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

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Graphical abstract



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 molecule or methylbenzenes. The latter process takes place for 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 associated with numerous biological activities.¹ Substituted aminopyrimidine nuclei are common in the marketed drugs such as anti-atherosclerotic Aronixil®, anti-histaminic Thonzylamine® (I), antianxielytic Buspirone® (II), anti-psoriatic Enazadrem® (III), and other medicinally relevant compounds (Fig. 1).²



Figure 1. Approved drugs containing aminopyrimidine scaffold

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 analgesic⁶ and anti-inflammatory.⁵

An essential role of these compounds as potential drugs for treating oncologic diseases makes 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



Scheme 1. Synthesis of 2-amonopyrimidines from chalcones and guanidine⁸

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 ketones⁹ has been successfully employed as the intermediate step for an efficient one-pot synthesis of 2-isoxazolines,¹⁰ 2-pyrazolines¹¹ and 1-formyl-2-pyrazolines,¹² benzoxepines,¹³ 2,5-diaryl furans^{9a,14} and acylated therphenyls.¹⁵

As further development of this original methodology for the assembly of valuable carboand 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 3,4 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.

Table 1. Synthesis of 2-aminopyrimidines **3** and **4** from ketones **1**, arylacetylenes **2** and guanidine^a









^{*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) H₂O (5 mmol, 0.09 g), (NH₂)₂C=NH·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 H₂O (5 mmol, 0.33 g), 70 °C, 0.5 h. ^{*b*}Isolated yield after the workup and column chromatography (Al₂O₃, benzene-diethyl ether with gradient from 1 : 0 to 10 : 1). ^{*c*}These experiments were carried out under the argon.

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

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 1,2), 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 chaclones (Scheme 1), the following advantages seem obvious: (i) one-step protocol, (ii) a greater diversity of the substituents nature, (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, 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 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 methyl benzenes from the dihydropyrimidine ring (identified by GLC) takes place to deliver benzyl-free aminopyrimidines **4** (Scheme 2).



Scheme 2. Plausible scheme of the assembly of 2-aminopyrimidines 3,4 from ketones 1, arylcetylenes 2 and guanidine

The experiments with cyclohexanone **1b** and 4-fluoromethylacetylene **2b** or 4methylphenylacetylene **2c** have shown that during both reactions, the elimination of the expected 1-methyl-4-fluorobenzene and 1,4-dimethylbenzene occur to result in approximately the same yields of the final products (Table 1). This demonstrates that aromatization of dihydropyrimidines with elimination of the expected methyl aromatics does not significantly influence by electron-donating and electron-withdrawing substituents (\mathbb{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.

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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 the argon with degassed solvent (DMSO) have been carried out. The results obtained shows that the aromatization does take place also in this case. By the way, those amounts of oxygen, which is contained in 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 wellknown classic chemistry, e.g. the Dumas-Stass name reaction.¹⁷

Also, according to¹⁸ one might 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.



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 for 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. Afterwards, the reaction could follow the way described by W. Guo.^{7f} However, the previous publications⁹ show that such isomerization does not take place to 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 1): 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, properties of the reaction medium, all those 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 sequential three-component reaction between ketones, arylacetylenes and guanidine. This methodology has several synthetically attractive features: operationally simple procedure, the 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. ¹H (400.1 MHz), ¹³C (100.6 MHz), ¹⁵N (40.5 MHz) NMR spectra were recorded in CDCl₃ 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 ¹H NMR spectra was made using COSY and NOESY experiments. Resonance signals of carbon atoms were assigned based on ¹H-¹³C HSQC and ¹H-¹³C HMBC experiments. The values of the δ ¹⁵N were measured through the 2D ¹H-¹⁵N HMBC experiment. The ¹⁵N chemical shifts were referenced to MeNO₂. 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 3,4. 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), H₂O (5 mmol, 90 mg) and (NH₂)₂C=NH·HNO₃ (6.0 mmol, 733 mg) or (NH₂)₂C=NH·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·0.5H₂O (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 H₂O (15 mL), neutralized with NH₄Cl and was extracted with CHCl₃ (10 mL × 4). The organic extract was washed with H₂O (5 mL × 3) and dried (MgSO₄). CHCl₃ was evaporated in vacuum and the residue was purified by column chromatography (Al₂O₃, eluent C₆H₆/Et₂O with gradient from 1:0 to 10:1).

