyrazolo[1,5-*a*]pyridin-3-yl}(phenyl)methanone (3e)

Yield: 53.1 mg (62%); white solid; mp 122 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.57 (d, *J* = 7.0 Hz, 1 H), 7.97 (d, *J* = 9.0 Hz, 1 H), 7.60 (d, *J* = 7.0 Hz, 2 H), 7.39 (q, *J* = 8.5 Hz, 4 H), 7.22 (t, *J* = 8.0 Hz, 2 H), 7.07 (d, *J* = 8.5 Hz, 2 H), 6.98 (t, *J* = 7.0 Hz, 1 H), 2.42 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 190.9, 155.6, 142.9, 139.2, 139.0, 131.7, 129.5, 129.2, 128.8, 128.5, 127.8, 127.3, 125.6, 119.0, 114.1, 109.2, 15.4.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{17}N_2OS$: 345.1062; found: 345.1057.

[2-(4-Fluorophenyl)pyrazolo[1,5-*a*]pyridin-3-yl](phenyl)methanone (3f)

Yield: 60.5 mg (77%); white solid; mp 142 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.57 (d, *J* = 7.0 Hz, 1 H), 8.00 (d, *J* = 9.0 Hz, 1 H), 7.58 (d, *J* = 7.0 Hz, 2 H), 7.45–7.34 (m, 4 H), 7.20 (t, *J* = 7.5 Hz, 2 H), 7.00 (t, *J* = 7.0 Hz, 1 H), 6.88 (t, *J* = 9.0 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 190.9, 163.8, 161.8, 155.3, 143.0, 139.0, 131.8 (d, *J* = 44.0 Hz), 131.4, 129.3, 128.6 (d, *J* = 22.8 Hz), 127.8, 127.5, 119.2, 115.0 (d, *J* = 21.6 Hz), 114.3, 109.4.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{14}N_2OF$: 317.1090; found: 317.1094.

[2-(4-Chlorophenyl)pyrazolo[1,5-*a*]pyridin-3-yl](phenyl)methanone (3g)

Yield: 62.2 mg (75%); white solid; mp 146 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.56 (d, *J* = 6.5 Hz, 1 H), 7.97 (d, *J* = 9.0 Hz, 1 H), 7.59 (d, *J* = 7.0 Hz, 2 H), 7.41–7.36 (m, 4 H), 7.21 (t, *J* = 8.0 Hz, 2 H), 7.17 (d, *J* = 8.5 Hz, 2 H), 7.00 (t, *J* = 7.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 190.8, 155.0, 142.9, 139.0, 134.5, 131.9, 130.8, 129.3, 128.6, 128.1, 127.9, 127.5, 119.2, 114.4, 109.4.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{14}ClN_2O$: 333.0795; found: 333.0800.

[2-(Naphthalen-1-yl)pyrazolo[1,5-*a*]pyridin-3-yl](phenyl)methanone (3i)

Yield: 70.7 mg (81%); white solid; mp 116 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.64 (d, *J* = 6.5 Hz, 1 H), 8.31 (d, *J* = 8.5 Hz, 1 H), 7.95 (t, *J* = 5.5 Hz, 1 H), 7.70–7.64 (m, 2 H), 7.47 (t, *J* = 8.0 Hz, 1 H), 7.40–7.36 (m, 3 H), 7.28 (q, *J* = 6.5 Hz, 3 H), 7.03 (t, *J* = 7.0 Hz, 1 H), 6.98 (t, *J* = 7.5 Hz, 1 H), 6.75 (t, *J* = 7.5 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 191.4, 155.3, 142.6, 139.0, 133.1, 131.9, 130.8, 130.1, 129.0, 128.8, 128.7, 128.1, 127.9, 127.8, 126.7, 126.3, 125.5, 125.3, 124.5, 119.4, 114.5, 111.6.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{17}N_2O$: 349.1341; found: 349.1342.

