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Base-catalyzed synthesis of bicyclic 4-aminopyrimidines from the reaction of dinitriles with mononitriles

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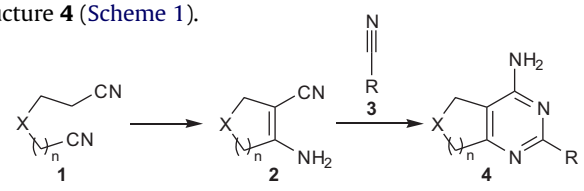
ABSTRACT

A convenient method for the synthesis of bicyclic 4-aminopyrimidines is described, involving the reaction of dinitriles with mononitriles in the presence of catalytic potassium *tert*-butoxide. These reactions proceed via the Thorpe–Ziegler cyclization of the dinitrile to form an intermediate β-cyanoenamine, which then undergoes annulation with the mononitrile in situ.

1. Introduction

Bicyclic 4-aminopyrimidines **4** are important heterocyclic scaffolds for drug discovery.[1] However, conventional methods for their synthesis are often lengthy, cumbersome, and not amenable to late-stage modification.[1] An attractive alternative route lies in the cyclization of a dinitrile **1** to provide a β-cyanoenamine **2**, which can then react with a mononitrile **3** in situ to provide the target structure **4** (Scheme 1).



Scheme 1. Proposed route to bicyclic 4-aminopyrimidines.

Both steps of this sequence are well-known: the classical Thorpe–Ziegler cyclization of dinitriles,[2] and annulation of β-cyanoenamines with nitriles.[3] Surprisingly however, the integration of these two steps into a one-pot domino reaction has not, to our knowledge, been described.[4,5] The realization of such a process would provide a convenient entry into bicyclic 4-aminopyrimidines **4** without having to isolate and purify the intermediate β-cyanoenamines. However, the principal challenge with this approach that must be overcome is minimization of side products resulting from self-coupling of one or both of the reaction partners. In this article, the successful implementation of this strategy is described.

2. Results and discussion

Our studies began with evaluation of various conditions in the reaction of adiponitrile (**1a**) with benzonitrile (**3a**). The best results were obtained by heating a mixture of **1a** (1.5 equiv), **3a** (1.0 equiv), and *t*-BuOK (20 mol %) in *p*-xylene at 120 °C for 4 h. Under these conditions, aminopyrimidine **5a** was isolated in 81% yield (Eq. 1), the structure of which was confirmed by X-ray crystallography (Fig. 1).[6] Side products **6**[5] and **7**[7] resulting from self-coupling of

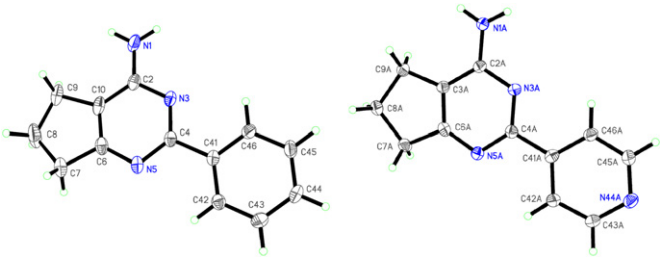


Fig. 1. X-ray crystal structures of **5a** and **5q**.

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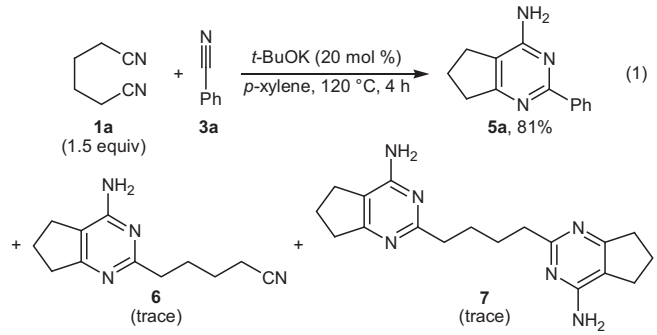
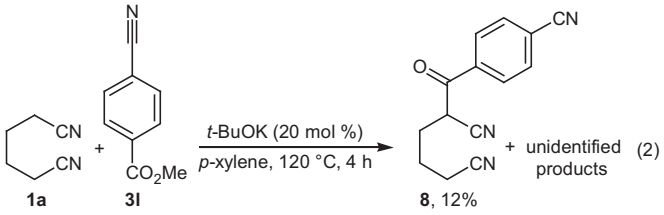
adiponitrile were also detected in the reaction mixture, but they were easily removed by column chromatography.



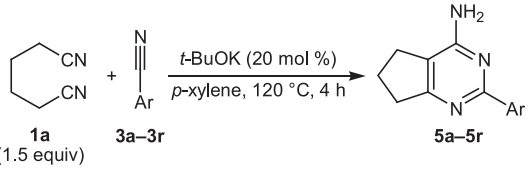
Next, further investigation of the reaction scope was undertaken using the aforementioned experimental protocol. These experiments demonstrated that reaction of adiponitrile (**1a**) with various aromatic (entries 1–10 and 13–15) and heteroaromatic nitriles (entries 16–18) was successful to provide bicyclic 4-aminopyrimidines (Table 1). In addition to benzonitrile itself (entry 1), benzonitriles containing alkyl (entry 2), aryl (entry 3), chloro (entry 4), bromo (entry 5), and trifluoromethyl (entry 7) substituents at the 4-position were among the better substrates, giving products in 75–90% yield. 4-Fluorobenzonitrile underwent cyclization in low yield (28%) due to the formation of side products resulting from displacement of the fluorine through S_NAr reactions.[8] In contrast, 3-fluorobenzonitrile afforded **5m** in excellent yield (96%) under the same conditions (entry 13). 3-Methoxybenzonitrile was also an effective substrate (entry 14). The reaction between adiponitrile (**1a**) and benzonitriles bearing electron-donating groups at the 4-position resulted in lower yields (21–65%) of the products (entries 8–10), with incomplete consumption of 4-amino-subsituted nitriles observed even after a reaction time of 20 h (entries 9 and 10). These results are as expected due to the lower electrophilicities of these substrates. Unsurprisingly, 4-cyanophenol failed to undergo reaction even in the presence of 2.0 equiv of *t*-BuOK (entry 11), presumably due to the phenoxide anion formed under the basic conditions deactivating the nitrile group toward nucleophilic attack. Attempted cyclization of adiponitrile (**1a**) with methyl 4-cyanobenzoate (**3l**) resulted in none of the desired bicyclic 4-aminopyridine **5l** being detected (entry 12). Instead, a complex mixture of products was formed, from which Claisen condensation product **8** (12% yield based on mononitrile) was isolated (Eq. 2). Evidently, the presence of the electrophilic ester substituent was detrimental to the desired reaction.

