

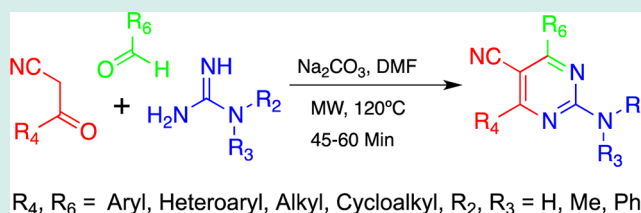
Three-Component Assembly of Structurally Diverse 2-Aminopyrimidine-5-carbonitriles

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S Supporting Information

ABSTRACT: An expedient route for the synthesis of libraries of diversely decorated 2-aminopyrimidine-5-carbonitriles is reported. This approach is based on a three-component reaction followed by spontaneous aromatization.



KEYWORDS: Multicomponent reactions, Biginelli Reaction, 2-aminopyrimidine

INTRODUCTION

The pyrimidine core is a ubiquitous structural motif in natural products.^{1,2} The diverse pharmacological activities exhibited by this highly versatile template have been extensively exploited in drug discovery (Figure 1),^{3,4} as well as in the optimization of molecular probes for the study of chemical/biological interfaces.^{5,6} In addition, pyrimidine derivatives constitute invaluable synthetic precursors in a variety of organic transformations and in coordination chemistry.^{7–9} The pursuit of protein kinase inhibitors,^{10–13} an emerging therapeutic class that has provided conceptually new therapeutic approaches for diseases that challenge the medical community, has triggered renewed interest in molecular architectures that incorporate the pyrimidine core. In particular, the role of the 2-aminopyrimidine template as a key binding fragment toward these targets has been extensively documented.^{14,15} Furthermore, this unit is one of a number of diverse molecular entities that exhibit protein kinase inhibitory activity, with the *bcr*-Abl kinase inhibitor Imatinib^{16,17} the first drug of this family to enter clinical trials.

The importance of the 2-aminopyrimidine chemotype notwithstanding, prevailing synthetic strategies to access these derivatives are rather limited in their scope and generality, being based either on the functionalization of an appropriately substituted pyrimidine ring or de novo construction thereof. Most approaches of the latter type rely on the cyclocondensation of 1,3-dicarbonyl compounds (or synthetic equivalents, such as enaminones, β -ketoenolethers, or ynones) and guanidines (e.g., Bredereck or Pinner pyrimidine syntheses).^{18–21} Densely substituted 2-aminopyrimidines are commonly obtained by the introduction of amino groups into a previously decorated pyrimidine ring^{18–21} by displacement of halides or other leaving groups at C-2 in nucleophilic aromatic substitution or metal-catalyzed C–N bond forming reactions.

Significant advances in both transformations have been made through the use of nonconventional heating modes (e.g., microwave irradiation)^{22,23} and the progress in cross-coupling chemistry^{24–28} (e.g., the development of more active catalysts). However, there are still limitations associated with these methods. In particular, the introduction of aromatic amines has not been fully addressed and these reactions generally give moderate or low yields and usually require prolonged heating at high temperatures with a large excess of amine. In addition, the multistep nature of these strategies make it difficult to implement parallel synthesis techniques and, consequently, to produce large numbers of analogs rapidly. Given this scenario, the discovery of robust synthetic strategies that enable the one-pot convergent assembly of 2-aminopyrimidines remains a vibrant research area.

The Biginelli synthesis^{29–31} is one of the classical multicomponent reactions^{32–35} and it enables rapid access to diverse pharmacologically active³⁶ collections of pyrimidine derivatives from commercially available precursors. Whereas the use of ureas and thioureas as reactive partners in the Biginelli reaction is well documented,^{29–31} similar transformations that employ guanidine derivatives are comparatively much less well developed.^{37–45} The reaction of guanidines (1) and benzyldene-3-oxoalkanoates (2) provided a proof of concept to access these heterocyclic derivatives (Figure 2), although the corresponding 2-amino-5-alkoxycarbonyl-1,4-dihydropyrimidines (3) were generally obtained in low to moderate yields.^{37,38} The concomitant formation of bicyclic compounds (e.g., diethyl 2,4,6,8-tetraaryl-4,6-dihydro-1*H*-pyrimido[1,2-*a*]-pyrimidine-3,7-dicarboxylates, compounds 4, Figure 2), which

Received: April 18, 2013

Revised: May 20, 2013

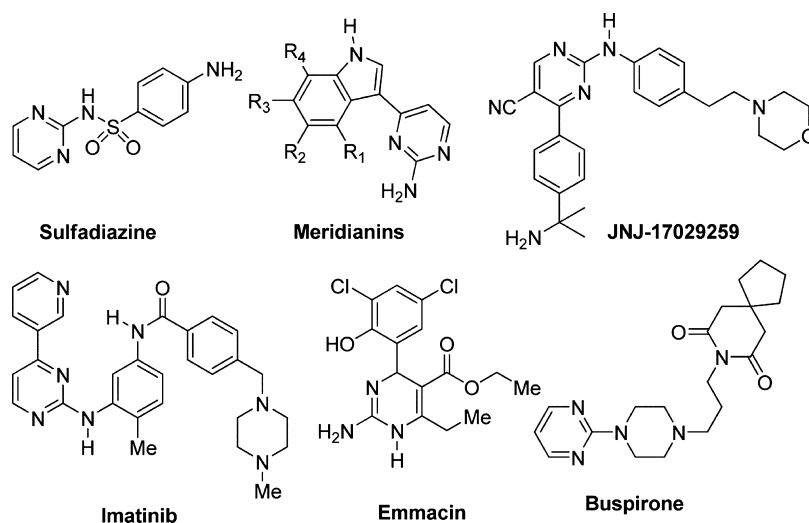


Figure 1. Representative bioactive structures that incorporate the 2-aminopyrimidine template.