Phenyl[2-(pyridin-2-yl)pyrazolo[1,5-*a*]pyridin-3-yl]methanone (3j)

Yield: 72.1 mg (97%); white solid; mp 118 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.62 (d, *J* = 7.0 Hz, 1 H), 8.43 (d, *J* = 9.5 Hz, 1 H), 8.07 (d, *J* = 9.0 Hz, 1 H), 7.61 (d, *J* = 7.0 Hz, 2 H), 7.50 (d, *J* = 5.0 Hz, 2 H), 7.41 (t, *J* = 8.5 Hz, 1 H), 7.32 (q, *J* = 7.5 Hz, 1 H), 7.17 (t, *J* = 7.5 Hz, 2 H), 7.09–7.07 (m, 1 H), 7.02 (t, *J* = 7.5 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 190.9, 154.8, 151.7, 149.2, 142.6, 139.6, 135.6, 131.4, 129.0, 128.8, 127.7, 127.4, 124.6, 122.7, 119.3, 114.5, 110.0.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{14}N_3O$: 300.1137; found: 300.1133.

[2-(4-Fluorophenyl)pyrazolo[1,5-*a*]pyridin-3-yl](pyridin-2-yl)methanone (3k)

Yield: 67.3 mg (85%); white solid; mp 152.6 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.56 (d, *J* = 7.0 Hz, 1 H), 8.20 (d, *J* = 4.5 Hz, 1 H), 8.16 (d, *J* = 9.0 Hz, 1 H), 7.84 (d, *J* = 7.5 Hz, 1 H), 7.72 (t, *J* = 7.5 Hz, 1 H), 7.47 (t, *J* = 8.0 Hz, 1 H), 7.40 (q, *J* = 5.5 Hz, 2 H), 7.21 (t, *J* = 5.5 Hz, 1 H), 7.03 (t, *J* = 7.0 Hz, 1 H), 6.86 (t, *J* = 8.5 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 189.4, 163.5, 161.5, 156.5, 155.5, 148.2, 143.2, 136.4, 131.1 (d, *J* = 8.0 Hz), 129.3 (d, *J* = 78.3 Hz), 128.1, 125.5, 123.5, 119.4, 114.8, 114.7 (d, *J* = 10.8 Hz), 109.0.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{13}FN_3O$: 318.1043; found: 318.1030.

[2-(4-Chlorophenyl)pyrazolo[1,5-*a*]pyridin-3-yl](pyridin-2-yl)methanone (3l)

Yield: 72.9 mg (88%); white solid; mp 151.9 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.57 (d, *J* = 7.0 Hz, 1 H), 8.18 (d, *J* = 5.0 Hz, 1 H), 8.14 (d, *J* = 8.5 Hz, 1 H), 7.85 (d, *J* = 7.5 Hz, 1 H), 7.74–7.71 (m, 1 H), 7.45 (t, *J* = 7.5 Hz, 1 H), 7.34 (d, *J* = 8.0 Hz, 2 H), 7.24 (q, *J* = 5.0 Hz, 1 H), 7.14 (d, *J* = 8.5 Hz, 2 H), 7.02 (t, *J* = 7.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 189.3, 156.3, 155.6, 148.2, 143.2, 136.5, 134.1, 131.8, 130.5, 128.7, 128.1, 127.9, 125.6, 123.5, 119.4, 114.5, 109.0.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{13}N_3OCl$: 334.0747; found: 334.0741.

Phenyl[2-(thiophen-2-yl)pyrazolo[1,5-*a*]pyridin-3-yl]methanone (3m)

Yield: 69.5 mg (91%); yellow solid; mp 138.8 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.53 (d, *J* = 7.0 Hz, 1 H), 7.72 (d, *J* = 7.0 Hz, 2 H), 7.59 (d, *J* = 9.0 Hz, 1 H), 7.46 (t, *J* = 7.0 Hz, 1 H), 7.34–7.25 (m, 5 H), 6.93 (t, *J* = 6.0 Hz, 1 H), 6.88 (t, *J* = 4.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 190.5, 149.8, 142.7, 139.2, 133.5, 132.1, 129.8, 129.2, 128.5, 128.1, 127.3, 127.2, 127.0, 118.7, 114.1, 108.9.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{13}N_2OS$: 305.0749; found: 305.0755.

(2-Phenylpyrazolo[1,5-*a*]pyridin-3-yl)(thiophen-2-yl)methanone (3n)

Yield: 63.0 mg (83%); white solid; mp 133 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.56 (d, *J* = 7.0 Hz, 1 H), 7.99 (d, *J* = 9.0 Hz, 1 H), 7.61 (q, *J* = 3.0 Hz, 2 H), 7.48 (d, *J* = 4.0 Hz, 1 H), 7.37 (t, *J* = 8.0 Hz, 1 H), 7.28 (t, *J* = 3.0 Hz, 3 H), 7.16 (d, *J* = 2.5 Hz, 1 H), 6.95 (t, *J* = 7.0 Hz, 1 H), 6.76 (t, *J* = 4.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 182.4, 155.0, 144.5, 142.5, 133.9, 132.8, 132.3, 129.4, 128.5, 128.1, 127.2, 126.9, 118.7, 114.0, 109.4.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{13}N_2OS$: 305.0749; found: 305.0765.