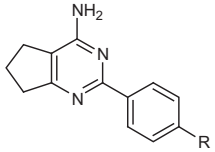
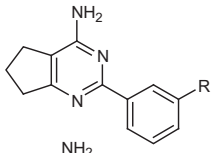
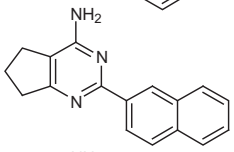
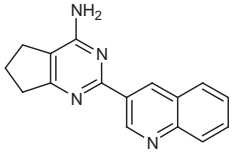
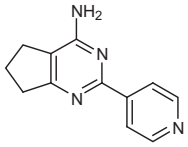
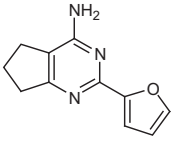


Heteroaromatic nitriles were problematic substrates, providing lower yields of products (entries 16–18) along with numerous side products. In the case of 2-furonitrile, halving the concentration of the reaction was beneficial, increasing the yield of **5r** from 26 to 41% (entry 18). The structure of 4-pyridyl-substituted product **5q** was further confirmed by X-ray crystallography (Fig. 1).[6]

Table 2 presents the results of reaction of adiponitrile (**1a**) with aliphatic mononitriles. Here, the presence of acidic α-protons in the mononitrile was expected to present chemoselectivity problems. Although benzyl cyanide (entry 1) was a competent substrate under the standard conditions employed in Table 1, cyclohexanecarbonitrile

Table 1
Reaction of adiponitrile (**1a**) with aromatic and heteroaromatic mononitriles[a]



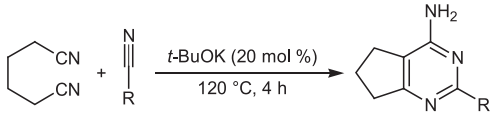
Entry	Product		Yield[b] (%)
1		R=H **5a**	81
2		R=*t*-Bu **5b**	75
3		R=Ph **5c**	80
4		R=Cl **5d**	90
5		R=Br **5e**	82
6		R=F **5f**	28
7		R=CF_3 **5g**	83
8		R=OMe **5h**	65
9[c]		R=NH_2 **5i**	38
10[c]		R=NMe_2 **5j**	21
11[d]		R=OH **5k**	0
12		R=CO_2Me **5l**	0[e]
13		R=F **5m**	96
14		R=OMe **5n**	86
15		**5o**	85
16		**5p**	31
17		**5q**	22
18[f]		**5r**	41

[a] Reactions were conducted using 1.95 mmol of adiponitrile (**1a**) and 1.30 mmol of mononitrile in *p*-xylene (1 mL).
[b] Isolated yield of product, based on mononitrile as the limiting reagent.
[c] Reaction time of 20 h.
[d] Using 2.0 equiv of *t*-BuOK with respect to 4-cyanophenol (**3k**).
[e] See text and Eq. 2.
[f] Reaction conducted in 2 mL of *p*-xylene. The yield of **5r** in a reaction conducted in 1 mL of *p*-xylene was 26%.

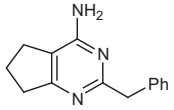
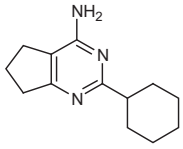
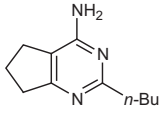
(entry 2) and valeronitrile (entry 3) had to be used in a large excess (10.0 equiv with respect to adiponitrile) for satisfactory yields of bicyclic 4-aminopyridines **9b** and **9c**, respectively. Presumably, competitive pathways resulting from self-condensation of the mononitrile reduce the efficiencies of these reactions.

Finally, the use of dinitriles other than adiponitrile (**1a**) was investigated (Table 3). In the presence of 50 mol % of *t*-BuOK, higher homologue pimelonitrile (**1b**) underwent cyclization with benzonitrile and 4-(trifluoromethyl)benzonitrile to provide products **10a** and **10b** in 90% and 57% yields, respectively (entries 1

Table 2
Reaction of adiponitrile (**1a**) with aliphatic mononitriles[a]

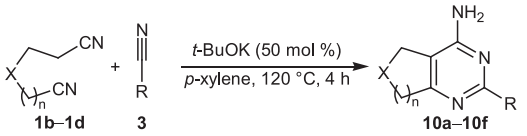


1a **3s–3u** (10.0 equiv) **9a–9c**

Entry	Product		Yield[b] (%)
1[c]		**9a**	53[c]
2		**9b**	48
3		**9c**	56

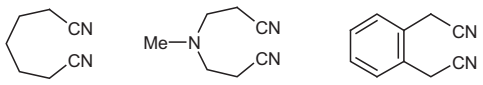
[a] Reactions were conducted using 1.30 mmol of adiponitrile (**1a**) and 13.0 mmol of mononitrile in the absence of solvent.
[b] Isolated yield of product, based on adiponitrile (**1a**) as the limiting reagent.
[c] Reaction was conducted using 1.95 mmol (1.5 equiv) of adiponitrile (**1a**) and 1.30 mmol of benzyl cyanide (**3s**) in *p*-xylene (1 mL). Reported yield is based on benzyl cyanide as the limiting reagent.