4-Benzyl-6-(*tert*-butyl)pyrimidin-2-amine (3a). Following *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), H₂O (0.090 g, 5 mmol), (NH₂)₂C=NH·HNO₃ (0.733 g, 6.0 mmol) and KOH·0.5H₂O (0.325 g, 5 mmol). 3a was isolated as a cream oil (0.615 g, 51% yield); elemental analysis calcd (%) for C₁₅H₁₉N₃ (241.33): C 74.65%; H 7.94%; N 17.41%; found: C 74.60%; H 7.98%; N 17.36%. IR (film): v_{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; ¹H NMR (400.1 MHz, CDCl₃): δ 1.20 (s, 9H, 3Me), 3.87 (s, 2H, CH₂Ph), 5.02 (br.s, 2H, NH₂), 6.44 (s, 1H, H⁵), 7.20-7.22 (m, 3H, H^{o,p}), 7.27-7.30 (m, 2H, H^m) ppm; ¹³C NMR (100.6 MHz, CDCl₃): δ 29.5 (Me), 37.3 (<u>C</u>-Me₃), 44.4 (<u>C</u>H₂Ph), 106.4 (C⁵), 126.7 (C^p), 128.7 (2C^m), 129.3 (2C^o), 138.5 (Cⁱ),

163.0 (C⁴), 170.1 (C²), 179.6 (C⁶) ppm; ¹⁵N NMR (40.5 MHz, CDCl₃): δ –138.8 (N³), –143.0 (N¹), –306.3 (NH₂) 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), 4flourophenylacetylene **2b** (0.601 g, 5.0 mmol), KOBu^t (0.673 g, 6.0 mmol), H₂O (0.090 g, 5 mmol), (NH₂)₂C=NH·HNO₃ (0.733 g, 6.0 mmol) and KOH·0.5H₂O (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): v_{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; ¹H NMR (400.1 MHz, CDCl₃): δ 1.20 (s, 9H, 3Me), 3.83 (s, 2H, CH₂Ph), 4.89 (br.s, 2H, NH₂), 6.42 (s, 1H, H⁵), 6.95-6.99 (m, 2H, H^m), 7.17-7.21 (m, 2H, H^o) ppm; 13 C NMR (100.6 MHz, CDCl₃): δ 29.4 (Me), 37.2 (C-Me₃), 43.4 (CH₂Ph), 106.2 (C⁵), 115.4 (d, J = 21.2 Hz, C^m), 130.6 (d, J = 8.1Hz, C^o), 134.0 (d, J = 3.1 Hz, Cⁱ), 161.8 (d, J = 244.4 Hz, C^p), 162.8 (C⁴), 169.8 (C²), 179.7 (C⁶) 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), H₂O (0.090 g, 5 mmol), (NH₂)₂C=NH·HNO₃ (0.733 g, 6.0 mmol) and KOH·0.5H₂O (0.325 g, 5 mmol). 3c was isolated as a cream solid (0.405 g, 32% yield); m.p. 132-136 °C; elemental analysis calcd (%) for C₁₆H₁₉N₃ (253.34): C 75.85%; H 7.56%; N 16.59%; found: C 75.77%; H 7.62%; N 16.69%. IR (film): v_{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; ¹H NMR (400.1 MHz, CDCl₃): δ 1.02 (d, J = 6.6 Hz, 3H, Me), 1.30-1.40 (m, 1H, 7-CH₂), 1.72-1.81 (m, 1H, H⁶), 1.82-1.90 (m, 1H, 7-CH₂), 2.04 (dd, J = 15.9, 10.3 Hz, 1H, 5-CH₂), 2.66 (dd, J = 15.9, 4.9 Hz, 1H, 5-CH₂), 2.65-2.70 (m, 2H, 8-CH₂), 3.92 (s, 2H, CH₂), 4.88 (br.s, 2H, NH₂), 7.17-7.23 (m, 3H, H^{o,p}), 7.25-7.27 (m, 2H, H^m) ppm; ¹³C NMR (100.6 MHz, CDCl₃): δ 21.7 (Me), 29.0 (C⁶), 30.3 (C⁷), 32.0 (C⁸), 32.5 (C⁵), 40.7 (CH₂Ph), 117.5 (C¹⁰), 126.3 (C^p), 128.5 (C^m), 128.7 (C^o), 137.6 (Cⁱ), 160.8 (C²), 166.4 (C⁹), 167.4 (C⁴) ppm; ¹⁵N NMR (40.5 MHz, CDCl₃): δ –134.6 (N³), -140.6 (N¹), -307.2 (NH₂) 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), H₂O (0.090 g, 5 mmol), (NH₂)₂C=NH·HCl (0.573 g, 6.0 mmol) and