[2-(Isoquinolin-1-yl)pyrazolo[1,5-*a*]pyridin-3-yl](phenyl)methanone (3o)

Yield: 64.4 mg (74%); white solid; mp 160 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.64 (d, *J* = 6.5 Hz, 1 H), 8.10 (d, *J* = 8.5 Hz, 1 H), 7.96 (d, *J* = 8.5 Hz, 1 H), 7.86 (d, *J* = 8.5 Hz, 1 H), 7.69–7.65 (m, 4 H), 7.58 (t, *J* = 7.0 Hz, 1 H), 7.44 (t, *J* = 7.5 Hz, 1 H), 7.40 (t, *J* = 9.0 Hz, 1 H), 7.12 (t, *J* = 7.0 Hz, 1 H), 7.05–6.99 (m, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 191.2, 154.6, 151.0, 147.5, 142.6, 139.9, 135.6, 131.2, 129.4, 129.2, 128.8, 127.6, 127.3, 127.1, 126.9, 126.7, 121.5, 119.2, 114.5, 110.4.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{16}N_3O$: 350.1293; found: 350.1299.

Furan-2-yl(2-phenylpyrazolo[1,5-*a*]pyridin-3-yl)methanone (3p)

Yield: 36.2 mg (50%); white solid; mp 98 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.58 (d, *J* = 7.0 Hz, 1 H), 7.73 (d, *J* = 7.5 Hz, 2 H), 7.58 (d, *J* = 9.0 Hz, 1 H), 7.50 (t, *J* = 7.5 Hz, 1 H), 7.38 (t, *J* = 9.0 Hz, 3 H), 7.29 (t, *J* = 8.0 Hz, 1 H), 6.97–6.93 (m, 2 H), 6.39 (q, *J* = 2.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 190.3, 146.3, 146.2, 143.4, 142.4, 139.7, 132.0, 128.9, 128.7, 128.2, 127.1, 118.8, 114.2, 112.7, 111.4, 108.6.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{13}N_2O_2$: 289.0977; found: 289.0973.

(4-Methyl-2-phenylpyrazolo[1,5-*a*]pyridin-3-yl)(phenyl)methanone (3q)

Yield: 46.2 mg (59%); white solid; mp 110–113 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 8.4 Hz, 1 H), 7.58 (q, *J* = 7.2 Hz, 2 H), 7.46 (t, *J* = 6.6 Hz, 2 H), 7.45 (t, *J* = 8.4 Hz, 1 H), 7.31 (t, *J* = 7.2 Hz, 1 H), 7.20–7.14 (m, 5 H), 6.88 (d, *J* = 8.4 Hz, 1 H), 2.87 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 191.4, 155.9, 138.8, 132.7, 131.5, 129.8, 129.4, 128.3, 127.9, 127.7, 127.6, 116.7, 113.7, 109.6, 17.9.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{16}N_2ONa$: 335.1160; found: 335.1175.

[2-(4-Fluorophenyl)-4-methylpyrazolo[1,5-*a*]pyridin-3-yl](phenyl)methanone (3r)

Yield: 52.1 mg (63%); white solid; mp 111–114 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.93 (t, *J* = 8.4 Hz, 1 H), 7.57 (q, *J* = 6.6 Hz, 2 H), 7.46 (t, *J* = 5.4 Hz, 2 H), 7.36 (q, *J* = 7.2 Hz, 2 H), 7.20 (q, *J* = 7.8 Hz, 2 H), 6.89–6.86 (m, 3 H), 2.86 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 191.3, 154.9, 139.2, 138.8, 131.7, 131.6, 131.5, 129.3, 127.8, 127.7, 116.7, 115.0, 114.8, 113.8, 109.6, 17.9.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{15}N_2OFNa$: 353.1066; found: 353.1055.