Table 3
Reaction of various dinitriles with a range of benzonitriles[a]

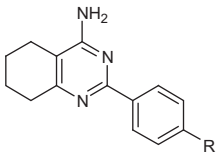
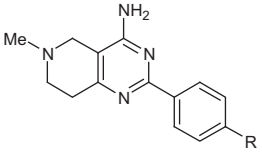
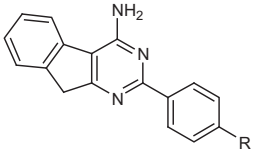


1b–1d **3** **10a–10f**

Dinitriles



1b **1c** **1d**

Entry	Product		Yield (%)
1		R=H **10a**	90
2		R=CF_3 **10b**	57
3		R=H **10c**	90
4		R=Br **10d**	92
5[b]		R=H **10e**	38
6[b]		R=*t*-Bu **10f**	40

[a] Reactions were conducted using 1.95 mmol of adiponitrile (**1a**) and 1.30 mmol of mononitrile in *p*-xylene (1 mL).
[b] Using 20 mol % of *t*-BuOK.

and 2). Conversions were significantly lower when only 20 mol % of *t*-BuOK was employed. We were pleased to observe that dinitrile **1c** containing a methylamino substituent in the tether also underwent smooth cyclization to form products **10c** and **10d** in high yields, without evidence of β-elimination (entries 3 and 4). However, the reactions of 1,2-phenylenediacetonitrile (**1d**) were less efficient (entries 5 and 6). Here, high conversions were observed using only 20 mol % of *t*-BuOK, but in addition to the desired bicyclic 4-aminopyrimidines, numerous other side products were also detected.

3. Conclusion

In conclusion, catalytic potassium *tert*-butoxide promotes the direct synthesis of bicyclic 4-aminopyrimidines from the reaction of dinitriles with mononitriles. This method tolerates a range of reaction partners to provide diverse bicyclic 4-aminopyrimidines in a more convenient and expedient fashion compared with existing methods.

4. Experimental

4.1. General

All commercially available reagents were dried before use. Solid reagents were dried under high vacuum for several hours. Liquid reagents were dried with 3 Å molecular sieves. Anhydrous *p*-xylene was purchased from Sigma–Aldrich. All reactions were performed in a Carousel 12 Plus Reaction Station under nitrogen. Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Infra-red spectra were recorded on a Perkin–Elmer Spectrum One FT-IR instrument as a thin film. Flash chromatography was carried out in air on pre-packed ISOLUTE® Flash Si II silica columns using an automated Biotage FlashMaster™ II purification system. High resolution mass spectra were recorded on a Bruker Apex IV instrument or a Thermofisher LTQ Orbitrap XL spectrometer. ^{1}H NMR spectra were recorded on a Bruker AVA400 (400 MHz) or a Bruker DPX360 (360 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using residual protonated solvent as internal standard ($CDCl_3$ at 7.27 ppm and DMSO-d_6 at 2.50 ppm). Abbreviations used in the description of resonances are: s (singlet), d (doublet), t (triplet), q (quartet), br (broad), m (multiplet). Coupling constants (J) are quoted to the nearest 0.1 Hz. Assignments were made using COSY, HMQC, HMBC, and ROESY experiments. Proton-decoupled ^{13}C NMR spectra were recorded on a Bruker AVA400 (100.6 MHz) spectrometer or a Bruker DPX360 (90.6 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using deuterated solvent as internal standard ($CDCl_3$ at 77.0 ppm and DMSO-d_6 at 39.5 ppm). Assignments were made using the DEPT sequence with secondary pulses at 90° and 135°.

4.2. Base-catalyzed reaction of adiponitrile with mononitriles: general procedure A

To a solution of adiponitrile (219 μL, 1.95 mmol) and the appropriate mononitrile (1.30 mmol) in *p*-xylene (1 mL) in a carousel tube was added *t*-BuOK (29.2 mg, 0.26 mmol) in one portion. The reaction vessel was heated in a carousel to 120 °C for 4 h. After

cooling to room temperature, CH_2Cl_2 (ca. 30 mL) was used to transfer the mixture onto a silica cartridge for purification.

*4.2.1. 2-Phenyl-6,7-dihydro-5H-cyclopentapyrimidin-4-ylamine (**5a**).* The title compound was prepared according to general procedure A using benzonitrile (133 μL, 1.30 mmol) and purified by flash chromatography (0% EtOAc/cyclohexane→100% EtOAc/cyclohexane) to give a white solid (223 mg, 81%). Mp 131–133 °C; IR (film) 3319 (NH), 3184, 2957, 1622, 1589, 1568, 1435, 1397, 758, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.33–8.30 (2H, m, Ar*H*), 7.44–7.42 (3H, m, Ar*H*), 4.91 (2H, br s, NH_2), 3.00–2.96 (2H, m, CH_2Ar), 2.73–2.69 (2H, m, CH_2Ar), 2.18–2.09 (2H, m, CH_2CH$_2$Ar); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 173.2 (C), 163.7 (C), 159.4 (C), 138.5 (C), 129.7 (CH), 128.2 (2× CH), 127.9 (2× CH), 113.9 (C), 34.2 (CH_2), 26.7 (CH_2), 21.6 (CH_2); HRMS (ES) exact mass calcd for $C_{13}H_{14}N_3$ $[M+H]^+$: 212.1182, found: 212.1181.