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KOH·0.5H₂O (0.325 g, 5 mmol). **3d** was isolated as a cream solid (0.431 g, 33% yield); m.p. 90-94 °C; elemental analysis calcd (%) for C₁₇H₁₅N₃ (261.32): C 78.13%; H 5.79%; N 16.08%; found: C 78.31%; H 5.65%; N 15.95%. IR (film): v_{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; ¹H NMR (400.1 MHz, CDCl₃): δ 3.90 (s, 2H, CH₂Ph), 5.41 (br.s, 2H, NH₂), 6.75 (s, 1H, H⁵), 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; ¹³C NMR (100.6 MHz, CDCl₃): δ 44.3 (<u>C</u>H₂Ph), 107.1 (C⁵), 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 (Cⁱ), 163.4 (C⁴), 165.8 (C⁶), 170.9 (C²) ppm; ¹⁵N NMR (40.5 MHz, CDCl₃): δ -136.8 (N³), – 145.2 (N¹), -304.2 (NH₂) 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), H₂O (0.090 g, 5 mmol), $(NH_2)_2C=NH\cdotHNO_3$ (0.733 g, 6.0 mmol) and KOH·0.5H₂O (0.325 g, 5 mmol). **3e** was isolated as a cream solid (0.564 g, 41% yield); m.p. 82-88 °C; elemental analysis calcd (%) for C₁₈H₁₇N₃ (275.35): C 78.52%; H 6.22%; N 15.26%; found: C 78.61%; H 6.15%; N 15.09%. IR (film): v_{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; ¹H NMR (400.1 MHz, CDCl₃): δ 2.30 (s, 3H, Me), 3.90 (s, 2H, CH₂Ph), 5.32 (br.s, 2H, NH₂), 6.80 (s, 1H, H⁵), 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; ¹³C NMR (100.6 MHz, CDCl₃): δ 20.9 (Me), 43.8 (CH₂Ph), 106.9 (C⁵), 126.9 (C^{o'}), 128.5 (C^m), 129.2 (C^o), 130.1 (C^{p'}), 130.9 (C^{m'}), 134.7 (Cⁱ), 136.1 (C^p), 137.4 (C^{i'}), 163.1 (C⁴), 165.6 (C⁶), 171.1 (C²) ppm; ¹⁵N NMR(40.5 MHz, CDCl₃): δ –136.6 (N³), –144.7 (N¹), –304.1 (NH₂) 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), H₂O (0.090 g, 5 mmol), (NH₂)₂C=NH·HCl (0.573 g, 6.0 mmol) and KOH·0.5H₂O (0.325 g, 5 mmol) under the argon. **3f** was isolated as a white solid (0.763 g, 49% yield); m.p. 163-168 °C; elemental analysis calcd (%) for C₂₁H₁₇N₃ (311.38): C 81.00%; H 5.50%; N 13.49%; found: C 80.81%; H 5.55%; N 13.58%. IR (film): v_{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; ¹H NMR (400.1 MHz, CDCl₃): δ 4.00 (s, 2H, C<u>H</u>₂Ph), 5.12 (br.s, 2H, NH₂), 6.98 (s, 1H, H⁵), 7.20-7.38 (m, 5H, H^{o,m,p}), 7.47-7.52 (m, 2H, H¹⁰, H¹¹), 7.82-7.92 (m, 3H, H⁹, H¹², H¹³), 7.98-8.01 (m, 1H, H¹⁴), 8.43 (s, 1H, H⁸) ppm; ¹³C NMR (100.6 MHz, CDCl₃): δ 44.4 (<u>C</u>H₂Ph), 107.3 (C⁵), 124.2 (C¹³), 126.5 (C^p), 126.8 (C⁹), 127.0 (C¹¹), 127.1 (C¹²), 127.7 (C¹⁴), 128.5 (C¹⁰), 128.8 (C^m), 129.0 (C⁸), 129.3 (C^o), 133.3 (C¹⁶),