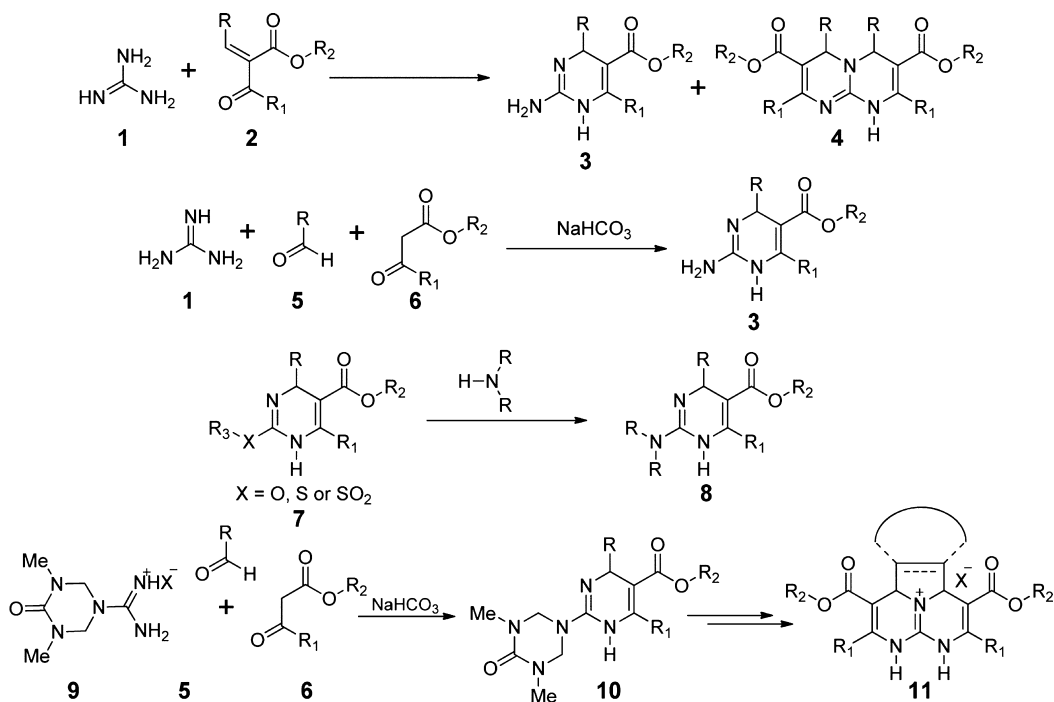


Figure 2. Biginelli-based approaches to 2-amino-3,4-dihydropyrimidines.

arise from Michael-type condensation of two ketoester molecules on the guanidine backbone, has been documented during the transformation.³⁹ An alternative approach^{29–31,40,41} has also been described and this is based on the aminolysis of Biginelli adducts containing alkyloxy- or alkylthio residues at position 2 of the heterocyclic backbone (7) for the synthesis of 2-amino-1,4-dihydropyrimidines (8) (Figure 2). The mechanistic rationalization of the available experimental data prompted Kappe to propose a three-component approach [by reacting guanidine (1), ethyl benzoylacetate (6) and carboxaldehydes (5)] to access diverse 2-amino-5-alkoxycarbonyl-3,4-dihydropyrimidines, although the method was unsuccessful with ethyl acetoacetate.⁴² The Biginelli-like approach, in addition to suppress the side-product formation, provided additional evidence for the advantages derived from the multicomponent approach. Incisive work by Overman⁴³

enabled the successful exploitation of acetoacetates as reactive partners in the Biginelli-based 2-amino-5-alkoxycarbonyl-3,4-dihydropyrimidine synthesis (Figure 2). An exhaustive experimental optimization validated the convenience of guanidine surrogates [e.g., *N*-pyrazole carboxamide or 1,3,5-triazin-4-one carboxamide (9)] as part of an expedient synthesis of guanidine alkaloid-like complex structures (batzelladine F-like derivatives (11), Figure 2). The one-pot base-catalyzed condensation of guanidine, carboxaldehydes and ketoesters has recently been employed during a diversity-oriented branching synthetic strategy that enabled the identification of Emmacin (Figure 1), the prototype of a new family of antibacterial agents.^{44,45}

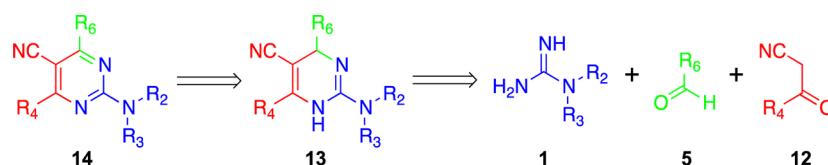
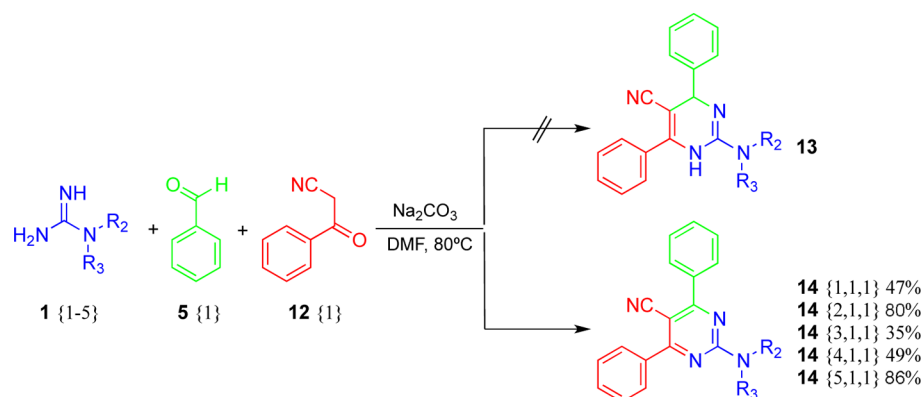


Figure 3. Retrosynthetic scheme to access targeted structures.

Scheme 1. Three-Component Synthesis of Pyrimidine-5-carbonitriles



RESULTS AND DISCUSSION

In the context of a medicinal chemistry program on the 2-aminopyrimidine chemotype, we needed to experimentally validate *in silico* bioactivities predicted for virtually generated new ligands that incorporated a cyano group at position 5 of the heterocyclic core. Given the limitations of published methods to access the target structures, we decided to assess the feasibility of a Biginelli-inspired approach (Figure 3). It was envisioned that the reaction of α -cyanoketones (**12**), carboxaldehydes (**5**), and guanidines (**1**) would enable the rapid assembly of 2-amino-1,4-dihydropyrimidine-5-carbonitriles (**13**) that could be subsequently aromatized to afford **14** (Figure 3).^{29–31}

To the best of our knowledge, α -cyanoketones and guanidines have not previously been employed in such a transformation. Following previous reports,^{42–45} we opted to apply a base-catalyzed experimental protocol (Scheme 1). A preliminary study to evaluate the feasibility of the method was developed employing benzoylacetone nitrile (**12**{1}), benzaldehyde (**5**{1}), and five guanidines (**1**{1–5}) as model substrates (Scheme 1). All of the experiments were performed in either DMF or dioxane as the solvents, while the effects of different inorganic bases (Na_2CO_3 , K_2CO_3 , and NaHCO_3), temperatures (70–100 °C), and reaction times (4–18 h) on reaction behavior were screened. From preliminary experimentation (Scheme 1) it became clear that the isolated products from the base-catalyzed reaction of benzoylacetone nitrile, benzaldehyde, and guanidines **1**{1–5} were not the corresponding 2-amino-1,4-dihydropyrimidine-5-carbonitriles (**13**) but rather the desired 2-aminopyrimidine-5-carbonitriles **14**.