*4.2.2. 2-(4-tert-Butylphenyl)-6,7-dihydro-5H-cyclopentapyrimidin-4-ylamine (**5b**).* The title compound was prepared according to general procedure A using 4-*tert*-butylbenzonitrile (220 μL, 1.30 mmol) and purified by flash chromatography (0% EtOAc/cyclohexane→100% EtOAc/cyclohexane) to give a white solid (261 mg, 75%). Mp 149–151 °C; IR (film) 3315 (NH), 3178, 2960, 2868, 1611, 1579, 1560, 1447, 1392, 906, 850, 787, 728 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (2H, d, J=8.5 Hz, Ar*H*), 7.46 (2H, d, J=8.5 Hz, Ar*H*), 4.99 (2H, br s, NH_2), 3.00 (2H, t, J=7.8 Hz, CH_2Ar), 2.75 (2H, t, J=7.4 Hz, CH_2Ar), 2.24–2.11 (2H, m, CH_2CH$_2$Ar), 1.35 (9H, s, C(CH_3)$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.2 (C), 163.8 (C), 159.3 (C), 153.0 (C), 135.5 (C), 127.7 (2× CH), 125.2 (2× CH), 113.6 (C), 34.7 (C), 34.2 (CH_2), 31.3 (3× CH_3), 26.7 (CH_2), 21.6 (CH_2); HRMS (ES) exact mass calcd for $C_{17}H_{22}N_3$ $[M+H]^+$: 218.1808, found: 218.1805.

*4.2.3. 2-Biphenyl-4-yl-6,7-dihydro-5H-cyclopentapyrimidin-4-ylamine (**5c**).* The title compound was prepared according to general procedure A using 4-phenylbenzonitrile (233 mg, 1.30 mmol) and purified by flash chromatography (0% EtOAc/cyclohexane→100% EtOAc/cyclohexane) to give a white solid (297 mg, 80%). Mp 235 °C (decomp.); IR (film) 3462, 3310 (NH), 3129, 1630, 1588, 1460, 1396, 859, 760, 695 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.37 (2H, d, J=8.3 Hz, Ar*H*), 7.75–7.72 (4H, m, Ar*H*), 7.51–7.47 (2H, m, Ar*H*), 7.40–7.37 (1H, m, Ar*H*), 6.68 (2H, br s, NH_2), 2.82 (2H, t, J=7.7 Hz, CH_2Ar), 2.69 (2H, t, J=7.4 Hz, CH_2Ar), 2.07–1.99 (2H, m, CH_2CH$_2$Ar); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 171.3 (C), 161.6 (C), 160.1 (C), 141.0 (C), 139.7 (C), 137.6 (C), 129.0 (2× CH), 128.0 (2× CH), 127.7 (CH), 126.6 (2× CH), 126.4 (2× CH), 113.7 (C), 33.7 (CH_2), 27.0 (CH_2), 21.1 (CH_2); HRMS (ES) exact mass calcd for $C_{19}H_{18}N_3$ $[M+H]^+$: 288.1501, found: 288.1492.

*4.2.4. 2-(4-Chlorophenyl)-6,7-dihydro-5H-cyclopentapyrimidin-4-ylamine (**5d**).* The title compound was prepared according to general procedure A using 4-chlorobenzonitrile (179 mg, 1.30 mmol) and purified by flash chromatography (0% EtOAc/cyclohexane→100% EtOAc/cyclohexane) to give a white solid (319 mg, 90%). Mp 158–160 °C; IR (film) 3429, 3349 (NH), 3136, 2920, 2179, 1612, 1587, 1564, 1454, 1409, 1085, 1010, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.25–8.22 (2H, m, Ar*H*), 7.42–7.38 (2H, m, Ar*H*), 4.94 (2H, br s, NH_2), 3.01–2.97 (2H, t, J=7.8 Hz, CH_2Ar), 2.76–2.73 (2H, t, J=7.4 Hz, CH_2Ar), 2.21–2.14 (2H, m, CH_2CH$_2$Ar); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.1 (C), 162.5 (C), 159.4 (C), 136.9 (C), 135.7 (C), 129.3 (2× CH), 128.3 (2× CH), 114.1 (C), 34.2 (CH_2), 26.7 (CH_2), 21.5 (CH_2); HRMS (ES) exact mass calcd for $C_{13}H_{13}N_3Cl$ $[M+H]^+$: 246.0798, found: 246.0800.

*4.2.5. 2-(4-Bromophenyl)-6,7-dihydro-5H-cyclopentapyrimidin-4-ylamine (**5e**).* The title compound was prepared according to general procedure A using 4-bromobenzonitrile (237 mg, 1.30 mmol) and purified by flash chromatography (0% EtOAc/cyclohexane→100% EtOAc/cyclohexane) to give a white solid (310 mg, 82%). Mp 177–179 °C; IR (film) 3654, 3291 (NH), 3145, 2954, 2913, 2182, 1625, 1586, 1564, 1457, 1389, 1009, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.23–8.20 (2H, m, Ar*H*), 7.57–7.54 (2H, m, Ar*H*), 4.81 (2H, br s, NH_2), 2.98 (2H, t, J=7.8 Hz, CH_2Ar), 2.74 (2H, t, J=7.5 Hz, CH_2Ar), 2.22–2.08 (2H, m, CH_2CH$_2$Ar); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.3 (C), 162.7 (C), 159.4 (C), 137.4 (C), 131.0 (2× CH), 129.6 (2× CH), 124.3 (C), 114.2 (C), 34.2 (CH_2), 26.8 (CH_2), 21.6 (CH_2); HRMS (ES) exact mass calcd for $C_{13}H_{13}N_3Br$ $[M+H]^+$: 290.0293, found: 290.0294.