[4-Methyl-2-(naphthalen-1-yl)pyrazolo[1,5-*a*]pyridin-3-yl](phenyl)methanone (3s)

Yield: 38.2 mg (42%); white solid; mp 121–125 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.24 (t, *J* = 8.4 Hz, 1 H), 7.97 (t, *J* = 4.2 Hz, 1 H), 7.70–7.69 (m, 1 H), 7.66 (d, *J* = 8.4 Hz, 1 H), 7.49 (q, *J* = 6.6 Hz, 1 H), 7.42–7.37 (m, 3 H), 7.28 (t, *J* = 8.4 Hz, 2 H), 7.29 (d, *J* = 1.8 Hz, 1 H), 6.99–6.95 (m, 2 H), 6.77–6.74 (m, 2 H), 2.89 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 191.8, 154.9, 130.7, 129.2, 128.8, 128.2, 126.8, 126.3, 125.5, 124.6, 117.1, 114.0, 111.8, 18.0.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{25}H_{18}N_2ONa$: 385.1317; found: 385.1335.

{4-Methyl-2-[4-(methylthio)phenyl]pyrazolo[1,5-*a*]pyridin-3-yl}(phenyl)methanone (3t)

Yield: 45.3 mg (51%); white solid; mp 109–112 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.89 (q, *J* = 8.4 Hz, 1 H), 7.60 (q, *J* = 6.6 Hz, 2 H), 7.41 (d, *J* = 9.0 Hz, 2 H), 7.35 (d, *J* = 7.2 Hz, 2 H), 7.21 (t, *J* = 7.8 Hz, 2 H), 7.07 (d, *J* = 8.4 Hz, 2 H), 6.86 (q, *J* = 6.0 Hz, 1 H), 2.85 (s, 3 H), 2.42 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 191.3, 155.3, 143.4, 139.0, 138.6, 131.6, 130.1, 129.4, 127.8, 127.5, 125.9, 116.6, 113.6, 109.5, 17.9, 15.7.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{19}N_2OS$: 359.1218; found: 359.1225.

1-(2-Phenylpyrazolo[1,5-*a*]pyridin-3-yl)ethanone (5a)

Yield: 43.7 mg (74%); white solid; mp 98 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.53 (d, *J* = 7.0 Hz, 1 H), 8.45 (d, *J* = 9.0 Hz, 1 H), 7.60 (q, *J* = 3.5 Hz, 2 H), 7.50 (q, *J* = 3.5 Hz, 4 H), 7.03 (t, *J* = 7.0 Hz, 1 H), 2.14 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 193.3, 156.2, 141.6, 131.1, 129.4, 129.2, 129.1, 128.8, 128.6, 128.2, 128.1, 119.9, 114.3, 111.3, 29.8.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{13}N_2O$: 237.1028; found: 237.1019.

1-[2-(3,4-Dimethylphenyl)pyrazolo[1,5-*a*]pyridin-3-yl]ethanone (5b)

Yield: 36.2 mg (55%); white solid; mp 124 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.51 (d, *J* = 7.0 Hz, 1 H), 8.43 (d, *J* = 9.0 Hz, 1 H), 7.46 (t, *J* = 7.5 Hz, 1 H), 7.36 (s, 1 H), 7.31 (d, *J* = 7.5 Hz, 1 H), 7.25 (t, *J* = 7.5 Hz, 1 H), 7.00 (t, *J* = 7.0 Hz, 1 H), 2.34 (d, *J* = 3.0 Hz, 6 H), 2.17 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 193.8, 157.0, 141.9, 137.6, 136.6, 130.7, 130.6, 129.5, 128.4, 128.2, 127.2, 120.1, 114.4, 111.5, 30.0, 19.7, 19.6.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{17}N_2O$: 265.1341; found: 265.1335.

1-[2-(4-Methoxyphenyl)pyrazolo[1,5-*a*]pyridin-3-yl]ethanone (5c)

Yield: 45.2 mg (68%); white solid; mp 173.5 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.43 (d, *J* = 7.0 Hz, 1 H), 8.34 (d, *J* = 8.5 Hz, 1 H), 7.45 (d, *J* = 9.0 Hz, 2 H), 7.39 (d, *J* = 7.5 Hz, 1 H), 6.96 (q, *J* = 8.5 Hz, 3 H), 3.80 (s, 3 H), 2.09 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 193.7, 160.3, 156.6, 142.0, 131.0, 128.4, 128.2, 125.5, 120.1, 114.5, 113.8, 111.5, 55.3, 30.0.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}N_2O_2$: 267.1134; found: 267.1146.