These experiments not only demonstrated the feasibility of the transformation in a shorter sequence, but also enabled the identification of a set of optimal conditions (Scheme 1) to prepare **14** in moderate to satisfactory yields. Preliminary screening of the experimental conditions evidenced the superior effectiveness of DMF as the solvent while confirming the key role exerted by catalysis. The other experimental conditions screened (e.g., temperatures and aerobic conditions

vs inert atmosphere) did not prove to be particularly influential on the reaction behavior at either the qualitative (compound isolated) or quantitative (yields) level. The best results were obtained in DMF using 3 equivalents of Na_2CO_3 at 80 °C during 6–12 h. The analytical and spectroscopic data obtained for compounds **14** unequivocally support the assigned structures and these were confirmed by X-ray crystallography data obtained on a monocrystal of 2-(ethylamino)-4,6-diphenylpyrimidine-5-carbonitrile **14**{3,1,1} (Figure 4).⁴⁶

Although the mechanism of the transformation [and particularly the intermediacy of 1,4-dihydropyrimidine-5-carbonitriles (**13**)] has not been experimentally established, a

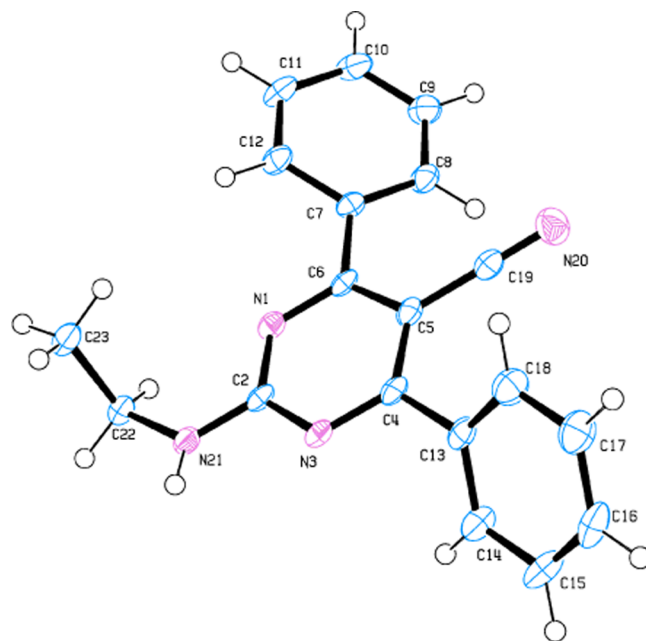


Figure 4. Plot showing the crystal structure and atomic numbering scheme for 2-(ethylamino)-4,6-diphenylpyrimidine-5-carbonitrile (**14**{3,1,1}) (CCDC 917600).⁴⁶

Scheme 2. Three-Component Synthesis of 2-Aminopyrimidine-5-carbonitriles

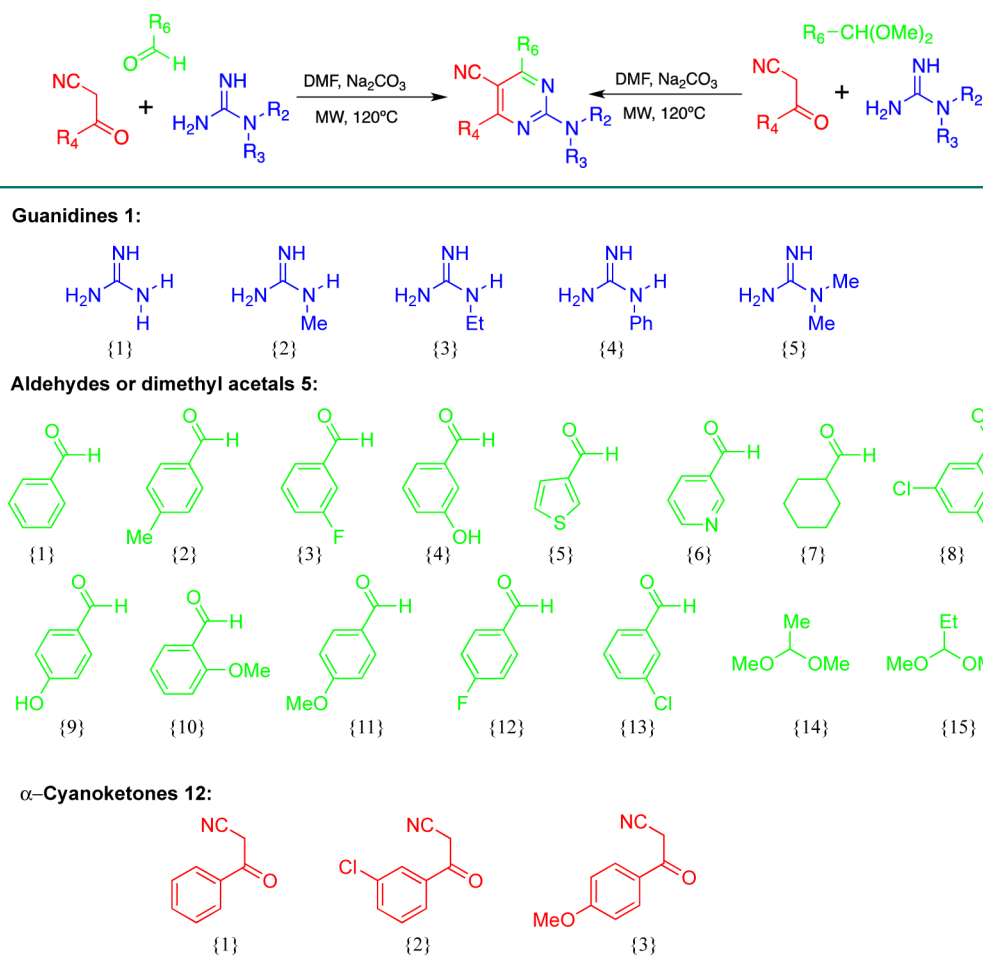


Figure 5. Diversity elements employed during library synthesis. Guanidines 1{1–5}, aldehydes 5{1–13} or dimethyl acetals {14–15}, and α -cyanoketones 12{1–3}.