134.5 (C¹⁵), 134.8 (C⁷), 138.1 (C^{*i*}), 163.5 (C⁴), 165.7 (C⁶), 171.0 (C²) ppm; ¹⁵N NMR (40.5 MHz, CDCl₃): δ –136.6 (N³), –144.7 (N¹), –304.9 (NH₂) 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), H₂O (0.090 g, 5 mmol), (NH₂)₂C=NH·HCl (0.573 g, 6.0 mmol) and KOH·0.5H₂O (0.325 g, 5 mmol) under the argon. **3g** was isolated as a cream solid (0.401 g, 30% yield); m.p. 180-185 °C; elemental analysis calcd (%) for C₁₅H₁₃N₃S (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): v_{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; ¹H NMR (400.1 MHz, CDCl₃): δ 3.93 (s, 2H, CH₂Ph), 5.05 (br.s, 2H, NH₂), 6.72 (s, 1H, H⁵), 7.06 (dd, *J* = 3.8, 5.0 Hz, 1H, H⁹), 7.20-7.42 (m, 5H, H^{o,m,p}), 7.41 (d, *J* = 5.0 Hz, 1H, H¹⁰), 7.57 (d, *J* = 3.8 Hz, 1H, H⁸) ppm; ¹³C NMR (100.6 MHz, CDCl₃): δ 44.2 (CH₂Ph), 105.4 (C⁵), 126.8 (C^p), 127.0 (C⁸), 128.1 (C⁹), 128.7 (C^m), 129.2 (C¹⁰), 129.3 (C^o), 138.0 (Cⁱ), 143.0 (C⁷), 160.3 (C⁶), 163.2 (C⁴), 170.9 (C²) ppm; ¹⁵N NMR (40.5 MHz, CDCl₃): δ -136.6 (N³), -148.3 (N¹), -305.6 (NH₂) 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), H₂O (0.090 g, 5 mmol), (NH₂)₂C=NH·HNO₃ (0.733 g, 6.0 mmol) and KOH·0.5H₂O (0.325 g, 5 mmol) out under the argon. **3h** was isolated as a cream solid (0.436 g, 31% yield); m.p. 123-126 °C; elemental analysis calcd (%) for C₁₆H₁₅N₃S (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): v_{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; ¹H NMR (400.1 MHz, CDCl₃): δ 2.32 (s, 3H, Me), 3.88 (s, 2H, C<u>H</u>₂Ph), 5.07 (br.s, 2H, NH₂), 6.72 (s, 1H, H⁵), 7.07 (dd, J = 3.7, 5.0 Hz, 1H, H⁹), 7.10-7.16 (m, 4H, H^{o,m}), 7.41 (d, J = 5.0 Hz, 1H, H¹⁰), 7.57 (d, J = 3.7 Hz, 1H, H⁸) ppm; ¹³C NMR (100.6 MHz, CDCl₃): δ 21.1 (Me), 43.9 (<u>C</u>H₂Ph), 105.3 (C⁵), 127.0 (C⁸), 128.0 (C⁹), 129.1 (C¹⁰), 129.2 (C^o), 129.4 (C^m), 134.9 (1C, Cⁱ), 136.4 (C^p), 143.0 (C⁷), 160.3 (C⁶), 163.1 (C⁴), 171.2 (C²) ppm; ¹⁵N NMR (40.5 MHz, CDCl₃): δ –136.6 (N³), –149.0 (N¹), –304.1 (NH₂) 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), H₂O (0.090 g, 5 mmol), (NH₂)₂C=NH·HNO₃ (0.733, g 6.0 mmol) and KOH·0.5H₂O (0.325 g, 5 mmol). 4a was isolated as a white solid (0.507 g, 68% yield); m.p. 182-187 °C; elemental analysis calcd (%) for C₈H₁₁N₃ (149.19): C 64.40%; H 7.43%; N 28.16%;