1-[2-(4-Fluorophenyl)pyrazolo[1,5-*a*]pyridin-3-yl]ethanone (5d)

Yield: 58.0 mg (91%); white solid; mp 153.5 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.43 (d, *J* = 6.5 Hz, 1 H), 8.33 (d, *J* = 9.0 Hz, 1 H), 7.51–7.48 (m, 2 H), 7.40 (t, *J* = 8.5 Hz, 1 H), 7.11 (d, *J* = 8.5 Hz, 2 H), 6.94 (t, *J* = 9.0 Hz, 1 H), 2.08 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.3, 162.3, 155.6, 141.9, 131.6 (d, *J* = 8.1 Hz), 129.3, 128.4 (d, *J* = 7.0 Hz), 120.1, 115.5 (d, *J* = 21.5 Hz), 114.7, 111.5, 30.1.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{12}N_2OF$: 255.0934; found: 255.0934.

1-[2-(4-Chlorophenyl)pyrazolo[1,5-*a*]pyridin-3-yl]ethanone (5e)

Yield: 46.5 mg (69%); white solid; mp 143.2 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.52 (d, *J* = 7.0 Hz, 1 H), 8.42 (d, *J* = 9.0 Hz, 1 H), 7.55 (d, *J* = 8.5 Hz, 2 H), 7.49 (t, *J* = 8.5 Hz, 3 H), 7.04 (t, *J* = 7.0 Hz, 1 H), 2.18 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 193.0, 155.4, 141.9, 135.4, 131.8, 131.0, 128.6, 128.5, 128.4, 120.1, 114.7, 111.6, 30.2.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{12}N_2OCl$: 271.0638; found: 271.0632.

1-[2-(4-Nitrophenyl)pyrazolo[1,5-*a*]pyridin-3-yl]ethanone (5f)

Yield: 66.4 mg (95%); white solid; mp 204.1 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.56 (d, *J* = 7.0 Hz, 1 H), 8.38 (q, *J* = 9.0 Hz, 3 H), 7.84 (d, *J* = 9.0 Hz, 2 H), 7.54 (t, *J* = 8.0 Hz, 1 H), 7.09 (t, *J* = 7.0 Hz, 1 H), 2.25 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.2, 154.1, 148.2, 141.9, 140.0, 130.9, 127.9, 123.4, 120.0, 115.0, 111.7, 30.4.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{12}N_3O_3$: 282.0879; found: 282.0866.

1-[2-(3-Nitrophenyl)pyrazolo[1,5-*a*]pyridin-3-yl]ethanone (5g)

Yield: 60.0 mg (85%); white solid; mp 190.3 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.56 (d, *J* = 7.0 Hz, 2 H), 8.37 (t, *J* = 9.0 Hz, 2 H), 7.99 (d, *J* = 7.5 Hz, 1 H), 7.70 (t, *J* = 8.0 Hz, 1 H), 7.54 (t, *J* = 8.0 Hz, 1 H), 7.09 (t, *J* = 7.0 Hz, 1 H), 2.26 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.1, 154.0, 148.0, 142.0, 135.8, 135.1, 129.3, 128.7, 124.9, 123.9, 120.0, 115.0, 111.5, 30.4.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{12}N_3O_3$: 282.0879; found: 282.0890.

1-[2-(Naphthalen-1-yl)pyrazolo[1,5-*a*]pyridin-3-yl]ethanone (5h)

Yield: 32.9 mg (46%); white solid; mp 142.3 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.56 (t, *J* = 6.5 Hz, 2 H), 8.00 (d, *J* = 8.0 Hz, 1 H), 7.93 (d, *J* = 8.0 Hz, 1 H), 7.65–7.57 (m, 3 H), 7.55–7.49 (m, 2 H), 7.43 (t, *J* = 7.0 Hz, 1 H), 7.05 (t, *J* = 6.5 Hz, 1 H), 1.80 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 193.4, 155.2, 141.8, 133.3, 132.5, 131.0, 129.5, 128.5, 128.2, 127.9, 126.8, 126.1, 125.3, 125.0, 120.3, 114.7, 113.1, 29.1.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{15}N_2O$: 287.1184; found: 287.1189.

