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A One-Pot Synthesis of 2-Aminopyrimidines from Ketones, Arylacetylenes, and Guanidine

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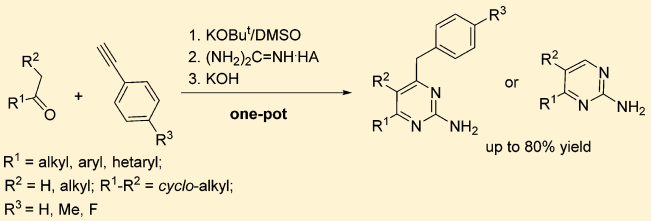
Supporting Information

ABSTRACT: The three-component reaction of ketones, arylacetylenes, and guanidine catalyzed by the KOBu^t/DMSO system leads to 2-aminopyrimidines in up to 80% yield. Depending on structure of the starting ketones, the aromatization of intermediate dihydropyrimidines occurs either with loss of hydrogen molecules or methylbenzenes. The latter process takes place in the ketones, in which one of the substituents is not a methyl group. The reaction conditions are tolerable for dialkyl-, aryl(hetaryl) alkyl-, and cycloalkyl ketones.



INTRODUCTION

The pyrimidine structural motif is a fundamental part of nucleic acids and is associated with numerous biological activities.[1] Substituted aminopyrimidine nuclei are common in the marketed drugs such as antiatherosclerotic Aronixil, antihistaminic Thonzylamine (**I**), antianxielytic Buspirone (**II**), antipsoriatic Enazadrem (**III**), and other medicinally relevant compounds (Figure 1).[2]

The discovery of a series of aminopyrimidine derivatives inhibiting the protein kinases is one of the most important advances in the field of synthetic chemistry of aminopyrimidines.[1a,3] Some other biological activities of these molecules include antitubercular,[4] adenosine receptor antagonists,[5] analgesic,[6] and anti-inflammatory.[5]

These compounds play an essential role as potential drugs for treating oncologic diseases, making the development of the methods for their preparation one of the priority goals of fine organic synthesis. The various routes to aminopyrimidines and their derivatives are known.[7] A popular approach is the condensation of chalcones with guanidine (Scheme 1).[8]

These methods are actually two step since they require preliminary preparation of chaclones and are limited in the substrate scope (mostly aromatic substituents). Despite a number of existing protocols for the construction of this exceptionally valuable heterocyclic core, there is still a lot of space for finding other rational approaches in terms of both interesting chemistry and novel structures.

RESULTS AND DISCUSSION

Nowadays, the recently discovered base-catalyzed addition of ketones to alkynes to afford β,γ-ethylenic ketones[9] has been successfully employed as the intermediate step for an efficient one-pot synthesis of 2-isoxazolines,[10] 2-pyrazolines[11] and 1-formyl-2-pyrazolines,[12] benzoxepines,[13] 2,5-diaryl furans,[9a,14] and acylated terphenyls.[15]

As further development of this original methodology for the assembly of valuable carbo- and heterocyclic compounds, we disclose here a new general one-pot strategy for the synthesis of 2-aminopyrimidines via the sequential three-component reaction between ketones **1**, arylacetylenes **2**, and guanidine (Table 1).

The overall synthesis of aminopyrimidines **3** and **4** is implemented as follows: To a mixture of ketone **1** and arylacetylene **2** in the KOBu^t/DMSO system kept at 100 °C for 30 min, water and guanidine salt (*e.g.*, nitrate, hydrochloride) are added at 70 °C, and after 0.5−4.0 h, the reaction mixture is treated with KOH (in equimolar ratio relative to the reactants) at the same temperature for 30 min.

As seen from Table 1, two series of aminopyrimidines can be separately obtained, 4-benzyl-substituted (**3a−h**) and unsubstituted at the position 4 (**4a−f**), i.e., those resulted from elimination of methylbenzenes. The latter are formed in the case when the substrates are not methyl ketones ($R^2 \neq H$).

The strategy for one-pot synthesis of aminopyrimidines is effective for a diversity of ketones **1** such as dialkyl **1a**, cycloalkyl **1b−e**, and alkylaryl **1f−h** as well as for the substituted arylacetylenes. Acetyl naphthalene **1i** and acetyl thiophene **1j** tolerate the reaction conditions and also afford the desired products, though in modest yields. Apart from 3,3-dimethyl-butan-2-one **1a** (Table 1, entries 1 and 2), two other dialkyl ketones (butan-2-one and 4-methyl-pentan-2-one), which could give mixtures of regioisomers, have also been tested in this reaction. In both the cases, complex mixtures of inseparable products were formed. Certainly, it is understood that each combination of the reactants requires its own optimization.

Upon comparison of this synthesis with the previous ones based on chalcones (Scheme 1), the following advantages seem

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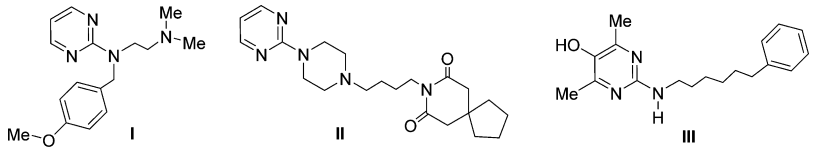
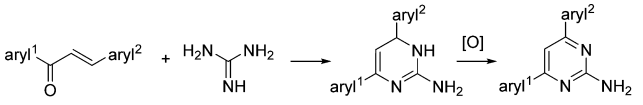


Figure 1. Approved drugs containing aminopyrimidine scaffold.

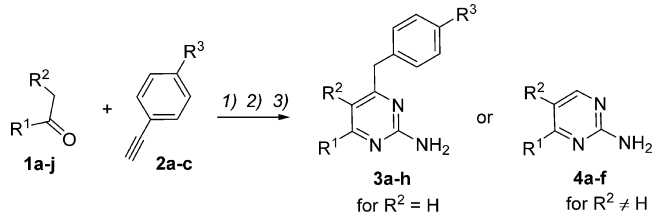
Scheme 1. Synthesis of 2-Aminopyrimidines from Chalcones and Guanidine[8]



obvious: (i) one-step protocol; (ii) a greater diversity of the substituents nature; and (iii) the possibility to introduce the above substituents in different combinations. All together this allows a better structural diversity to be attained.