rational reaction sequence would involve a Biginelli-like heterocyclization mechanism⁴⁷ followed by a spontaneous aromatization process. It should be noted that, in contrast to Hantzsch-type 1,4-dihydropyrimidines (where the aromatization to pyridines is typically facile) the dehydrogenation of dihydropyrimidines is known to be nontrivial^{30,48,49} [usually requiring stoichiometric reagents (DDQ, CAN, Pd/C, CuCl₂), harsh reaction conditions, or both]. A comparative analysis of herein documented results with the experiments reported by Kappe (employing β -keto esters) suggests the presence of a cyano group at position 5 of the heterocyclic core (instead an ester function) facilitate the aromatization process.

Having established the viability of the method (Scheme 1), we wondered if it would be possible to improve these results (e.g., yields, reaction times) by performing the three-component reaction under a nonconventional energy source, such as microwave irradiation. Preliminary experimentation on model compounds revealed that only slight modifications of optimized conditions (Scheme 1) were required to obtain target molecules in analogous yields (40–85%), while drastically shortening reaction times (<1 h). Optimal experimental conditions are depicted in Scheme 2.

Encouraged by the general interest of this convergent and experimentally simple transformation, we decided to evaluate its scope and efficiency in the generation of 2-aminopyrimidine-5-carbonitrile arrays by recourse to a diverse range of

commercially available starting materials [e.g., α -cyanoketones (12), aldehydes (5), and guanidines (1)] (Figure 5). These inputs were selected to address the generality of the transformation, while simultaneously expecting to modify the electronic, steric, and lipo-/hydrophilic features of the scaffold itself.

It was gratifyingly to observe that most of the tested substrates exhibited satisfactory reactivity profiles, in all cases leading to a smooth heterocyclization/aromatization sequence that readily afforded the target structures (Table 1). It can be seen that the transformation enables the rapid assembly of 2-aminopyrimidines that incorporate diverse residues at the heterocyclic core, a characteristic that is particularly valuable in the context of medicinal chemistry programs. As observed, the method is broadly robust with a variety of components and is not influenced by the electronic or steric variations in the reactants. Significant structural variation is well tolerated for aryl and heteroaryl aldehyde partners (including some sterically hindered derivatives), while the reaction generally failed during the introduction of aliphatic moieties (entries 20–25), which required the use of dimethyl acetals instead of the corresponding carbaldehydes to afford moderated yields (34–55%) of targeted compounds. Excellent reactivity profile was found for all guanidines (1), which proved successful for the introduction of diverse amine residues in the heterocyclic backbone (Table 1). The optimized conditions probed to be

Table 1. Structure, Time, and Yields of 2-Aminopyrimidine-5-carbonitriles Assembled^a

Reaction scheme: 1 (1-5) + 5 {1-15} + 12 {1-3} → 14. Reagents: DMF, Na₂CO₃, MW, 120 °C. Z = CHO or CH(OMe)₂.

entry	1	5	12	product	time (min)	yield (%) ^b
1	{1}	{1}	{1}	14{1,1,1}	60	47
2	{2}	{1}	{1}	14{2,1,1}	60	80
3	{3}	{1}	{1}	14{3,1,1}	60	35
4	{4}	{1}	{1}	14{4,1,1}	60	49
5	{5}	{1}	{1}	14{5,1,1}	60	86
6	{1}	{2}	{1}	14{1,2,1}	60	65
7	{1}	{3}	{1}	14{1,3,1}	60	58
8	{1}	{4}	{1}	14{1,4,1}	60	66
9	{1}	{5}	{1}	14{1,5,1}	60	74
10	{1}	{6}	{1}	14{1,6,1}	60	57
11	{1}	{7}	{1}	14{1,7,1}	60	45
12	{1}	{8}	{2}	14{1,8,2}	60	64
13	{2}	{9}	{1}	14{2,9,1}	60	71
14	{2}	{10}	{1}	14{2,10,1}	60	76
15	{2}	{6}	{1}	14{2,6,1}	60	78
16	{4}	{9}	{1}	14{4,9,1}	60	70
17	{4}	{11}	{3}	14{4,11,3}	60	73
18	{5}	{12}	{1}	14{5,12,1}	60	81
19	{5}	{13}	{1}	14{5,13,1}	60	75
20	{1}	{14}	{1}	14{1,14,1}	45	34
21	{2}	{14}	{1}	14{2,14,1}	45	48
22	{4}	{14}	{1}	14{4,14,1}	45	55
23	{1}	{15}	{1}	14{1,15,1}	45	37
24	{2}	{15}	{1}	14{2,15,1}	45	46
25	{4}	{15}	{1}	14{4,15,1}	45	51

^aReaction conditions: **1** (1.2 mmol), **5** (1.0 mmol), **12** (1.0 mmol), Na₂CO₃ (3.0 mmol), DMF (4 mL), MW heating 120 °C. ^bIsolated yields.

general, with only slight differences in the required reaction times (Table 1).

In summary, a convergent and robust three-component approach that enables the assembly of 2-aminopyrimidine-5-carbonitriles from simple starting materials has been developed. By virtue of its operational simplicity, efficiency, and wide scope, the herein documented methodology constitutes a very attractive protocol addressing the access to diversely substituted pyrimidine derivatives in a cost- and time-effective manner.