Pyrazolo[1,5-*a*]pyridine-3-carbonitrile (7a)[23]

Yield: 14.7 mg (41%); white solid; mp 73–76 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.59 (d, *J* = 7.0 Hz, 1 H), 8.25 (s, 1 H), 7.80 (d, *J* = 8.5 Hz, 1 H), 7.48 (t, *J* = 7.5 Hz, 1 H), 7.05 (t, *J* = 7.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 145.2, 142.5, 129.7, 127.8, 117.2, 114.4, 113.7, 82.3.

Ethyl Pyrazolo[1,5-*a*]pyridine-3-carboxylate (7b)

Yield: 40.0 mg (84%); light yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.44 (d, *J* = 7.0 Hz, 1 H), 8.32 (s, 1 H), 8.08 (d, *J* = 9.0 Hz, 1 H), 7.31 (t, *J* = 8.0 Hz, 1 H), 6.85 (t, *J* = 6.5 Hz, 1 H), 4.32 (q, *J* = 7.0 Hz, 2 H), 1.33 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.3, 144.7, 140.7, 129.1, 127.1, 119.0, 113.5, 103.8, 59.8, 14.4.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{11}N_2O_2$: 191.0821; found: 191.0817.

Diethyl Pyrazolo[1,5-*a*]pyridine-2,3-dicarboxylate (7c)

Yield: 49.2 mg (75%); colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.44 (d, *J* = 7.0 Hz, 1 H), 8.08 (d, *J* = 9.0 Hz, 1 H), 7.36 (t, *J* = 8.0 Hz, 1 H), 6.94 (t, *J* = 7.0 Hz, 1 H), 4.44 (q, *J* = 7.0 Hz, 2 H), 4.32 (q, *J* = 7.0 Hz, 2 H), 1.36 (t, *J* = 7.0 Hz, 3 H), 1.31 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.1, 162.1, 147.8, 141.2, 129.1, 127.8, 119.7, 114.9, 112.5, 62.1, 60.4, 14.2, 14.1.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{15}N_2O_4$: 263.1032; found: 263.1047.

Ethyl 2-Phenylpyrazolo[1,5-*a*]pyridine-3-carboxylate (7d)[19]

Yield: 13.4 mg (20%); white solid; mp 69–73 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.54 (d, *J* = 7.0 Hz, 1 H), 8.23 (d, *J* = 9.0 Hz, 1 H), 7.79 (q, *J* = 7.5 Hz, 2 H), 7.47–7.41 (m, 4 H), 6.97 (t, *J* = 7.0 Hz, 1 H), 4.34 (q, *J* = 7.5 Hz, 2 H), 1.31 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.5, 129.9, 128.8, 127.7, 127.2, 119.7, 113.8, 59.9, 14.2.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588753.

References

(1) (a) Guo, X.-X.; Gu, D.-W.; Wu, Z.; Zhang, W. *Chem. Rev.* **2015**, *115*, 1622. (b) Marina, J. D. P.; Diogo, L. P.; Manuel, M. B. M. *Eur. J. Org. Chem.* **2015**, *33*, 7197.

(2) (a) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 4th ed.; Blackwell: Oxford, **1990**. (b) Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 627. For recent reviews on the chemistry and properties of pyrazoles, see: (c) Janin, Y. L. *Chem. Rev.* **2012**, *112*, 3924. (d) Fustero, S.; Sánchez-Roselló, M.; Barrio, P.; Simón-Fuentes, A. *Chem. Rev.* **2011**, *111*, 6984. (e) Schmidt, A.; Dreger, A. *Curr. Org. Chem.* **2011**, *15*, 1423. (f) Yoon, J.-Y.; Lee, S.-g.; Shin, H. *Curr. Org. Chem.* **2011**, *15*, 657. (g) Fustero, S.; Simón-Fuentes, A.; Sanz-Cervera, J. F. *Org. Prep. Proced. Int.* **2009**, *41*, 253. (h) Seung, H. C.; Ji, Y. K.; Jaesung, K.; Sukbok, C. *Chem. Soc. Rev.* **2011**, *40*, 4879. (i) Nicolaou, K. C.; Rao, P. B.; Hao, J.; Reddy, M. V.; Rassias, G.; Huang, X.; Chen, D.-K.; Snyder, S. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 1753.

(3) Hansen, B. J.; Weis, J.; Suzdak, P. D.; Eskesen, K. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 695.