The mechanism of the aminopyrimidine formation deserves a special physical-chemical investigation. In this paper, which is focused mainly on the synthesis, it could be relevant to consider just plausible schemes. It might be assumed that the assembly of 2-aminopyrimidines **3** and **4** consists of the following key steps (Scheme 2): dienolates **A**, the primary adducts of ketones **1** to arylacetylenes **2**,[9] react with water to release *β,γ*-unsaturated ketones **B**, which interact with guanidine giving the open-chain intermediates **C**. The latter undergo the ring

Table 1. Synthesis of 2-Aminopyrimidines 3 and 4 from Ketones 1, Arylacetylenes 2, and Guanidine[a]



entry	ketone	arylacetylene	product, yield (%)[b]
1	**1a**	**2a**	**3a**, 51
2	**1a**	**2b**	**3b**, 56
3	**1b**	**2a**	**4a**, 68
4	**1b**	**2b**	**4a**, 60
5	**1b**	**2c**	**4a**, 63
6	**1c**	**2a**	**3c**, 32 **4b**, 31
7	**1d**	**2a**	**4c**, 70
8[c]	**1e**	**2a**	**4d**, 80
9	**1f**	**2a**	**3d**, 33
10	**1f**	**2c**	**3e**, 41
11[c]	**1g**	**2a**	**4e**, 60
12	**1h**	**2a**	**4f**, 58
13[c]	**1i**	**2a**	**3f**, 49
14[c]	**1j**	**2a**	**3g**, 30
15[c]	**1j**	**2c**	**3h**, 31

[a]Reagents and conditions: (1) ketone **1** (5 mmol), arylacetylene **2** (5 mmol), KOBu^t (6 mmol, 0.67 g), DMSO (10 mL), 100 °C, 30 min; (2) H_2O (5 mmol, 0.09 g), $(NH_2)_2C{=}NH{\cdot}HA$ (6 mmol), 70 °C, 0.5 h for ketones **1f,i,j**, 3 h for ketones **1a**−**e**, 4 h for ketones **1g,h**; (3) KOH·0.5 H_2O (5 mmol, 0.33 g), 70 °C, 0.5 h. [b]Isolated yield after the workup and column chromatography (Al_2O_3, benzene-diethyl ether with gradient from 1:0 to 10:1). [c]These experiments were carried out under the argon.

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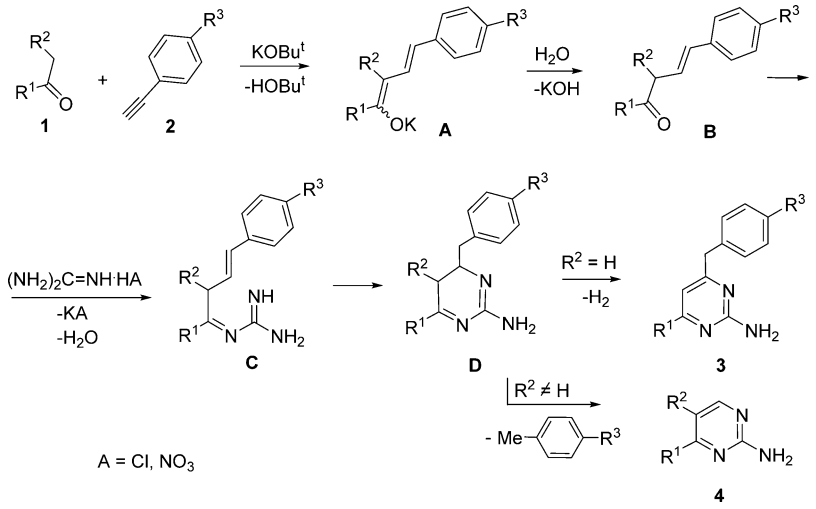
Scheme 2. Plausible Scheme of the Assembly of 2-Aminopyrimidines 3 and 4 from Ketones 1, Arylcetylenes 2, and Guanidine



closure to dihydropyrimidines **D**. The cyclization does not require the preliminary conversion of the adducts **C** to the corresponding α,β-unsaturated isomers since the nucleophilic addition to the styrene moiety is also possible.[16] The further aromatization of dihydropyrimidines **D** leads to products **3** or **4**.

The aromatization follows the two pathways: when R^2 = H, intermediates **D** normally lose a hydrogen molecule to give aminopyrimidines **3** (Scheme 2), while when $R^2 \neq$ H, the elimination of methylbenzenes from the dihydropyrimidine ring (identified by GLC) takes place to deliver benzyl-free aminopyrimidines **4** (Scheme 2).

The experiments with cyclohexanone **1b** and 4-fluoromethylacetylene **2b** or 4-methylphenylacetylene **2c** have shown that during both reactions, the elimination of the expected 1-methyl-4-fluorobenzene and 1,4-dimethylbenzene results in approximately the same yields of the final products (Table 1). This demonstrates that aromatization of dihydropyrimidines with elimination of the expected methyl aromatics is not significantly influenced by electron-donating and electron-withdrawing substituents (R^3). Recently,[15] the same aromatization with elimination of methyl aromatics from the dihydrobenzene moiety under similar conditions (KOBu^t/DMSO) has been observed during the synthesis of terphenyls from ketones and arylacetylenes.

The only exception, when both dehydrogenation and debenzylation takes place, is the reaction with 4-methylcyclohexanone **1c**. This interesting fact does not find so far a clear-cut rationalization and will be specially addressed during further investigations.

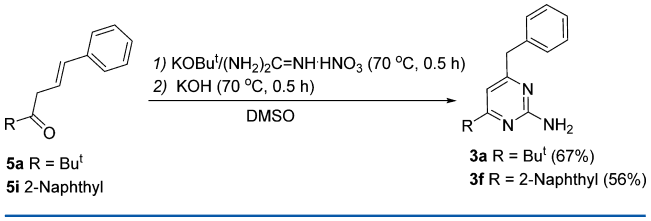
Since the aromatization of the intermediate dihydropyrimidines **D** does not proceed without addition of KOH, it may be suggested that the ambient oxygen probably does not participate in this process. To check whether the air oxygen is involved in the aromatization, the selected experiments (Table 1, entries 8, 11, 13–15) under argon with degassed solvent (DMSO) have been carried out. The results obtained show that the aromatization does take place also in this case. By the way, the amounts of oxygen, which is contained in the volume of closed reaction vessel (5 mmol of the reactants, 10 mL of DMSO in 30 mL vessel), would be enough only to aromatize just a few percent of dihydropyrimidines **D**.