found: C 64.32%; H 7.49%; N 28.10%. IR (film): v_{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; ¹H NMR (400.1 MHz, CDCl₃): δ 1.75-1.77 (m, 2H, 6-CH₂), 1.81-1.83 (m, 2H, 7-CH₂), 2.55-2.58 (m, 2H, 5-CH₂), 2.64-2.67 (m, 2H, 8-CH₂), 4.94 (br.s, 2H, NH₂), 7.95 (s, 1H, H⁴) ppm; ¹³C NMR (100.6 MHz, CDCl₃): δ 21.9 (C⁷), 22.1 (C⁶), 24.4 (C⁵), 31.3 (C⁸), 119.4 (C¹⁰), 157.7 (C⁴), 160.8 (C²), 166.3 (C⁹) 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), H₂O (0.090 g, 5 mmol), (NH₂)₂C=NH·HNO₃ (0.733, g 6.0 mmol) and KOH·0.5H₂O (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), H₂O (0.090 g, 5 mmol), (NH₂)₂C=NH·HNO₃ (0.733, g 6.0 mmol) and KOH·0.5H₂O (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), H₂O (0.090 g, 5 mmol), (NH₂)₂C=NH·HNO₃ (0.733, g 6.0 mmol) and KOH·0.5H₂O (0.325 g, 5 mmol). **4b** was isolated as a white solid (0.253 g, 31% yield); m.p. 170-172 °C; elemental analysis calcd (%) for C₉H₁₃N₃ (163.22): C 66.23%; H 8.03%; N 25.74%; found: C 66.11%; H 8.10%; N 25.69%. IR (film): v_{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; ¹H NMR (400.1 MHz, CDCl₃): δ 1.05 (d, *J* = 6.6 Hz, 3H, Me), 1.43-1.47 (m, 1H, 7-CH₂), 1.80-1.86 (m, 1H, H⁶), 1.87-1.91 (m, 1H, 7-CH₂), 2.16 (dd, *J* = 15.8, 10.5 Hz, 1H, 5-CH₂), 2.61 (dd, *J* = 15.8, 5.2 Hz, 1H, 5-CH₂), 2.65-2.72 (m, 2H, 8-CH₂), 4.89 (br.s, 2H, NH₂), 7.95 (s, 1H, H⁴) ppm; ¹³C NMR (100.6 MHz, CDCl₃): δ 21.5 (Me), 28.9 (C⁶), 30.6 (C⁷), 31.6 (C⁸), 33.4 (C⁵), 119.6 (C¹⁰), 158.2 (C⁴), 161.3 (C²), 166.7 (C⁹) ppm; ¹⁵N NMR (40.5 MHz, CDCl₃): δ -135.3 (N¹), -139.1 (N³), -308.8 (NH₂) ppm.

6,7,8,9-Tetrahydro-5*H*-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), H₂O (0.090 g, 5 mmol), (NH₂)₂C=NH·HCl (0.573, g 6.0 mmol) and KOH·0.5H₂O (0.325 g, 5 mmol). 4c was isolated as a white solid (0.571 g, 70% yield); m.p. 132-136 °C; elemental analysis calcd (%) for C₉H₁₃N₃ (163.22): C 66.23%;