(4) Stevens, K. L.; Jung, D. K.; Alberti, M. J.; Badiang, J. G.; Peckham, G. E.; Veal, J. M.; Cheung, M. P.; Harris, A. S.; Chamberlain, D.; Peel, M. R. *Org. Lett.* **2005**, *7*, 4753.

(5) (a) Löber, S.; Hübner, H.; Utz, W.; Gmeiner, P. *J. Med. Chem.* **2001**, *44*, 2691. (b) Bettinetti, L.; Schlotter, K.; Hübner, H.; Gmeiner, P. *J. Med. Chem.* **2002**, *45*, 4594. (c) Löber, S.; Aboul-Fadl, T.; Hübner, H.; Gmeiner, P. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 633. (d) Löber, S.; Ortner, B.; Bettinetti, L.; Hübner, H.; Gmeiner, P. *Tetrahedron: Asymmetry* **2002**, *13*, 2296. (e) Boeckler, F.; Russig, H.; Zhang, W. N.; Löber, S.; Schetz, J.; Hübner, H.; Ferger, B.; Gmeiner, P.; Feldon, J. *Psychopharmacology* **2004**, *175*, 331. (f) Bettinetti, L.; Hübner, H.; Gmeiner, P. *Arch. Pharm.* **2005**, *338*, 276. (g) Prante, O.; Hocke, C.; Löber, S.; Hübner, H.; Gmeiner, P.; Kuwert, T. *Nuklearmed.* **2006**, *45*, 235. (h) Lysenkova, L. N.; Turchin, K. F.; Danilenko, V. N.; Korolev, A. M.; Preobrazhenskaya, M. N. *J. Antibiot.* **2010**, *63*, 17.

(6) Zoni-Berisso, M.; Lercari, F.; Carazza, T.; Domenicucci, S. *Clin. Epidemiol.* **2014**, *6*, 213.

(7) Aboul-Fadl, T.; Löber, S.; Gmeiner, P. *Synthesis* **2000**, 1727.

(8) (a) Yokoe, I.; Matsumoto, S.; Shirataki, Y.; Komatsu, M. *Heterocycles* **1985**, *23*, 1395. (b) Harada, N.; Nakanishi, K. *J. Chem. Soc. D* **1970**, 310. (c) Tamura, Y.; Tsujimoto, N.; Sumida, Y.; Ikeda, M. *Tetrahedron* **1972**, *28*, 21. (d) Potts, K. T.; Youzwak, H. P.; Zurawel, S. J. Jr. *J. Org. Chem.* **1980**, *45*, 90. (e) Tominaga, Y.; Ichihara, Y.; Mori, T.; Kamio, C.; Hosomi, A. *J. Heterocycl. Chem.* **1990**, *27*, 263.

(9) (a) Wu, H. C.; Hwang, L. C.; Wu, M. J. *Org. Biomol. Chem.* **2011**, *9*, 670. (b) Ling, L.; Chen, J.; Song, J.; Zhang, Y.; Li, X.; Song, L.; Shi, F.; Li, Y.; Wu, C. *Org. Biomol. Chem.* **2013**, *11*, 3894. (c) Chen, Z.; Gao, L.; Ye, S.; Ding, Q.; Wu, J. *Chem. Commun.* **2012**, *48*, 3975. (d) Ding, S.; Yan, Y.; Jiao, N. *Chem. Commun.* **2013**, *49*, 4250.

(10) (a) Mousseau, J. J.; Bull, J. A.; Ladd, C. L.; Fortier, A.; Roman, D. S.; Charette, A. B. *J. Org. Chem.* **2011**, *76*, 8243. (b) Mousseau, J. J.; Fortier, A.; Charette, A. B. *Org. Lett.* **2010**, *12*, 516.

(11) Wu, H.-C.; Yang, C.-W.; Hwang, L.-C.; Wu, M.-J. *Org. Biomol. Chem.* **2012**, *10*, 6640.

(12) (a) Huang, P.; Yang, Q.; Chen, Z.; Ding, Q.; Xu, J.; Peng, Y. *J. Org. Chem.* **2012**, *77*, 8092. (b) Chen, Z.; Wu, J. *Org. Lett.* **2012**, *14*, 5385.