Dehydrogenation with the hydride ion abstraction/transfer in strongly basic media is a well-known classic chemistry, e.g., the Dumas–Stass, reaction.[17] According to ref 18, one might also suppose that DMSO plays a role of an oxidant in this case. However, the GC-MS analysis does not detect even traces of Me_2S in the reaction mixture after completion of aminopyrimidines synthesis, thus clearly indicating that DMSO is not an oxidant in this process.

It is worthwhile to underline again that without additional feeding of KOH after neutralization of KOBu^t on the first stage of the reaction, the aromatization does not occur; the reaction products represent a mixture of isomeric dihydropyrimidines **D**. It means that the basicity function (i.e., ability of the medium to deprotonate intermediates) is a key factor in the aromatization of intermediate dihydropyrimidines **D**. Besides, as it has been shown in the previous publications,[9] the addition of ketones to acetylenes (the first step of the reaction, Scheme 2) did not proceed in solvents other than DMSO (benzene, THF, DMF, *N*-methylpyrrolidone).

As an additional test of the proposed scheme of 2-aminopyrimidines **3** formation, we have implemented the reaction of the preliminarily isolated intermediates **B** (β,γ-unsaturated ketones **5a,i**) with guanidine nitrate under the above conditions. The expected pyrimidines **3a,f** were obtained in reasonable yields (Scheme 3).

Scheme 3. Transformation of Intermediate β,γ-Unsaturated Ketones 5a,i into 2-Aminopyrimidines 3a,f



The loss of a benzyl group was also observed, when the reaction of intermediate **B** (β,γ-unsaturated ketone **5b**), preliminarily obtained from cyclohexanone **1b** and phenylacetylene **2a**, was treated with guanidine nitrate under the above conditions (Scheme 4). The expected aminopyrimidine **4a** was isolated in 72% yield.

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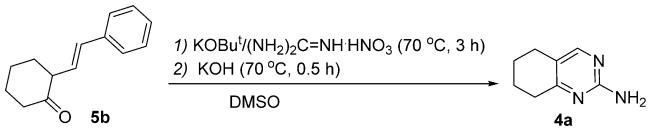
Scheme 4. Transformation of Intermediate β,γ-Unsaturated Ketone 5b into 2-Aminopyrimidine 4a



The reaction of cyclohexanone **1b** with guanidine nitrate without phenylacetylene does not result in the formation of aminopyrimidine **4a** (except a complex mixture of the ketone autocondensation products has been formed), thus indicating that the additional carbon atom in the aminopyrimidine ring is delivered from phenylacetylene.

As an alternative one might suppose that the aminopyrimidine assembly is preceded by isomerization of enolates **A** or β,γ-ethylenic ketones **B** to the corresponding α,β-ethylenic isomers. Afterward, the reaction could follow the way described by W. Guo.[7f] However, the previous publications[9] show that such an isomerization does not take place to a significant degree for these substrates; it has been found that α,β-ethylenic ketones were minor admixtures (5−10%) in major β,γ-isomers. Consequently, if the former participate in this cyclization, it could be just a minor channel compared to a major reaction via β,γ-ethylenic ketones.

The variable yields of aminopyrimidines appear to be indicative of the fact that, as shown above, the overall process involves several mechanistic steps (Scheme 2): addition of ketones to arylacetylenes, the reaction of the resulted β,γ-unsaturated ketones **B** with guanidine, cyclization of the adducts **C**, and aromatization. Consequently, in this case, the yield is a complex function of a number of parameters: substituents effect, reaction temperature and time, catalyst concentration, basicity/acidity, and properties of the reaction medium; all of these being altered during the process. Therefore, it is not surprising that a range of the yield was obtained.

In conclusion, a one-pot synthesis of 2-aminopyrimidines, medicinally important building blocks, has been developed via a sequential three-component reaction between ketones, arylacetylenes, and guanidine. This methodology has several synthetically attractive features: operationally simple procedure, use of readily available starting materials (ketones and arylacetylenes), simple transition-metal-free catalytic system (KOBu^t, KOH), and diverse structural variation in the products.

EXPERIMENTAL SECTION

General Remarks. ^{1}H (400.1 MHz), ^{13}C (100.6 MHz), ^{15}N (40.5 MHz) NMR spectra were recorded in $CDCl_3$ with hexamethyldisiloxane (HMDS) as an internal standard. Chemical shifts (δ) are given in ppm, coupling constants (J) in Hz. The assignment of signals in the ^{1}H NMR spectra was made using COSY and NOESY experiments. Resonance signals of carbon atoms were assigned based on ^{1}H−^{13}C HSQC and ^{1}H−^{13}C HMBC experiments. The values of the δ ^{15}N were measured through the 2D ^{1}H−^{15}N HMBC experiment. The ^{15}N chemical shifts were referenced to $MeNO_2$. IR spectra were taken with FT-IR. All chemicals and solvents are commercially available and were used without further purification. The elaborated procedure does not require degassing of DMSO or use of inert atmosphere. The benefit of DMSO as a solvent is that it is stable up to 150 °C for a long time (24 h, weight lost 0.1−1.0%).[19] The formation of methylbenzenes was detected by GLC analysis of reaction mixture using standards.

General Procedure for the Synthesis of Aminopyrimidines 3 and 4. A mixture of ketone **1** (5 mmol), arylacetylene **2** (5 mmol), and KOBu^t (6 mmol, 673 mg) in DMSO (10 mL) was heated (100 °C) and stirred at 100 °C for 30 min. After cooling (70 °C), H_2O (5 mmol, 90 mg) and $(NH_2)_2C{=}NH{\cdot}HNO_3$ (6.0 mmol, 733 mg) or $(NH_2)_2C{=}NH{\cdot}HCl$ (6.0 mmol, 573 mg) were added to the reaction mixture and stirred at 70 °C for 0.5 h (for ketones **1f,i,j**), 3.0 h (for ketones **1a−e**), and 4.0 h (for ketones **1g,h**). Then $KOH{\cdot}0.5H_2O$ (5 mmol, 325 mg) was added, and the mixture was stirred at 70 °C for 30 min. The reaction mixture, after cooling (rt), was diluted with H_2O (15 mL), neutralized with NH_4Cl, and extracted with $CHCl_3$ (10 mL × 4). The organic extract was washed with H_2O (5 mL × 3) and dried ($MgSO_4$). $CHCl_3$ was evaporated in vacuum, and the residue was purified by column chromatography (Al_2O_3, eluent C_6H_6/Et_2O with gradient from 1:0 to 10:1).