H 8.03%; N 25.74%; found: C 66.29%; H 8.01%; N 25.66%. IR (film): v_{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, CDCl₃): δ 1.59-1.60 (m, 2H, 6-CH₂), 1.66-1.67 (m, 2H, 8-CH₂), 1.81-1.84 (m, 2H, 7-CH₂), 2.57-2.59 (m, 2H, 5-CH₂), 2.75-2.77 (m, 2H, 9-CH₂), 5.00 (br.s, 2H, NH₂), 7.91 (s, 1H, H⁴) ppm; ¹³C NMR (100.6 MHz, CDCl₃): δ 26.1 (C⁸), 28.5 (C⁶), 31.2 (C⁵), 32.5 (C⁷), 39.1 (C⁹), 125.2 (C¹¹), 156.9 (C⁴), 161.7 (C²), 172.6 (C¹⁰) ppm; ¹⁵N NMR (40.5 MHz, CDCl₃): δ -133.0 (N¹), -140.6 (N³), -307.2 (NH₂) 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), H₂O (0.090 g, 5 mmol), (NH₂)₂C=NH·HNO₃ (0.733, g 6.0 mmol) and KOH·0.5H₂O (0.325 g, 5 mmol) under the argon. **4d** was isolated as a white solid (0.705 g, 80% yield); m.p. 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): v_{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, CDCl₃): δ 1.30-1.48 (m, 4H, 7-CH₂, 8-CH₂), 1.60-1.66 (m, 2H, 6-CH₂), 1.72-1.78 (m, 2H, 9-CH₂), 2.55-2.61 (m, 2H, 5-CH₂), 2.68-2.75 (m, 2H, 10-CH₂), 4.85 (br.s, 2H, NH₂), 7.95 (s, 1H, H⁴) ppm; ¹³C NMR (100.6 MHz, CDCl₃): δ 25.7 (C⁹), 25.9 (C⁶), 28.3 (C⁷), 29.8 (C⁸), 32.2 (C⁵), 33.9 (C¹⁰), 123.6 (C¹²), 157.5 (C⁴), 162.0 (C²), 170.4 (C¹¹) ppm; ¹⁵N NMR (40.5 MHz, CDCl₃): δ -133.7 (N¹), -138.8 (N³), -307.1 (NH₂) 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), KOBu¹ (0.673 g, 6.0 mmol), H₂O (0.090 g, 5 mmol), (NH₂)₂C=NH·HNO₃ (0.733 g, 6.0 mmol) and KOH·0.5H₂O (0.325 g, 5 mmol) under the argon. **4e** was isolated as a cream solid (0.556 g, 60% yield); m.p. 122-128 °C; elemental analysis calcd (%) for C₁₁H₁₁N₃ (185.23): C 71.33%; H 5.99%; N 22.69%; found: C 71.41%; H 5.93%; N 22.61%. IR (film): v_{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, CDCl₃): δ 2.16 (s, 3H, Me), 5.16 (br.s, 2H, NH₂), 7.35-7.47 (m, 3H, H^{*m*,*p*}), 7.49-7.55 (m, 2H, H^{*o*}), 8.17 (s, 1H, H⁴) ppm; ¹³C NMR (100.6 MHz, CDCl₃): δ 15.9 (Me), 117.4 (C⁵), 128.3 (C^{*m*}), 128.4 (C^{*o*}), 128.9 (C^{*p*}), 138.6 (C^{*i*}), 159.9 (C⁴), 161.7 (C²), 166.2 (C⁶) ppm; ¹⁵N NMR (40.5 MHz, CDCl₃): δ –133.8 (N¹), –135.9 (N³), –307.1 (NH₂) 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), H₂O (0.090 g, 5 mmol), (NH₂)₂C=NH·HNO₃ (0.733 g, 6.0 mmol) and KOH·0.5H₂O (0.325 g, 5 mmol). **4f** was isolated as a cream solid (0.577 g, 58% yield); m.p. 84-88 °C; elemental analysis calcd (%) for C₁₂H₁₃N₃ (199.25): C 72.33%; H 6.58%; N 21.09%; found: C 72.40%; H 6.55%; N 21.00%. IR (film): v_{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, CDCl₃): δ 1.02 (t, *J* = 7.5 Hz, 3H, Me), 2.47 (q, *J* = 7.5 Hz, 2H, CH₂), 5.61 (br.s, 2H, NH₂), 7.38-7.42 (m, 5H, H^{o,m,p}), 8.18 (s, 1H, H⁴) ppm; ¹³C NMR (100.6 MHz, CDCl₃): δ 15.3 (Me), 22.1 (CH₂), 123.3 (C⁵), 128.0 (C^m), 128.1 (C^o), 128.6 (C^p), 138.5 (Cⁱ), 158.9 (C⁴), 161.5 (C²), 166.2 (C⁶) ppm; ¹⁵N NMR (40.5 MHz, CDCl₃): δ –133.7 (N¹), –136.6 (N³), –304.9 (NH₂) ppm.

Supporting Information Available: Copies of ¹H and ¹³C NMR spectra of all compounds. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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