*4.2.6. 2-(4-Fluorophenyl)-6,7-dihydro-5H-cyclopentapyrimidin-4-ylamine (**5f**).* The title compound was prepared according to general procedure A using 4-fluorobenzonitrile (157 mg, 1.30 mmol) and purified by flash chromatography (0% EtOAc/cyclohexane→50% EtOAc/cyclohexane) to give a white solid (84 mg, 28%). Mp 186–188 °C; IR (film) 3294 (NH), 3159, 1621, 1603, 1573, 1510, 1390, 1217, 1159, 849, 782 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.33–8.30 (2H, m, Ar*H*), 7.26–7.21 (2H, m, Ar*H*), 6.69 (2H, br s, NH_2), 2.79 (2H, t, J=7.7 Hz, CH_2Ar), 2.67 (2H, t, J=7.3 Hz, CH_2Ar), 2.04–1.97 (2H, m, CH_2CH$_2$Ar); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 171.2 (C), 163.2 (C, d, J_F=246.4 Hz), 160.9 (C), 160.1 (C), 135.0 (C, d, J_F=2.7 Hz), 129.5 (2× CH, d, J_F=8.5 Hz), 114.9 (2× CH, d, J_F=21.4 Hz), 113.5 (C), 33.7 (CH_2), 26.9 (CH_2), 21.1 (CH_2); HRMS (ES) exact mass calcd for $C_{13}H_{13}N_3F$ $[M+H]^+$: 230.1094, found: 230.1095.

*4.2.7. 2-(4-Trifluoromethylphenyl)-6,7-dihydro-5H-cyclopentapyrimidin-4-ylamine (**5g**).* The title compound was prepared according to general procedure A using 4-(trifluoromethyl)benzonitrile (222 mg, 1.30 mmol) and purified by flash chromatography (0% EtOAc/cyclohexane→100% EtOAc/cyclohexane) to give a white solid (300 mg, 83%). Mp 155–157 °C; IR (film) 3494, 3430, 3351 (NH), 3291, 3237, 3129, 2957, 2181, 1628, 1567, 1460, 1320, 1157, 1108, 1062, 784 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 8.46–8.44 (2H, m, Ar*H*), 7.69–7.67 (2H, m, Ar*H*), 4.85 (2H, br s, NH_2), 3.02–2.97 (2H, m, CH_2Ar), 2.77–2.73 (2H, m, CH_2Ar), 2.21–2.15 (2H, m, CH_2CH$_2$Ar); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 173.3 (C), 162.2 (C), 159.4 (C), 141.7 (C), 131.3 (C, q, J_F=32.2 Hz), 128.2 (2× CH), 125.1 (2× CH, q, J_F=3.4 Hz), 124.2 (C, q, J_F=272.3 Hz), 114.7 (C), 34.2 (CH_2), 26.7 (CH_2), 21.5 (CH_2); HRMS (ES) exact mass calcd for $C_{14}H_{13}N_3F_3$ $[M+H]^+$: 280.1062, found: 280.1067.

*4.2.8. 2-(4-Methyoxyphenyl)-6,7-dihydro-5H-cyclopentapyrimidin-4-ylamine (**5h**).* The title compound was prepared according to general procedure A using 4-methoxybenzonitrile (173 mg, 1.30 mmol) and purified by flash chromatography (0% EtOAc/cyclohexane→100% EtOAc/cyclohexane→20% MeOH/CH_2Cl_2) to give a white solid (204 mg, 65%). Mp 242–244 °C (decomp.); IR (film) 3471, 3317 (NH), 3179, 2955, 1613, 1588, 1434, 1395, 1383, 907, 728, 700 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.22 (2H, d, J=8.8 Hz, Ar*H*), 6.97 (2H, d, J=8.8 Hz, Ar*H*), 6.62 (2H, br s, NH_2), 3.79 (3H, s, OCH_3), 2.77 (2H, t, J=7.7 Hz, CH_2Ar), 2.66 (2H, t, J=7.4 Hz, CH_2Ar), 2.02–1.98 (2H, m, CH_2CH$_2$Ar); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 171.1 (C), 161.7 (C), 160.6 (C), 160.0 (C), 131.0 (C), 129.0 (2× CH), 113.4 (2× CH), 112.9 (C), 55.2 (CH_3), 33.7 (CH_2), 26.9 (CH_2), 21.1 (CH_2); HRMS (ES) exact mass calcd for $C_{14}H_{16}N_3O$ $[M+H]^+$: 242.1293, found: 242.1291.

*4.2.9. 2-(4-Aminophenyl)-6,7-dihydro-5H-cyclopentapyrimidin-4-ylamine (**5i**).* The title compound was prepared according to a modification of general procedure A using 4-aminobenzonitrile (154 mg, 1.30 mmol) for an increased reaction time of 20 h and purified by flash chromatography (0% EtOAc/cyclohexane→100% EtOAc/cyclohexane→20% MeOH/CH_2Cl_2) to give a white solid (112 mg, 38%). Mp 199–201 °C (decomp.); IR (film) 3326 (NH), 3191,

2961; 1608; 1568; 1452, 1433, 1387, 1172, 786 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.02–8.00 (2H, m, Ar*H*), 6.58–6.56 (2H, m, Ar*H*), 6.41 (2H, br s, NH_2), 5.37 (2H, br s, NH_2), 2.74 (2H, t, J=7.6 Hz, CH_2Ar), 2.64 (2H, t, J=7.2 Hz, CH_2Ar), 2.01–1.94 (2H, m, CH_2CH_2Ar); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 171.1 (C), 162.6 (C), 159.8 (C), 150.2 (C), 128.8 (2× CH), 126.1 (C), 113.0 (2× CH), 111.8 (C), 33.7 (CH_2), 26.8 (CH_2), 21.1 (CH_2); HRMS (ES) exact mass calcd for $C_{13}H_{15}N_4$ $[M+H]^+$: 227.1297, found: 227.1287.