*4-Benzyl-6-(tert-butyl)pyrimidin-2-amine (**3a**).* Following the general procedure, **3a** was prepared from 3,3-dimethyl-2-butanone **1a** (0.501 g, 5.0 mmol), phenylacetylene **2a** (0.510 g, 5.0 mmol), KOBu^t (0.673 g, 6.0 mmol), H_2O (0.090 g, 5 mmol), $(NH_2)_2C{=}NH{\cdot}HNO_3$ (0.733 g, 6.0 mmol), and $KOH{\cdot}0.5H_2O$ (0.325 g, 5 mmol). **3a** was isolated as a cream oil (0.615 g, 51% yield); elemental analysis calcd (%) for $C_{15}H_{19}N_3$ (241.33): C 74.65%; H 7.94%; N 17.41%; found: C 74.60%; H 7.98%; N 17.36%. IR (film): ν_{max} 3487, 3398, 3325, 3317, 3062, 3028, 2962, 2928, 2870, 1953, 1885, 1811, 1613, 1577, 1552, 1487, 1448, 1396, 1359, 1237, 1201 1174, 1155, 1076, 1029, 965, 926, 853, 804, 758, 703, 574, 552, 524 cm^{-1}; ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 1.20 (s, 9H, 3Me), 3.87 (s, 2H, C$\underline{H}_2$Ph), 5.02 (br.s, 2H, NH_2), 6.44 (s, 1H, H^5), 7.20−7.22 (m, 3H, H^{o,p}), 7.27−7.30 (m, 2H, H^m) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 29.5 (Me), 37.3 (C-Me$_3$), 44.4 (C$\underline{H}_2$Ph), 106.4 (C^5), 126.7 (C^p), 128.7 (2C^m), 129.3 (2C^o), 138.5 (C^i), 163.0 (C^4), 170.1 (C^2), 179.6 (C^6) ppm; ^{15}N NMR (40.5 MHz, $CDCl_3$): δ −138.8 (N^3), −143.0 (N^1), −306.3 (NH_2) ppm.

*4-(4-Fluorobenzyl)-6-(tert-butyl)pyrimidin-2-amine (**3b**).* Following general procedure, **3b** was prepared from 3,3-dimethyl-2-butanone **1a** (0.501 g, 5.0 mmol), 4-fluorophenylacetylene **2b** (0.601 g, 5.0 mmol), KOBu^t (0.673 g, 6.0 mmol), H_2O (0.090 g, 5 mmol), $(NH_2)_2C{=}NH{\cdot}HNO_3$ (0.733 g, 6.0 mmol), and $KOH{\cdot}0.5H_2O$ (0.325 g, 5 mmol). **3b** was isolated as a cream oil (0.726 g, 56% yield); elemental analysis calcd (%) for $C_{15}H_{18}FN_3$ (259.32): C 69.47%; H 7.00%; F 7.33%; N 16.20%; found: C 69.60%; H 7.04%; F 7.21%; N 16.11%. IR (film): ν_{max} 3477, 3399, 3318, 3200, 2867, 2187, 1891, 1608, 1576, 1551, 1509, 1446, 1394, 1356, 1271, 1227, 1159, 1092, 1019, 926, 832, 773, 715, 677, 514 cm^{-1}; ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 1.20 (s, 9H, 3Me), 3.83 (s, 2H, C$\underline{H}_2$Ph), 4.89 (br.s, 2H, NH_2), 6.42 (s, 1H, H^5), 6.95−6.99 (m, 2H, H^m), 7.17−7.21 (m, 2H, H^o) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 29.4 (Me), 37.2 (C-Me$_3$), 43.4 (C$\underline{H}_2$Ph), 106.2 (C^5), 115.4 (d, J = 21.2 Hz, C^m), 130.6 (d, J = 8.1 Hz, C^o), 134.0 (d, J = 3.1 Hz, C^i), 161.8 (d, J = 244.4 Hz, C^p), 162.8 (C^4), 169.8 (C^2), 179.7 (C^6) ppm.

*4-Benzyl-6-methyl-5,6,7,8-tetrahydroquinazolin-2-amine (**3c**).* Following general procedure, **3c** was prepared from 4-methylcyclohexanone **1c** (0.561 g, 5.0 mmol), phenylacetylene **2a** (0.510 g, 5.0 mmol), KOBu^t (0.673 g, 6.0 mmol), H_2O (0.090 g, 5 mmol), $(NH_2)_2C{=}NH{\cdot}HNO_3$ (0.733 g, 6.0 mmol), and $KOH{\cdot}0.5H_2O$ (0.325 g, 5 mmol). **3c** was isolated as a cream solid (0.405 g, 32% yield); mp 132−136 °C; elemental analysis calcd (%) for $C_{16}H_{19}N_3$ (253.34): C 75.85%; H 7.56%; N 16.59%; found: C 75.77%; H 7.62%; N 16.69%. IR (film): ν_{max} 3479, 3387, 3309, 3185, 3085, 3062, 3029, 2949, 2926, 2886, 2867, 1948, 1805, 1633, 1603, 1574, 1557, 1494, 1470, 1454, 1374, 1362, 1345,1337, 1321, 1302, 1288, 1259, 1244, 1223, 1191, 1180, 1165, 1151, 1136, 1096, 1085, 1075, 1030, 1011, 994, 966, 949, 909, 867, 827, 792, 782, 750, 732, 723, 695, 645, 615, 593, 569, 529, 485, 457 cm^{-1}; ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 1.02 (d, J = 6.6 Hz, 3H, Me), 1.30−1.40 (m, 1H, 7-CH_2), 1.72−1.81 (m, 1H, H^6), 1.82−1.90 (m, 1H, 7-CH_2), 2.04 (dd, J = 15.9, 10.3 Hz, 1H, 5-CH_2), 2.66 (dd, J = 15.9, 4.9 Hz, 1H, 5-CH_2), 2.65−2.70 (m, 2H, 8-CH_2), 3.92 (s, 2H, CH_2), 4.88 (br.s, 2H, NH_2), 7.17−7.23 (m, 3H, H^{o,p}), 7.25−7.27 (m, 2H, H^m) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 21.7 (Me), 29.0 (C^6), 30.3 (C^7), 32.0 (C^8), 32.5 (C^5), 40.7 (C$\underline{H}_2$Ph), 117.5 (C^{10}),

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126.3 (C^p), 128.5 (C^m), 128.7 (C^o), 137.6 (C^i), 160.8 (C^2), 166.4 (C^9), 167.4 (C^4) ppm; ^{15}N NMR (40.5 MHz, $CDCl_3$): δ −134.6 (N^3), −140.6 (N^1), −307.2 (NH_2) ppm.