EXPERIMENTAL PROCEDURES

Commercially available starting materials and reagents were purchased and used without further purification from freshly opened containers. All solvents were purified and dried by standard methods. Organic extracts were dried with anhydrous Na₂SO₄. The reactions were monitored by TLC and purified compounds showed a single spot. Unless stated otherwise, UV light or iodine vapor were used for the detection of compounds. The synthesis and purification of all compounds were accomplished using the equipment routinely available in organic chemistry laboratories. Most of the preparative experiments were performed in coated vials on an organic synthesizer with orbital stirring. Purification of isolated products was carried out by column chromatography. Compounds were routinely characterized by spectroscopic and analytical methods. Melting points were determined on a melting point apparatus and are uncorrected. The chemical

structures of the obtained compounds were characterized by nuclear magnetic resonance spectroscopy (¹H and ¹³C) and high-resolution mass spectra (HRMS). Unless otherwise quoted, NMR spectra were recorded in CDCl₃. Chemical shifts are given as δ values against tetramethylsilane as internal standard and *J* values are given in hertz (Hz). Microwave-assisted syntheses were performed in a Monowave 300 oven (Anton-Paar), reaction temperature was measured by surface sensor.

General Procedure for the Conventional Synthesis of 2,4,6-Substituted Pyrimidine-5-carbonitriles. Guanidine salt (1.2 mmol) and sodium carbonate (3 mmol) were added to an equimolecular (1.0 mmol) mixture of the α -cyanoketone and the corresponding aldehyde (or dimethyl acetal) in DMF (4 mL), and the mixture was heated at 80 °C until the starting materials had been consumed (6–12 h). The mixture was cooled to room temperature, and the solvent was evaporated to dryness to give an oily residue, which was poured into water. After extraction with ethyl acetate, the organic phase was dried (Na₂SO₄) and evaporated under reduced pressure. The oily residue was precipitated by the addition of MeOH and the isolated solid was purified by column chromatography (silica gel) and then recrystallized.

General Procedure for the Microwave-Assisted Synthesis of 2,4,6-Substituted Pyrimidine-5-carbonitriles. Guanidine salt (1.2 mmol) and sodium carbonate (3 mmol) were added to an equimolecular (1.0 mmol) mixture of the α -

cyanoketone and the corresponding aldehyde (or dimethyl acetal) in DMF (4 mL). The mixture was heated at 120 °C by irradiation in a microwave synthesizer (surface sensor) until the starting materials had been consumed (30–60 min). The mixture was cooled to room temperature, and the solvent was evaporated to dryness to give an oily residue, which was poured into water. After extraction with ethyl acetate, the organic phase was dried (Na₂SO₄) and evaporated under reduced pressure. The oily residue was precipitated by the addition of MeOH, and the isolated solid was purified by column chromatography (silica gel) and then recrystallized.

2-Amino-4,6-diphenylpyrimidine-5-carbonitrile 14{1,1,1}: Purified by flash chromatography (DCM/MeOH = 8:2) and then recrystallized (EtOH); mp 227–228 °C (EtOH); white solid; yield 47% (168 mg); ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 7.94–7.91 (m, 4H), 7.57–7.49 (m, 6H), 5.93 (s, 2H); ¹³C NMR (CDCl₃, 75.5 MHz) δ (ppm) 171.0, 162.0, 135.9, 131.1, 128.7, 128.5, 117.8, 71.6; HRMS-ESI m/z calcd. for C₁₇H₁₂N₄ [M]⁺ 272.1056, found 272.1056.

2-(Methylamino)-4,6-diphenylpyrimidine-5-carbonitrile 14{2,1,1}: Purified by flash chromatography (DCM/MeOH = 9:1) and then recrystallized (EtOH); mp 214–216 °C (EtOH); white solid; yield 80% (228 mg); ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 8.05–7.89 (m, 4H), 7.54–7.52 (m, 6H), 5.86 (bs, 1H), 3.11 (d J = 5.1 Hz, 3H); ¹³C NMR (CDCl₃, 75.5 MHz) δ (ppm) 171.0, 161.7, 136.3, 131.0, 128.9, 128.6, 118.5, 91.7, 28.1; HRMS-ESI m/z calcd. for C₁₈H₁₄N₄ [M + H]⁺ 287.1296, found 287.1291.

2-(Ethylamino)-4,6-diphenylpyrimidine-5-carbonitrile 14{3,1,1}: Purified by flash chromatography (DCM/MeOH = 9:1) and then recrystallized (EtOH); mp 178–180 °C (EtOH); yield 35%; ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 8.02–7.90 (m, 4H), 7.50–7.25 (m, 6H), 5.86 (t, 1H, J = 4.63), 3.58 (m, 2H, CH₂), 1.26 (t, 3H, J = 7.2, CH₃); HRMS m/z calcd. for C₁₉H₁₆N₄ (M⁺) 300.3571, found 300.3567.

4,6-Diphenyl-2-(phenylamino)pyrimidine-5-carbonitrile 14{4,1,1}: Purified by flash chromatography (DCM/MeOH = 9:1) and then recrystallized (EtOH); mp 165–167 °C (EtOH); white solid; yield 49% (191 mg); ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 8.04–8.02 (m, 4H), 7.72 (m, 3H), 7.60–7.55 (m, 6H), 7.38 (t J = 7.5 Hz, 2H), 7.13 (t J = 7.5 Hz, 1H); ¹³C NMR (CDCl₃, 75.5 MHz) δ (ppm) 171.1, 158.9, 138.0, 136.0, 131.2, 128.9, 128.8, 128.5, 123.8, 119.8, 118.0, 93.9; HRMS-ESI m/z calcd for C₂₃H₁₆N₄ [M + H]⁺ 349.1453, found 349.1448.

2-(Dimethylamino)-4,6-diphenylpyrimidine-5-carbonitrile 14{5,1,1}: Purified by flash chromatography (DCM/MeOH = 9:1) and then recrystallized (EtOH); mp 233–234 °C (EtOH); white solid; yield 86% (258 mg); ¹H NMR (DMSO-*d*₆, 300 MHz) δ (ppm) 7.92 (m, 4H), 7.58 (m, 6H), 3.49 (s, 6H); ¹³C NMR (DMSO-*d*₆, 75.5 MHz) δ (ppm) 169.8, 136.8, 131.1, 129.0, 128.5, 123.5, 107.0, 93.1, 36.9; HRMS-ESI m/z calcd. for C₁₉H₁₆N₄ [M + H]⁺ 301.1453, found 301.1448.