*4.2.10. 2-(4-Dimethylaminophenyl)-6,7-dihydro-5H-cyclopentapyrimidin-4-ylamine (**5j**).* The title compound was prepared according to a modification of general procedure A using 4-dimethylaminobenzonitrile (190 mg, 1.30 mmol) for an increased reaction time of 20 h and purified by flash chromatography (0% EtOAc/cyclohexane→100% EtOAc/cyclohexane→20% MeOH/CH_2Cl_2) to give a white solid (68 mg, 21%). Mp 253–256 °C (decomp.); IR (film) 3484, 3298 (NH), 3183, 2905, 1604, 1572, 1381, 1176, 826, 783 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.14–8.12 (2H, m, Ar*H*), 6.73–6.70 (2H, m, Ar*H*), 6.48 (2H, br s, NH_2), 2.96 (6H, s, N(CH_3)$_2$), 2.76 (2H, t, J=7.7 Hz, CH_2Ar), 2.65 (2H, t, J=7.4 Hz, CH_2Ar), 2.02–1.95 (2H, m, CH_2CH_2Ar); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 171.0 (C), 162.3 (C), 159.8 (C), 151.2 (C), 128.6 (2× CH), 126.2 (C), 112.0 (C), 111.2 (2× CH), 39.9 (2× CH_3), 33.7 (CH_2), 26.9 (CH_2), 21.1 (CH_2); HRMS (ES) exact mass calcd for $C_{15}H_{19}N_4$ $[M+H]^+$: 255.1610, found: 255.1601.

*4.2.11. 2-[(4-Cyanophenyl)carbonyl]hexanedinitrile (**8**).* The title compound was prepared according to general procedure A using methyl 4-cyanobenzoate (210 mg, 1.30 mmol) and purified by flash chromatography (0% EtOAc/cyclohexane→100% EtOAc/cyclohexane) to give a colorless oil (38 mg, 12%). IR (film) 2927, 2238 (C≡N), 2232 (C≡N), 2225 (C≡N), 1699, 1406, 1265, 1221, 983, 910, 852 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.11–8.08 (2H, m, Ar*H*), 7.88–7.85 (2H, m, Ar*H*), 4.39 (1H, dd, J=7.9, 6.0 Hz, C*H*CN), 2.56–2.45 (2H, m, CH_2CN), 2.25–2.12 (2H, m, CH_2CH_2CH_2CN), 2.05–1.88 (2H, m, CH_2CH_2CN); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 188.6 (C), 136.5 (C), 133.0 (2× CH), 129.2 (2× CH), 118.5 (C), 118.0 (C), 117.3 (C), 115.8 (C), 39.1 (CH), 27.6 (CH_2), 22.6 (CH_2), 16.8 (CH_2); HRMS (EI) exact mass calcd for $C_{14}H_{11}N_3O$ $[M]^+$: 237.0897, found: 237.0900.

*4.2.12. 2-(3-Fluorophenyl)-6,7-dihydro-5H-cyclopentapyrimidin-4-ylamine (**5m**).* The title compound was prepared according to general procedure A using 3-fluorobenzonitrile (139 μL, 1.30 mmol) and purified by flash chromatography (0% EtOAc/cyclohexane→100% EtOAc/cyclohexane) to give a white solid (285 mg, 96%). Mp 116–118 °C; IR (film) 3311 (NH), 3179, 2957, 2906, 1624, 1571, 1434, 1398, 1381, 851, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10–8.09 (1H, m, Ar*H*), 8.03–7.99 (1H, m, Ar*H*), 7.45–7.40 (1H, m, Ar*H*), 7.17–7.13 (1H, m, Ar*H*), 5.09 (2H, br s, NH_2), 2.99 (2H, t, J=7.8 Hz, CH_2Ar), 2.74 (2H, t, J=7.4 Hz, CH_2Ar), 2.23–2.15 (2H, m, CH_2CH_2Ar); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.3 (C), 163.0 (C, d, J_F=244.3 Hz), 162.5 (C, d, J_F=3.1 Hz), 159.3 (C), 140.9 (C, d, J_F=7.8 Hz), 129.6 (CH, d, J_F=7.9 Hz), 123.5 (CH, d, J_F=2.8 Hz), 116.5 (CH, d, J_F=21.4 Hz), 114.8 (CH, d, J_F=23.0 Hz), 114.4 (C), 34.2 (CH_2), 26.7 (CH_2), 21.6 (CH_2); HRMS (ES) exact mass calcd for $C_{13}H_{13}N_3F$ $[M+H]^+$: 230.1094, found: 230.1096.

*4.2.13. 2-(3-Methyoxyphenyl)-6,7-dihydro-5H-cyclopentapyrimidin-4-ylamine (**5n**).* The title compound was prepared according to general procedure A using 3-methoxybenzonitrile (159 μL, 1.30 mmol) and purified by flash chromatography (0% EtOAc/cyclohexane→100% EtOAc/cyclohexane) to give a white solid (270 mg, 86%). Mp 166–168 °C; IR (film) 3429, 3314 (NH), 3175, 2960, 2841, 1648, 1570, 1454, 1432, 1394, 1378, 1235, 1043, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.93–7.89 (2H, m, Ar*H*), 7.37–7.33 (1H, m, Ar*H*), 6.99–6.97 (1H, m, Ar*H*), 4.85 (2H, br s, NH_2), 3.89 (3H, s, OCH_3), 2.99 (2H, t, J=7.8 Hz, CH_2Ar), 2.74 (2H, t, J=7.4 Hz, CH_2Ar), 2.20–2.12 (2H, m, CH_2CH_2Ar); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.2 (C), 163.5 (C), 159.7 (C), 159.3 (C), 140.0 (C), 129.2 (CH), 120.5 (CH), 116.3 (CH), 114.0 (C), 112.6 (CH), 55.3 (CH_3), 34.2 (CH_2), 26.7 (CH_2), 21.6 (CH_2); HRMS (ES) exact mass calcd for $C_{14}H_{16}N_3O$ $[M+H]^+$: 242.1293, found: 242.1297.