*4-Benzyl-6-phenylpyrimidin-2-amine (**3d**).* Following general procedure, **3d** was prepared from acetophenone **1f** (0.605 g, 5.0 mmol), phenylacetylene **2a** (0.510 g, 5.0 mmol), KOBu^t (0.673 g, 6.0 mmol), H_2O (0.090 g, 5 mmol), $(NH_2)_2C{=}NH{\cdot}HCl$ (0.573 g, 6.0 mmol), and $KOH{\cdot}0.5H_2O$ (0.325 g, 5 mmol). **3d** was isolated as a cream solid (0.431 g, 33% yield); mp 90−94 °C; elemental analysis calcd (%) for $C_{17}H_{15}N_3$ (261.32): C 78.13%; H 5.79%; N 16.08%; found: C 78.31%; H 5.65%; N 15.95%. IR (film): ν_{max} 3477, 3317, 3183, 3085, 3062, 3029, 2924, 2852, 1954, 1891, 1811, 1626, 1600, 1573, 1548, 1495, 1454, 1359, 1238, 1181, 1073, 1030, 1002, 909, 872, 844, 769, 733, 699, 655, 605, 532 cm^{-1}; ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 3.90 (s, 2H, C$\underline{H}_2$Ph), 5.41 (br.s, 2H, NH_2), 6.75 (s, 1H, H^5), 7.17−7.27 (m, 5H, $H^{o,p,m'}$), 7.28−7.35 (m, 3H, $H^{m,p'}$), 7.78−7.88 (m, 2H, $H^{o'}$) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 44.3 (C$\underline{H}_2$Ph), 107.1 (C^5), 126.8 (C^p), 127.1 ($C^{o'}$), 128.7 (C^m, $C^{m'}$), 129.3 (C^o), 130.4 ($C^{p'}$), 137.6 ($C^{i'}$), 138.0 (C^i), 163.4 (C^4), 165.8 (C^6), 170.9 (C^2) ppm; ^{15}N NMR (40.5 MHz, $CDCl_3$): δ −136.8 (N^3), −145.2 (N^1), −304.2 (NH_2) ppm.

*4-(4-Methylbenzyl)-6-phenylpyrimidin-2-amine (**3e**).* Following general procedure, **3e** was prepared from acetophenone **1f** (0.605 g, 5.0 mmol), 4-tolylacetylene **2c** (0.581 g, 5.0 mmol), KOBu^t (0.673 g, 6.0 mmol), H_2O (0.090 g, 5 mmol), $(NH_2)_2C{=}NH{\cdot}HNO_3$ (0.733 g, 6.0 mmol), and $KOH{\cdot}0.5H_2O$ (0.325 g, 5 mmol). **3e** was isolated as a cream solid (0.564 g, 41% yield); mp 82−88 °C; elemental analysis calcd (%) for $C_{18}H_{17}N_3$ (275.35): C 78.52%; H 6.22%; N 15.26%; found: C 78.61%; H 6.15%; N 15.09%. IR (film): ν_{max} 3478, 3315, 3184, 3061, 2925, 2854, 1959, 1902, 1801, 1629, 1565, 1455, 1359, 1234, 1180, 1147, 1078, 1028, 913, 811, 765, 733, 696, 643, 555 cm^{-1}; ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 2.30 (s, 3H, Me), 3.90 (s, 2H, C$\underline{H}_2$Ph), 5.32 (br.s, 2H, NH_2), 6.80 (s, 1H, H^5), 7.08−7.20 (m, 4H, $H^{o,m}$.), 7.39−7.41 (m, 3H, $H^{m',p'}$), 7.86−7.89 (m, 2H, $H^{o'}$) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 20.9 (Me), 43.8 (C$\underline{H}_2$Ph), 106.9 (C^5), 126.9 ($C^{o'}$), 128.5 (C^m), 129.2 (C^o), 130.1 ($C^{p'}$), 130.9 ($C^{m'}$), 134.7 (C^i), 136.1 (C^p), 137.4 ($C^{i'}$), 163.1 (C^4), 165.6 (C^6), 171.1 (C^2) ppm; ^{15}N NMR(40.5 MHz, $CDCl_3$): δ −136.6 (N^3), −144.7 (N^1), −304.1 (NH_2) ppm.