(13) (a) Zhao, J.; Wu, C.; Li, P.; Ai, W.; Chen, H.; Wang, C.; Larock, R. C.; Shi, F. *J. Org. Chem.* **2011**, *76*, 6837. (b) Zhao, J.; Li, P.; Wu, C.; Chen, H.; Ai, W.; Sun, R.; Ren, H.; Larock, R. C.; Shi, F. *Org. Biomol. Chem.* **2012**, *10*, 1922. (c) Ravi, C.; Mohan, D. C.; Reddy,

N. N. K.; Adimurthy, S. *RSC Adv.* **2015**, *5*, 42961. (d) Tao, W.; Ailong, S.; Haiyan, F.; Shuwu, Y.; Meng, G.; Jun, T.; Lei, A. *Tetrahedron* **2015**, *71*, 4473.
(14) Chen, Z.; Wu, J. *Org. Lett.* **2010**, *12*, 4856.
(15) Ou, Y.; Jiao, N. *Chem. Commun.* **2013**, *49*, 3473.
(16) Zheng, Q. Z.; Feng, P.; Liang, Y. F.; Jiao, N. *Org. Lett.* **2013**, *15*, 4202.
(17) (a) Xie, F.; Qi, Z.; Li, X. *Angew. Chem. Int. Ed.* **2013,** *52,* 11862. (b) Boekelheide, V.; Lehn, W. L. *J. Org. Chem.* **1961,** *26,* 428.
(18) Stevens, K. L.; Jung, D. K.; Alberti, M. J.; Badiang, J. G.; Peckham, G. E.; Veal, J. M.; Cheung, M.; Harris, P. A.; Chamberlain, S. D.; Peel, M. R. *Org. Lett.* **2005**, *7*, 4653.
(19) (a) Fustero, S.; Román, R.; Asensio, A.; Maestro, M. A.; Aceña, J. L.; Simón-Fuentes, A. *Eur. J. Org. Chem.* **2013**, 7164. (b) Kendall, J. D.; Marshall, A. J.; Giddens, A. C.; Tsang, K. Y.; Boyd, M.; Frédérick, R.; Lill, C. L.; Lee, W.-J.; Kolekar, S.; Chao, M.; Malik, A.; Yu, S.; Chaussade, C.; Buchanan, C. M.; Rewcastle, G. W.; Baguley, B. C.; Flanagan, J. U.; Denny, W. A.; Shepherd, P. R. *Med. Chem. Commun.* **2014**, *5*, 41.
(20) (a) Yan, R.; Luo, J.; Wang, C.; Ma, C. W.; Huang, G.; Liang, Y.-M. *J. Org. Chem.* **2010**, *75*, 5395. (b) Bethel, P. A.; Campbell, A. D.; Goldberg, F. W.; Kemmitt, P. D.; Lamont, G. M.; Suleman, A. *Tetrahedron* **2012**, *68*, 5434. (c) Deng, X.; Liang, J. T.; Peterson, M.; Rynberg, R.; Cheung, E.; Mani, N. S. *J. Org. Chem.* **2010**, *75*, 1940. (d) Takahashi, Y.; Hibi, S.; Hoshino, Y.; Kikuchi, K.; Shin, K.; Murata-Tai, K.; Fujisawa, M.; Ino, M.; Shibata, H.; Yonaga, M. *J. Med. Chem.* **2012**, *55*, 5255. (e) Liu, C.; Lu, Q.; Huang, Z.; Zhang, J.; Liao, F.; Peng, P.; Lei, A. *Org. Lett.* **2015**, *17*, 6034. (f) Jawaid, A.; Nepal, D.; Park, K.; Jespersen, M.; Qualley, A.; Mirau, P.; Drummy, L. F.; Vaia, R. A. *Chem. Mater.* **2016**, *28*, 337.
(21) (a) Mohan, D. C.; Ravi, C.; Rao, S. N.; Adimurthy, S. *Org. Biomol. Chem.* **2015**, *13*, 3556. (b) Chunavala, K. C.; Joshi, G.; Suresh, E.; Adimurthy, S. *Synthesis* **2011**, 635.
(22) Patnaik, S.; Dietz, H. C.; Zheng, W.; Austin, C.; Marugan, J. J. *J. Org. Chem.* **2009**, *74*, 8870.
(23) (a) Gmeiner, P.; Schunemann, J. *Arch. Pharm.* **1988**, *321*, 517. (b) Ibaraki, Y. S.; Hyogo, A. A.; Nishinomiya, H. K.; Ashiya, T. M. US Patent 5338743, **1994**.