2-Amino-6-phenyl-4-*p*-tolylpyrimidine-5-carbonitrile 14{1,2,1}: Purified by flash chromatography (DCM/MeOH = 8:2) and then recrystallized (EtOH); mp 192–193 °C (EtOH); white solid; yield 65% (185 mg); ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 7.93 (m, 2H), 7.85 (d J = 8.0 Hz, 2H), 7.54 (m, 3H), 7.33 (m, 2H), 5.73 (s, 2H), 2.48 (s, 3H); ¹³C NMR (CDCl₃, 75.5 MHz) δ (ppm) 171.1, 170.8, 163.1, 141.3, 137.0, 134.1, 132.4, 131.2, 129.3, 129.2, 128.7, 119.1, 91.2, 21.4; HRMS-ESI m/z calcd for C₁₈H₁₄N₄ [M + H]⁺ 287.1297; found 287.1291.

2-Amino-4-(3-fluorophenyl)-6-phenylpyrimidine-5-carbonitrile 14{1,3,1}: Purified by flash chromatography (DCM/

MeOH = 8:2) and then recrystallized (EtOH); mp 245–246 °C (EtOH); white solid; yield 58% (168 mg); ¹H NMR (DMSO-*d*₆, 300 MHz) δ (ppm) 7.96 (bs, 2H), 7.89–7.85 (m, 2H), 7.73–7.54 (m, 6H), 7.53–7.40 (m, 1H); ¹³C NMR (DMSO-*d*₆, 75.5 MHz) δ (ppm) 170.7, 169.4, 163.8, 162.8, 159.9, 138.9, 136.5, 131.0, 128.8, 128.5, 125.1, 118.4, 117.9, 115.9, 91.2; HRMS-ESI m/z calcd. for C₁₇H₁₁FN₄ [M + H]⁺ 291.1046, found 291.1041.

2-Amino-4-(3-hydroxyphenyl)-6-phenylpyrimidine-5-carbonitrile 14{1,4,1}: Purified by flash chromatography (DCM/MeOH = 8:2) and then recrystallized (EtOH); mp 249–251 °C (EtOH); white solid; yield 66% (190 mg); ¹H NMR (DMSO-*d*₆, 300 MHz) δ (ppm) 9.75 (s, 1H, OH), 7.85–7.82 (m, 4H), 7.55–7.52 (m, 3H), 7.36–7.32 (m, 3H), 6.96–6.93 (m, 1H); ¹³C NMR (DMSO-*d*₆) δ (ppm) 170.8, 170.7, 162.8, 157.3, 137.8, 136.6, 130.9, 129.5, 128.8, 128.4, 119.5, 118.6, 117.8, 115.6, 91.0; HRMS-ESI m/z calcd. for C₁₇H₁₂N₄O [M + H]⁺ 289.1089, found 289.1084.

2-Amino-6-phenyl-4-(thiophen-3-yl)pyrimidine-5-carbonitrile 14{1,5,1}: Purified by flash chromatography (DCM/MeOH = 8:2) and then recrystallized (EtOH); mp 181–182 °C (EtOH); white solid; Yield 74% (205 mg); ¹H NMR (DMSO-*d*₆, 300 MHz) δ (ppm) 8.64 (dd, J = 1.6 Hz, J = 1.0 Hz, 1H), 7.91–7.88 (m, 3H), 7.55–7.51 (m, 3H), 7.44–7.41 (m, 1H, aromatic), 5.60 (bs, 2H); ¹³C NMR (DMSO-*d*₆, 75.5 MHz) δ (ppm) 171.1, 164.4, 162.9, 138.1, 136.6, 130.9, 130.1, 128.8, 128.4, 127.8, 127.1, 119.1, 89.8; HRMS-ESI m/z calcd. for C₁₅H₁₀N₄S [M + H]⁺ 279.0704, found 279.0699.

2-Amino-6-phenyl-4-(pyridin-3-yl)pyrimidine-5-carbonitrile 14{1,6,1}: Purified by flash chromatography (DCM/MeOH = 8:2) and then recrystallized (EtOH); mp 243–244 °C (EtOH); white solid; yield 57% (155 mg); ¹H NMR (DMSO-*d*₆, 300 MHz) δ (ppm) 9.17 (d, J = 1.6 Hz, 1H), 8.75–8.70 (m, 1H), 8.25 (m, 1H), 8.01 (m, 2H), 7.90–7.86 (m, 2H), 7.62–7.55 (m, 4H); ¹³C NMR (DMSO-*d*₆, 75.5 MHz) δ (ppm) 187.9, 170.6, 168.5, 162.9, 151.5, 149.2, 136.4, 132.5, 131.1, 128.8, 128.5, 123.5, 118.4, 91.5; HRMS-ESI m/z calcd. for C₁₆H₁₁N₅ [M + H]⁺ 274.1093, found 274.1087.

2-Amino-4-cyclohexyl-6-phenylpyrimidine-5-carbonitrile 14{1,7,1}: Purified by flash chromatography (DCM/MeOH = 8:2) and then recrystallized (EtOH); mp 186–187 °C (EtOH); white solid; yield 45% (125 mg); ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 7.98–7.87 (m, 2H), 7.50–7.22 (m, 3H), 5.62 (s, 2H), 3.11–2.99 (m, 1H), 1.85–1.20 (m, 10H); ¹³C NMR (CDCl₃, 75.5 MHz) δ (ppm) 180.4, 162.3, 136.5, 172.5, 169.5, 130.9, 128.4, 117.2, 93.7, 44.3, 30.9, 25.8, 25.6; HRMS-ESI m/z calcd. for C₁₇H₁₈N₄ [M + H]⁺ 279.1610, found 279.1604.

2-Amino-6-(3-chlorophenyl)-4-(3,5-dichlorophenyl)pyrimidine-5-carbonitrile 14{1,8,2}: Purified by flash chromatography (DCM/MeOH = 8:2) and then recrystallized (EtOH); mp 274–275 °C (EtOH); white solid; yield 64% (239 mg); ¹H NMR (DMSO-*d*₆) δ (ppm) 8.11 (s, 2H), 7.93–7.84 (m, 5H), 7.66–7.59 (m, 2H); ¹³C NMR (DMSO-*d*₆) δ (ppm) 169.1, 167.9, 162.8, 139.6, 138.3, 134.3, 133.3, 130.9, 130.6, 130.4, 128.6, 127.6, 127.5, 118.0, 91.5; HRMS-ESI m/z calcd. for C₁₇H₉Cl₃N₄ [M + H]⁺ 374.9971, found 374.9966.