*4-Benzyl-6-(naphthalene-2-yl) pyrimidin-2-amine (**3f**).* Following general procedure, **3f** was prepared from 2-acetylnaphthalene **1i** (0.851 g, 5.0 mmol), phenylacetylene **2a** (0.510 g, 5.0 mmol), KOBu^t (0.673 g, 6.0 mmol), H_2O (0.090 g, 5 mmol), $(NH_2)_2C{=}NH{\cdot}HCl$ (0.573 g, 6.0 mmol), and $KOH{\cdot}0.5H_2O$ (0.325 g, 5 mmol) under the argon. **3f** was isolated as a white solid (0.763 g, 49% yield); mp 163−168 °C; elemental analysis calcd (%) for $C_{21}H_{17}N_3$ (311.38): C 81.00%; H 5.50%; N 13.49%; found: C 80.81%; H 5.55%; N 13.58%. IR (film): ν_{max} 3476, 3313, 3184, 3061, 3027, 2923, 2860, 1918, 1629, 1568, 1551, 1503, 1454, 1366, 1233, 1178, 1144, 1076, 1027, 904, 852, 808, 752, 704, 568, 471 cm^{-1}; ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 4.00 (s, 2H, C$\underline{H}_2$Ph), 5.12 (br.s, 2H, NH_2), 6.98 (s, 1H, H^5), 7.20−7.38 (m, 5H, $H^{o,m,p}$), 7.47−7.52 (m, 2H, H^{10}, H^{11}), 7.82−7.92 (m, 3H, H^9, H^{12}, H^{13}), 7.98−8.01 (m, 1H, H^{14}), 8.43 (s, 1H, H^8) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 44.4 (C$\underline{H}_2$Ph), 107.3 (C^5), 124.2 (C^{13}), 126.5 (C^p), 126.8 (C^9), 127.0 (C^{11}), 127.1 (C^{12}), 127.7 (C^{14}), 128.5 (C^{10}), 128.8 (C^m), 129.0 (C^8), 129.3 (C^o), 133.3 (C^{16}), 134.5 (C^{15}), 134.8 (C^7), 138.1 (C^i), 163.5 (C^4), 165.7 (C^6), 171.0 (C^2) ppm; ^{15}N NMR (40.5 MHz, $CDCl_3$): δ −136.6 (N^3), −144.7 (N^1), −304.9 (NH_2) ppm.

*4-Benzyl-6-(thiophen-2-yl)pyrimidin-2-amine (**3g**).* Following general procedure, **3g** was prepared from 2-acethylthiophene **1j** (0.631 g, 5.0 mmol), phenylacetylene **2a** (0.510 g, 5.0 mmol), KOBu^t (0.673 g, 6.0 mmol), H_2O (0.090 g, 5 mmol), $(NH_2)_2C{=}NH{\cdot}HCl$ (0.573 g, 6.0 mmol), and $KOH{\cdot}0.5H_2O$ (0.325 g, 5 mmol) under the argon. **3g** was isolated as a cream solid (0.401 g, 30% yield); mp 180−185 °C; elemental analysis calcd (%) for $C_{15}H_{13}N_3S$ (267.35): C 67.39%; H 4.90%; N 15.72%; S 11.99%; found: C 67.37%; H 4.91%; N 15.62%; S 11.94%. IR (film): ν_{max} 3485, 3289, 3166, 3100, 3083, 3028, 2920, 1622, 1573, 1556, 1548, 1518, 1494, 1459, 1446, 1416, 1366, 1342, 1227, 1194, 1172, 1074, 1044, 1030, 908, 862, 839, 826, 791, 736, 728, 707, 622, 608, 577, 568, 520 cm^{-1}; ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 3.93 (s, 2H, C$\underline{H}_2$Ph), 5.05 (br.s, 2H, NH_2), 6.72 (s, 1H, H^5), 7.06 (dd, J = 3.8, 5.0 Hz, 1H, H^9), 7.20−7.42 (m, 5H, $H^{o,m,p}$), 7.41 (d, J = 5.0 Hz, 1H, H^{10}), 7.57 (d, J = 3.8 Hz, 1H, H^8) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 44.2 (C$\underline{H}_2$Ph), 105.4 (C^5), 126.8 (C^p), 127.0 (C^8), 128.1 (C^9), 128.7 (C^m), 129.2 (C^{10}), 129.3 (C^o), 138.0 (C^i), 143.0 (C^7), 160.3 (C^6), 163.2 (C^4), 170.9 (C^2) ppm; ^{15}N NMR (40.5 MHz, $CDCl_3$): δ −136.6 (N^3), −148.3 (N^1), −305.6 (NH_2) ppm.

*4-(4-Methylbenzyl)-6-(thiophen-2-yl)pyrimidin-2-amine (**3h**).* Following general procedure, **3h** was prepared from 2-acetylthiophene **1j** (0.631 g, 5.0 mmol), 4-tolylacetylene **2c** (0.581 g, 5.0 mmol), KOBu^t (0.673 g, 6.0 mmol), H_2O (0.090 g, 5 mmol), $(NH_2)_2C{=}NH{\cdot}HNO_3$ (0.733 g, 6.0 mmol), and $KOH{\cdot}0.5H_2O$ (0.325 g, 5 mmol) out under the argon. **3h** was isolated as a cream solid (0.436 g, 31% yield); mp 123−126 °C; elemental analysis calcd (%) for $C_{16}H_{15}N_3S$ (281.38): C 68.30%; H 5.37%; N 14.93%; S 11.40%; found: C 68.23%; H 5.28%; N 14.78%; S 11.40%. IR (film): ν_{max} 3474, 3318, 3186, 3104, 3025, 2921, 2866, 1626, 1570, 1548, 1446, 1424, 1366, 1232, 1174, 1042, 910, 820, 791, 758, 713, 637, 535 cm^{-1}; ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 2.32 (s, 3H, Me), 3.88 (s, 2H, C$\underline{H}_2$Ph), 5.07 (br.s, 2H, NH_2), 6.72 (s, 1H, H^5), 7.07 (dd, J = 3.7, 5.0 Hz, 1H, H^9), 7.10−7.16 (m, 4H, $H^{o,m}$), 7.41 (d, J = 5.0 Hz, 1H, H^{10}), 7.57 (d, J = 3.7 Hz, 1H, H^8) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 21.1 (Me), 43.9 (C$\underline{H}_2$Ph), 105.3 (C^5), 127.0 (C^8), 128.0 (C^9), 129.1 (C^{10}), 129.2 (C^o), 129.4 (C^m), 134.9 (1C, C^i), 136.4 (C^p), 143.0 (C^7), 160.3 (C^6), 163.1 (C^4), 171.2 (C^2) ppm; ^{15}N NMR (40.5 MHz, $CDCl_3$): δ −136.6 (N^3), −149.0 (N^1), −304.1 (NH_2) ppm.