*4.2.14. 2-Naphthalen-2-yl-6,7-dihydro-5H-cyclopentapyrimidin-4-ylamine (**5o**).* The title compound was prepared according to general procedure A using naphthalene-2-carbonitrile (199 mg, 1.30 mmol) and purified by flash chromatography (0% EtOAc/cyclohexane→100% EtOAc/cyclohexane) to give a white solid (288 mg, 85%). Mp 176–178 °C; IR (film) 3325 (NH), 3183, 2957, 1613, 1568, 1451, 1433, 1400, 788 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.85 (1H, s, Ar*H*), 8.45 (1H, dd, J=8.5, 1.5 Hz, Ar*H*), 8.04–8.02 (1H, m, Ar*H*), 7.96–7.92 (2H, m, Ar*H*), 7.55–7.52 (2H, m, Ar*H*), 6.75 (2H, br s, NH_2), 2.85 (2H, t, J=7.7 Hz, CH_2Ar), 2.71 (2H, t, J=7.3 Hz, CH_2Ar), 2.08–2.00 (2H, m, CH_2CH_2Ar); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 171.4 (C), 163.2 (C), 161.8 (C), 160.2 (C), 136.0 (C), 133.7 (C), 132.8 (CH), 128.7 (CH), 127.5 (CH), 126.9 (CH), 126.7 (CH), 126.2 (CH), 125.2 (CH), 113.8 (C), 33.7 (CH_2), 27.0 (CH_2), 21.1 (CH_2); HRMS (ES) exact mass calcd for $C_{17}H_{16}N_3$ $[M+H]^+$: 262.1339, found: 262.1337.

*4.2.15. 2-Quinolin-3-yl-6,7-dihydro-5H-cyclopentapyrimidin-4-ylamine (**5p**).* The title compound was prepared according to general procedure A using 3-quinolinecarbonitrile (200 mg, 1.30 mmol) and purified by flash chromatography (0% EtOAc/cyclohexane→100% EtOAc/cyclohexane→20% MeOH/CH_2Cl_2) to give a white solid (105 mg, 31%). Mp 250–252 °C (decomp.); IR (film) 3395, 3306 (NH), 3180, 2905, 1639, 1581, 1562, 1465, 1428, 1394, 852, 786, 750 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.80 (1H, d, J=2.0 Hz, Ar*H*), 9.11 (1H, d, J=1.8 Hz, Ar*H*), 8.13 (1H, d, J=7.8 Hz, Ar*H*), 8.06 (1H, d, J=8.5 Hz, Ar*H*), 7.81–7.77 (1H, m, Ar*H*), 7.66–7.62 (1H, m, Ar*H*), 6.88 (2H, br s, NH_2), 2.86 (2H, t, J=7.7 Hz, CH_2Ar), 2.72 (2H, t, J=7.4 Hz, CH_2Ar), 2.09–2.01 (2H, m, CH_2CH_2Ar); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 171.4 (C), 160.2 (C), 149.9 (CH), 148.0 (C), 134.3 (CH), 131.0 (CH), 130.1 (CH), 129.0 (CH), 128.7 (C), 127.3 (CH), 126.9 (C), 114.4 (C), 33.7 (CH_2), 27.0 (CH_2), 21.1 (CH_2); HRMS (ES) exact mass calcd for $C_{16}H_{15}N_4$ $[M+H]^+$: 263.1297, found: 263.1290.

*4.2.16. 2-Pyridin-4-yl-6,7-dihydro-5H-cyclopentapyrimidin-4-ylamine (**5q**).* The title compound was prepared according to general procedure A using 4-cyanopyridine (135 mg, 1.30 mmol) and purified by flash chromatography (0% EtOAc/cyclohexane→100% EtOAc/cyclohexane→20% MeOH/CH_2Cl_2) to give a white solid (60 mg, 22%). Mp 158–160 °C; IR (film) 3324 (NH), 3182, 2957, 1681, 1630, 1587, 1553, 1456, 1414, 1397, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.69–8.68 (2H, m, Ar*H*), 8.18–8.16 (2H, m, Ar*H*), 5.02 (2H, br s, NH_2), 2.98 (2H, t, J=7.9 Hz, CH_2Ar), 2.74 (2H, t, J=7.4 Hz, CH_2Ar), 2.18–2.15 (2H, m, CH_2CH_2Ar); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.3 (C), 161.4 (C), 159.5 (C), 150.0 (2× CH), 145.8 (C), 122.0 (2× CH), 115.5 (C), 34.1 (CH_2), 26.8 (CH_2), 21.5 (CH_2); HRMS (ES) exact mass calcd for $C_{12}H_{13}N_4$ $[M+H]^+$: 213.1140, found: 213.1135.

*4.2.17. 2-Furan-2-yl-6,7-dihydro-5H-cyclopentapyrimidin-4-ylamine (**5r**).* The title compound was prepared according to a modification of general procedure A using 2-furonitrile (114 μL, 1.30 mmol) in double (2 mL) the standard amount of *p*-xylene and purified by flash chromatography (0% EtOAc/cyclohexane→100% EtOAc/cyclohexane) to give a white solid (107 mg, 41%). Mp 174–175 °C (decomp.); IR (film) 3491, 3316 (NH), 3185, 2956, 1646, 1562, 1459, 1395, 1020, 781, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55–7.53 (1H, m, Ar*H*), 7.18 (1H, d, J=3.3 Hz, Ar*H*), 6.50–6.49 (1H, m, Ar*H*), 5.01 (2H, br s, NH_2), 2.97 (2H, t, J=7.8 Hz, CH_2Ar), 2.72 (2H,

t, J=7.4 Hz, CH_2Ar), 2.15–2.08 (2H, m, CH_2CH_2Ar); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.9 (C), 159.3 (C), 156.5 (C), 152.6 (C), 143.9 (CH), 113.8 (C), 111.7 (CH), 111.6 (CH), 34.2 (CH_2), 26.8 (CH_2), 21.4 (CH_2); HRMS (ES) exact mass calcd for $C_{11}H_{12}N_3O$ $[M+H]^+$: 202.0980, found: 202.0981.