4-(4-Hydroxyphenyl)-2-(methylamino)-6-phenylpyrimidine-5-carbonitrile 14{2,9,1}: Purified by flash chromatography (DCM/MeOH = 9:1) and then recrystallized (EtOH); mp 307–308 °C (EtOH); white solid; yield 71% (214 mg); ¹H NMR (CDCl₃, 300 MHz) δ (ppm) (DMSO-*d*₆) 10.15 (bs, 1H, OH), 8.23 (bs, 1H, –NH), 7.92–7.78 (m, 4H), 7.56–7.52 (m, 3H), 6.93–6.88 (m, 2H), 2.95 (d J = 3.8 Hz, 3H); ¹³C NMR

(CDCl₃, 75.5 MHz) δ (ppm) 170.3, 169.6, 161.5, 160.5, 137.0, 130.9, 129.0, 128.4, 127.4, 127.1, 119.3, 115.2, 89.8, 28.0; HRMS-ESI m/z calcd. for C₁₈H₁₄N₄O [M + H]⁺ 303.1246, found 303.1240.

4-(2-Methoxyphenyl)-2-(methylamino)-6-phenylpyrimidine-5-carbonitrile 14{2,10,1}: Purified by flash chromatography (DCM/MeOH = 9:1) and then recrystallized (EtOH); mp 229–230 °C (EtOH); white solid; yield 76% (240 mg); ¹H NMR (DMSO-*d*₆, 300 MHz) δ (ppm) 8.32–8.30 (m, 1H), 7.94–7.90 (m, 1H), 7.85–7.81 (m, 1H), 7.57–7.35 (m, 5H), 7.28–7.27 (d *J* = 4.1 Hz, 1H), 7.20–7.04 (m, 1H), 3.81 (s, 3H), 2.95 (d *J* = 4.7 Hz, 3H); ¹³C NMR (DMSO-*d*₆, 75.5 MHz) δ (ppm) 171.2, 168.7, 162.0, 156.6, 136.7, 131.8, 131.1, 130.2, 129.9, 128.8, 126.1, 120.6, 118.1, 111.9, 93.3, 55.7, 28.1; HRMS-ESI m/z calcd. for C₁₉H₁₆N₄O [M + H]⁺ 317.1402, found 317.1397.

2-(Methylamino)-6-phenyl-4-(pyridin-3-yl)pyrimidine-5-carbonitrile 14{2,6,1}: Purified by flash chromatography (DCM/MeOH = 9:1) and then recrystallized (EtOH); mp 248–249 °C (EtOH); white solid; yield 78% (223 mg); ¹H NMR (DMSO-*d*₆, 300 MHz) δ (ppm) 9.11–9.01 (bs, 1H), 8.78–8.74 (m, 1H), 8.44 (m, 1H), 8.34–8.23 (m, 1H), 7.97–7.85 (m, 2H), 7.62–7.54 (m, 4H), 2.96 (d *J* = 4.7 Hz, 3H); ¹³C NMR (DMSO-*d*₆, 75.5 MHz) δ (ppm) 187.9, 170.3, 168.9, 161.6, 151.7, 149.4, 136.4, 132.7, 131.2, 128.9, 123.5, 118.6, 112.3, 91.3, 28.0; HRMS-ESI m/z calcd. for C₁₇H₁₃N₅ [M + H]⁺ 288.1249, found 288.1244.

4-(4-Hydroxyphenyl)-6-phenyl-2-(phenylamino)pyrimidine-5-carbonitrile 14{4,9,1}: Purified by flash chromatography (DCM/MeOH = 9:1) and then recrystallized (EtOH); mp 286–287 °C (EtOH); white solid; yield 70% (254 mg); ¹H NMR (DMSO-*d*₆, 300 MHz) δ (ppm) 10.51 (m, 1H), 10.24 (s, 1H), 7.96–7.90 (m, 4H), 7.83–7.80 (d *J* = 7.6 Hz, 2H), 7.60–7.57 (m, 3H), 7.34 (m, 2H), 7.04–7.01 (m, 1H), 6.95 (d *J* = 7.6 Hz, 2H); ¹³C NMR (CDCl₃, 75.5 MHz) δ (ppm) 170.7, 169.7, 160.6, 159.0, 139.3, 136.6, 131.1, 129.1, 129.0, 128.8, 128.6, 126.9, 123.2, 120.4, 118.8, 115.4, 92.2; HRMS-ESI m/z calcd. for C₂₃H₁₆N₄O [M + H]⁺ 365.1402, found 365.1397.

4,6-Bis(4-methoxyphenyl)-2-(phenylamino)pyrimidine-5-carbonitrile 14{4,11,3}: Purified by flash chromatography (DCM/MeOH = 9:1) and then recrystallized (EtOH); mp 210–211 °C (EtOH); white solid; yield 73% (297 mg); ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 10.50 (bs, 1H), 7.97 (d *J* = 8.7 Hz, 4H), 7.82 (d *J* = 7.6 Hz, 2H), 7.33 (m, 2H), 7.13 (d *J* = 8.7 Hz, 4H), 7.05 (t *J* = 7.6 Hz, 1H), 3.85 (s, 6H); ¹³C NMR (CDCl₃, 75.5 MHz) δ (ppm) 169.7, 161.8, 159.0, 139.3, 131.0, 128.8, 123.1, 120.3, 119.0, 114.0, 91.8, 55.6; HRMS-ESI m/z calcd. for C₂₅H₂₀N₄O₂ [M + H]⁺ 409.1665, found 409.1659.

2-(Dimethylamino)-4-(4-fluorophenyl)-6-phenylpyrimidine-5-carbonitrile 14{5,12,1}: Purified by flash chromatography (DCM/MeOH = 9:1) and then recrystallized (EtOH); mp 237–238 °C (EtOH); white solid; yield 81% (257 mg); ¹H NMR (DMSO-*d*₆, 300 MHz) δ (ppm) 8.04–8.01 (m, 2H), 7.99–7.91 (m, 2H), 7.57–7.55 (m, 3H), 7.43–7.37 (m, 2H), 3.32 (s, 6H); ¹³C NMR (DMSO-*d*₆, 75.5 MHz) δ (ppm) 170.2, 169.7, 160.6, 137.1, 133.6, 132.0, 131.5, 129.3, 128.9, 119.2, 116.1, 115.8, 90.3, 37.3; HRMS-ESI m/z calcd. for C₁₉H₁₅N₄F [M + H]⁺ 319.1359, found 319.1354.