*5,6,7,8-Tetrahydroquinazolin-2-amine (**4a**).* Following general procedure, **4a** was prepared from cyclohexanone **1b** (0.491 g, 5.0 mmol), phenylacetylene **2a** (0.510 g, 5.0 mmol), KOBu^t (0.673 g, 6.0 mmol), H_2O (0.090 g, 5 mmol), $(NH_2)_2C{=}NH{\cdot}HNO_3$ (0.733, g 6.0 mmol), and $KOH{\cdot}0.5H_2O$ (0.325 g, 5 mmol). **4a** was isolated as a white solid (0.507 g, 68% yield); mp 182−187 °C; elemental analysis calcd (%) for $C_8H_{11}N_3$ (149.19): C 64.40%; H 7.43%; N 28.16%; found: C 64.32%; H 7.49%; N 28.10%. IR (film): ν_{max} 3299, 3157, 2991, 2927, 2849, 2838, 2762, 1656, 1650, 1632, 1595, 1572, 1557, 1536, 1510, 1503, 1478, 1454, 1441, 1422, 1416, 1346, 1335, 1314, 1276, 1244, 1213, 1180, 1154, 1143, 1107, 1097, 1077, 1065, 959, 944, 937, 858, 822, 788, 772, 762, 749, 727, 670, 665, 637, 593, 558, 505 cm^{-1}; ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 1.75−1.77 (m, 2H, 6-CH_2), 1.81−1.83 (m, 2H, 7-CH_2), 2.55−2.58 (m, 2H, 5-CH_2), 2.64−2.67 (m, 2H, 8-CH_2), 4.94 (br.s, 2H, NH_2), 7.95 (s, 1H, H^4) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 21.9 (C^7), 22.1 (C^6), 24.4 (C^5), 31.3 (C^8), 119.4 (C^{10}), 157.7 (C^4), 160.8 (C^2), 166.3 (C^9) ppm.

Following general procedure, **4a** was also prepared (0.447 g, 60% yield) from cyclohexanone **1b** (0.491 g, 5.0 mmol), 4-fluorophenylacetylene **2b** (0.601 g, 5.0 mmol), KOBu^t (0.673 g, 6.0 mmol), H_2O (0.090 g, 5 mmol), $(NH_2)_2C{=}NH{\cdot}HNO_3$ (0.733, g 6.0 mmol), and $KOH{\cdot}0.5H_2O$ (0.325 g, 5 mmol).

Following general procedure, **4a** was also prepared (0.470 g, 63% yield) from cyclohexanone **1b** (0.491 g, 5.0 mmol), 4-methylphenylacetylene **2c** (0.581 g, 5.0 mmol), KOBu^t (0.673 g, 6.0 mmol), H_2O (0.090 g, 5 mmol), $(NH_2)_2C{=}NH{\cdot}HNO_3$ (0.733, g 6.0 mmol), and $KOH{\cdot}0.5H_2O$ (0.325 g, 5 mmol).

*6-Methyl-5,6,7,8-tetrahydroquinazolin-2-amine (**4b**).* Following general procedure, **4b** was prepared from 4-methylcyclohexanone **1c** (0.561 g, 5.0 mmol), phenylacetylene **2a** (0.510 g, 5.0 mmol), KOBu^t (0.673 g, 6.0 mmol), H_2O (0.090 g, 5 mmol), $(NH_2)_2C{=}NH{\cdot}HNO_3$ (0.733, g 6.0 mmol), and $KOH{\cdot}0.5H_2O$ (0.325 g, 5 mmol). **4b** was isolated as a white solid (0.253 g, 31% yield); mp 170−172 °C; elemental analysis calcd (%) for $C_9H_{13}N_3$ (163.22): C 66.23%; H 8.03%; N 25.74%; found: C 66.11%; H 8.10%; N 25.69%. IR (film): ν_{max} 3301, 3153, 2989, 2952, 2922, 2849, 1659, 1594, 1555, 1486, 1453, 1435, 1416, 1377, 1350, 1322, 1298, 1265, 1225, 1202, 1180, 1148, 1134, 1095, 1076, 1022, 958, 948, 929, 909, 863, 814, 798, 781, 752, 730, 695, 646, 603, 513 cm^{-1}; ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 1.05 (d, J = 6.6 Hz, 3H, Me), 1.43−1.47 (m, 1H, 7-CH_2), 1.80−1.86 (m, 1H, H^6), 1.87−1.91 (m, 1H, 7-CH_2), 2.16 (dd, J = 15.8, 10.5 Hz, 1H, 5-CH_2), 2.61 (dd, J = 15.8, 5.2 Hz, 1H, 5-CH_2), 2.65−2.72 (m, 2H, 8-CH_2), 4.89 (br.s, 2H, NH_2), 7.95 (s, 1H, H^4) ppm; ^{13}C NMR

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(100.6 MHz, $CDCl_3$): δ 21.5 (Me), 28.9 (C^6), 30.6 (C^7), 31.6 (C^8), 33.4 (C^5), 119.6 (C^{10}), 158.2 (C^4), 161.3 (C^2), 166.7 (C^9) ppm; ^{15}N NMR (40.5 MHz, $CDCl_3$): δ −135.3 (N^1), −139.1 (N^3), −308.8 (NH_2) ppm.

*6,7,8,9-Tetrahydro-5H-cyclohepta[d]pyrimidin-2-amine (**4c**).* Following general procedure, **4c** was prepared from cycloheptanone **1d** (0.561 g, 5.0 mmol), phenylacetylene **2a** (0.510 g, 5.0 mmol), $KOBu^t$ (0.673 g, 6.0 mmol), H_2O (0.090 g, 5 mmol), $(NH_2)_2C{=}NH{\cdot}HCl$ (0.573, g 6.0 mmol), and $KOH{\cdot}0.5H_2O$ (0.325 g, 5 mmol). **4c** was isolated as a white solid (0.571 g, 70% yield); mp 132−136 °C; elemental analysis calcd (%) for $C_9H_{13}N_3$ (163.22): C 66.23%; H 8.03%; N 25.74%; found: C 66.29%; H 8.01%; N 25.66%. IR (film): ν_{max} 3319, 3168, 2960, 2918, 2849, 2745, 1661, 1596, 1558, 1488, 1439, 1350, 1335, 1326, 1284, 1267, 1236, 1193, 1181, 1151, 1143, 977, 947, 941, 883, 870, 834, 801, 757, 730, 701, 604, 571, 546, 517, 492, 444 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$): δ 1.59−1.60 (m, 2H, 6-CH_2), 1.66−1.67 (m, 2H, 8-CH_2), 1.81−1.84 (m, 2H, 7-CH_2), 2.57−2.59 (m, 2H, 5-CH_2), 2.75−2.77 (m, 2H, 9-CH_2), 5.00 (br.s, 2H, NH_2), 7.91 (s, 1H, H^4) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 26.1 (C^8), 28.5 (C^6), 31.2 (C^5), 32.5 (C^7), 39.1 (C^9), 125.2 (C^{11}), 156.9 (C^4), 161.7 (C^2), 172.6 (C^{10}) ppm; ^{15}N NMR (40.5 MHz, $CDCl_3$): δ −133.0 (N^1), −140.6 (N^3), −307.2 (NH_2) ppm.