4-(3-Chlorophenyl)-2-(dimethylamino)-6-phenylpyrimidine-5-carbonitrile 14{5,13,1}: Purified by flash chromatography (DCM/MeOH = 9:1) and then recrystallized (EtOH); mp 178–179 °C (EtOH); white solid; yield 75% (250 mg); ¹H

NMR (DMSO-*d*₆, 300 MHz) δ (ppm) 7.94–7.86 (m, 4H), 7.66–7.52 (m, 5H), 3.27 (s, 6H); (DMSO-*d*₆ 75.5 MHz) δ (ppm) 170.1, 168.7, 160.5, 139.1, 137.0, 133.6, 131.5, 131.2, 130.8, 129.3, 129.0, 128.9, 128.0, 119.0, 90.3, 37.3; HRMS-ESI m/z calcd. for C₁₉H₁₅ClN₄ [M + H]⁺ 335.1063, found 335.1058.

2-Amino-6-methyl-4-phenylpyrimidine-5-carbonitrile 14{1,14,1}: Purified by flash chromatography (DCM/MeOH = 8:2) and then recrystallized (EtOH); mp 170–172 °C (EtOH); white solid; yield 34% (71 mg); ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 7.91–7.88 (m, 2H), 7.52–7.50 (m, 3H), 5.70 (bs, 2H), 2.62 (s, 3H); ¹³C NMR (CDCl₃, 75.5 MHz) δ (ppm) 173.3, 162.0, 135.5, 131.1, 128.5, 128.4, 117.1, 107.5, 95.5, 23.5; HRMS-EI m/z calcd. for C₁₂H₁₀N₄ [M]⁺ 210.0905, found 210.0910.

6-Methyl-2-(methylamino)-4-phenylpyrimidine-5-carbonitrile 14{2,14,1}: Purified by flash chromatography (DCM/MeOH = 8:2) and then recrystallized (EtOH); mp 174–176 °C (EtOH); white solid; yield 48% (107 mg); ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 8.00–7.86 (m, 2H), 7.51–7.49 (m, 3H), 5.88 (bs, 1H), 3.01 (d *J* = 8.3 Hz, 3H), 3.14 (s, 3H); ¹³C NMR (CDCl₃, 75.5 MHz) δ (ppm) 177.1, 169.8, 161.7, 136.1, 130.8, 128.6, 128.4, 117.5, 28.1, 23.9, 23.5; HRMS-EI m/z calcd. for C₁₃H₁₂N₄ [M]⁺ 224.1062, found 224.1068.

6-Methyl-4-phenyl-2-(phenylamino)pyrimidine-5-carbonitrile 14{4,14,1}: Purified by flash chromatography (DCM/MeOH = 8:2) and then recrystallized (EtOH); mp 168–169 °C (EtOH); white solid; yield 55% (157 mg); ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 8.02–7.99 (m, 2H), 7.67–7.52 (m, 6H), 7.12 (m, 2H), 7.12 (m, 1H), 2.69 (s, 3H); ¹³C NMR (CDCl₃, 75.5 MHz) δ (ppm) 173.0, 169.0, 158.8, 137.9, 135.7, 131.2, 128.9, 128.7, 128.6, 123.7, 119.9, 117.3, 95.6, 23.8. HRMS-ESI m/z calcd. for C₁₈H₁₄N₄ [M + H]⁺ 287.1297, found 287.1291.

2-Amino-4-ethyl-6-phenylpyrimidine-5-carbonitrile 14{1,15,1}: Purified by flash chromatography (DCM/MeOH = 8:2) and then recrystallized (EtOH); mp 123–125 °C (EtOH); white solid; yield 37% (82 mg); ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 7.90–7.86 (m, 2H), 7.52–7.46 (m, 3H), 5.75 (bs, 2H), 2.93 (d *J* = 7.5 Hz, 2H), 1.34 (d *J* = 7.5 Hz, 3H); ¹³C NMR (CDCl₃, 75.5 MHz) δ (ppm) 173.0, 169.8, 162.2, 135.8, 131.0, 128.5, 128.4, 117.1, 111.0, 30.1, 12.1; HRMS-EI m/z calcd. for C₁₃H₁₂N₄ [M]⁺ 224.1062, found 224.1068.

6-Ethyl-2-(methylamino)-4-phenylpyrimidine-5-carbonitrile 14{2,15,1}: Purified by flash chromatography (DCM/MeOH = 8:2) and then recrystallized (EtOH); mp 143–144 °C (EtOH); white solid; yield 46% (109 mg); ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 7.99–7.85 (m, 2H), 7.51–7.49 (m, 3H), 5.65 (bs, 1H), 3.07 (s, 3H), 2.91 (q *J* = 7.2 Hz, 2H), 1.23 (t *J* = 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 75.5 MHz) δ (ppm) 176.7, 169.3, 162.0, 136.5, 130.8, 128.7, 128.5, 117.8, 92.8, 30.0, 28.2, 12.1; HRMS-EI m/z calcd. for C₁₄H₁₄N₄ [M]⁺ 238.1218, found 238.1228.

4-Ethyl-6-phenyl-2-(phenylamino)pyrimidine-5-carbonitrile 14{4,15,1}: Purified by flash chromatography (DCM/MeOH = 9:1) and then recrystallized (EtOH); mp 151–152 °C (EtOH); white solid; yield 51% (153 mg); ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 8.01–7.98 (m, 2H), 7.71–7.68 (m, 2H), 7.57–7.51 (m, 4H), 7.37 (m, 2H), 7.12 (m, 1H), 3.07 (t *J* = 7.5 Hz, 2H), 1.41 (t *J* = 7.5 Hz, 3H); ¹³C NMR (CDCl₃, 75.5 MHz) δ (ppm) 169.1, 159.0, 138.1, 135.9, 133.5, 131.1, 128.9, 128.6, 128.5, 123.6, 119.7, 117.1, 95.0, 30.1, 11.8;

HRMS-EI m/z calcd. for $C_{19}H_{16}N_4$ $[M]^+$ 300.1375, found 300.1367.

■ ASSOCIATED CONTENT

■ Supporting Information

Copies of 1H and ^{13}C NMR spectra for all compounds and crystallographic information files (CIF) of compound **14**{3,1,1}. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Funding

This work was financially supported by the Fondo Europeo de Desarrollo Social (FEDER) and the Galician Government (Project: 09CSA016234PR). E.S. is the recipient of a Consolidation Group Research Grant from the Conselleria de Educación (Xunta de Galicia).

Notes

The authors declare no competing financial interest.

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