*5,6,7,8,9,10-Hexahydrocycloocta[d]pyrimidin-2-amine (**4d**).* Following general procedure, **4d** was prepared from cyclooctanone **1e** (0.631 g, 5.0 mmol), phenylacetylene **2a** (0.510 g, 5.0 mmol), $KOBu^t$ (0.673 g, 6.0 mmol), H_2O (0.090 g, 5 mmol), $(NH_2)_2C{=}NH{\cdot}HNO_3$ (0.733, g 6.0 mmol), and $KOH{\cdot}0.5H_2O$ (0.325 g, 5 mmol) under the argon. **4d** was isolated as a white solid (0.705 g, 80% yield); mp 151−156 °C; elemental analysis calcd (%) for $C_{10}H_{15}N_3$ (177.25): C 67.76%; H 8.53%; N 23.71%; found: C 67.68%; H 8.57%; N 23.67%. IR (film): ν_{max} 3295, 3147, 2918, 2844, 2779, 1663, 1597, 1560, 1489, 1445, 1421, 1347, 1319, 1268, 1225, 1168, 1150, 1131, 1090, 996, 921, 917, 883, 866, 836, 819, 794, 762, 731, 699, 650, 594, 526, 488, 441 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$): δ 1.30−1.48 (m, 4H, 7-CH_2, 8-CH_2), 1.60−1.66 (m, 2H, 6-CH_2), 1.72−1.78 (m, 2H, 9-CH_2), 2.55−2.61 (m, 2H, 5-CH_2), 2.68−2.75 (m, 2H, 10-CH_2), 4.85 (br.s, 2H, NH_2), 7.95 (s, 1H, H^4) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 25.7 (C^9), 25.9 (C^6), 28.3 (C^7), 29.8 (C^8), 32.2 (C^5), 33.9 (C^{10}), 123.6 (C^{12}), 157.5 (C^4), 162.0 (C^2), 170.4 (C^{11}) ppm; ^{15}N NMR (40.5 MHz, $CDCl_3$): δ −133.7 (N^1), −138.8 (N^3), −307.1 (NH_2) ppm.

*5-Methyl-6-phenylpyrimidin-2-amine (**4e**).* Following general procedure, **4e** was prepared from propiophenone **1g** (0.671 g, 5.0 mmol), phenylacetylene **2a** (0.510 g, 5.0 mmol), $KOBu^t$ (0.673 g, 6.0 mmol), H_2O (0.090 g, 5 mmol), $(NH_2)_2C{=}NH{\cdot}HNO_3$ (0.733 g, 6.0 mmol), and $KOH{\cdot}0.5H_2O$ (0.325 g, 5 mmol) under the argon. **4e** was isolated as a cream solid (0.556 g, 60% yield); mp 122−128 °C; elemental analysis calcd (%) for $C_{11}H_{11}N_3$ (185.23): C 71.33%; H 5.99%; N 22.69%; found: C 71.41%; H 5.93%; N 22.61%. IR (film): ν_{max} 3344, 3295, 3163, 2936, 1633, 1593, 1573, 1543, 1477, 1441, 1409, 1385, 1289, 1202, 1180, 1143, 1078, 989, 913, 806, 777, 745, 710, 639, 595, 563 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$): δ 2.16 (s, 3H, Me), 5.16 (br.s, 2H, NH_2), 7.35−7.47 (m, 3H, $H^{m,p}$), 7.49−7.55 (m, 2H, H^o), 8.17 (s, 1H, H^4) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 15.9 (Me), 117.4 (C^5), 128.3 (C^m), 128.4 (C^o), 128.9 (C^p), 138.6 (C^i), 159.9 (C^4), 161.7 (C^2), 166.2 (C^6) ppm; ^{15}N NMR (40.5 MHz, $CDCl_3$): δ −133.8 (N^1), −135.9 (N^3), −307.1 (NH_2) ppm.

*5-Ethyl-6-phenylpyrimidin-2-amine (**4f**).* Following general procedure, **4f** was prepared from butyrophenone **1h** (0.741 g, 5.0 mmol), phenylacetylene **2a** (0.510 g, 5.0 mmol), $KOBu^t$ (0.673 g, 6.0 mmol), H_2O (0.090 g, 5 mmol), $(NH_2)_2C{=}NH{\cdot}HNO_3$ (0.733 g, 6.0 mmol), and $KOH{\cdot}0.5H_2O$ (0.325 g, 5 mmol). **4f** was isolated as a cream solid (0.577 g, 58% yield); mp 84−88 °C; elemental analysis calcd (%) for $C_{12}H_{13}N_3$ (199.25): C 72.33%; H 6.58%; N 21.09%; found: C 72.40%; H 6.55%; N 21.00%. IR (film): ν_{max} 3479, 3315, 3183, 3068, 2968, 2924, 2872, 1958, 1889, 1800, 1629, 1585, 1543, 1471, 1411, 1377, 1350, 1326, 1293, 1201, 1071, 1023, 961, 916, 812, 773, 703, 641, 570, 449 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$): δ 1.02 (t, J = 7.5 Hz, 3H, Me), 2.47 (q, J = 7.5 Hz, 2H, CH_2), 5.61 (br.s, 2H, NH_2), 7.38−7.42 (m, 5H, $H^{o,m,p}$), 8.18 (s, 1H, H^4) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 15.3 (Me), 22.1 (CH_2), 123.3 (C^5), 128.0 (C^m), 128.1 (C^o), 128.6 (C^p), 138.5 (C^i), 158.9 (C^4), 161.5 (C^2), 166.2 (C^6) ppm; ^{15}N NMR (40.5 MHz, $CDCl_3$): δ −133.7 (N^1), −136.6 (N^3), −304.9 (NH_2) ppm.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02233.

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

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Notes

The authors declare no competing financial interest.

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