*4.2.18. 2-Benzyl-6,7-dihydro-5H-cyclopentapyrimidin-4-ylamine (**9a**).* The title compound was prepared according to general procedure A using benzyl cyanide (150 μL, 1.30 mmol) and purified by flash chromatography (0% EtOAc/cyclohexane→100% EtOAc/cyclohexane→20% MeOH/CH_2Cl_2) to give a white solid (154 mg, 53%). Mp 185–187 °C; IR (film) 3081, 2951, 1667, 1581, 1476, 1432, 1407, 690 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.38–7.34 (5H, m, Ar*H*), 4.89 (2H, br s, NH_2), 4.05 (2H, s, CH_2Ph), 2.91–2.89 (2H, m, CH_2Ar), 2.64–2.60 (2H, m, CH_2Ar), 2.13–2.05 (2H, m, CH_2CH_2Ar); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 172.7 (C), 167.9 (C), 159.6 (C), 139.1 (C), 129.0 (2× CH), 128.3 (2× CH), 126.2 (CH), 113.2 (C), 45.5 (CH_2), 34.2 (CH_2), 26.6 (CH_2), 21.5 (CH_2); HRMS (ES) exact mass calcd for $C_{14}H_{16}N_3$ [M+H]: 226.1339, found: 226.1336.

*4.2.19. 2-Cyclohexyl-6,7-dihydro-5H-cyclopentapyrimidin-4-ylamine (**9b**).* The title compound was prepared according to a modification of general procedure A in that: (i) 10 equiv of cyclohexanecarbonitrile (1.54 mL, 13.0 mmol) was used, and (ii) the reaction was conducted in the absence of solvent. Purification was carried by flash chromatography (0% EtOAc/cyclohexane→100% EtOAc/cyclohexane) to give a white solid (135 mg, 48%). Mp 196–198 °C; IR (film) 3315 (NH), 3186, 2929, 2852, 1638, 1577, 1460, 1404 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.81 (2H, br s, NH_2), 2.86 (2H, t, J=7.8 Hz, CH_2Ar), 2.70–2.60 (3H, m, CH_2Ar and CH$_2$C*H*CH$_2$), 2.15–1.97 (2H, m, (CH_2)$_5$), 1.96–1.84 (2H, m, (CH_2)$_5$), 1.84–1.73 (2H, m, (CH_2)$_5$), 1.69–1.66 (1H, m, (CH_2)$_5$), 1.61–1.51 (2H, m, (CH_2)$_5$), 1.43–1.15 (3H, m, (CH_2)$_5$); ^{13}C NMR ($CDCl_3$) δ 173.2 (C), 172.6 (C), 159.3 (C), 112.9 (C), 47.4 (CH), 34.2 (CH_2), 31.9 (2× CH_2), 26.6 (CH_2), 26.3 (2× CH_2), 25.9 (CH_2), 21.5 (CH_2); HRMS (ES) exact mass calcd for $C_{13}H_{20}N_3$ $[M+H]^+$: 218.1657, found: 218.1650.

*4.2.20. 2-Butyl-6,7-dihydro-5H-cyclopentapyrimidin-4-ylamine (**9c**).* The title compound was prepared according to a modification of general procedure A in that: (i) 10 equiv of valernonitrile (1.36 mL, 13.0 mmol) was used, and (ii) the reaction was conducted in the absence of solvent. Purification was carried out by flash chromatography (0% EtOAc/cyclohexane→100% EtOAc/cyclohexane) to give a white solid (140 mg, 56%). Mp 142–143 °C; IR (film) 3309 (NH), 3131, 2952, 2928, 2862, 1657, 1574, 1468, 1408 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.98 (2H, br s, NH_2), 2.86 (2H, t, J=7.8 Hz, CH_2Ar), 2.69–2.63 (4H, m, CH_2Ar and CH_2CH$_2$CH$_2$CH$_3$), 2.11–2.04 (2H, m, CH_2CH$_2$Ar), 1.73–1.65 (2H, m, CH_2CH$_2$CH$_3$), 1.41–1.32 (2H, m, CH_2CH$_3$), 0.89 (3H, t, J=7.3 Hz, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.6 (C), 169.9 (C), 159.3 (C), 112.7 (C), 39.1 (CH_2), 34.1 (CH_2), 31.3 (CH_2), 26.6 (CH_2), 22.7 (CH_2), 21.5 (CH_2), 13.9 (CH_3); HRMS (ES) exact mass calcd for $C_{11}H_{18}N_3$ $[M+H]^+$: 192.1501, found: 192.1497.

4.3. Base-catalyzed reaction of various dinitriles with various mononitriles: general procedure B

To a solution of the appropriate dinitrile (1.95 mmol) and the appropriate mononitrile (1.30 mmol) in *p*-xylene (1 mL) in a carousel tube was added *t*-BuOK (73 mg, 0.65 mmol) in one portion. The reaction vessel was heated in a carousel to 120 °C for 4 h. After cooling to room temperature, CH_2Cl_2 (ca. 30 mL) was used to transfer the mixture onto a silica cartridge for purification.

*4.3.1. Phenyl-5,6,7,8-tetrahydroquinazolin-4-ylamine (**10a**).* The title compound was prepared according to general procedure B using pimelonitrile (251 μL, 1.95 mmol) and benzonitrile (133 μL, 1.30 mmol) and purified by flash chromatography (0% EtOAc/cyclohexane→100% EtOAc/cyclohexane) to give a white solid (263 mg, 90%). Mp 121–123 °C; IR (film) 3319 (NH), 2937, 1613, 1587, 1565, 1556, 1445, 1401, 759, 702 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.31–8.28 (2H, m, Ar*H*), 7.46–7.40 (3H, m, Ar*H*), 4.90 (2H, br s, NH_2), 2.83–2.80 (2H, m, CH_2Ar), 2.43–2.37 (2H, m, CH_2Ar), 1.89–1.86 (4H, m, CH_2CH_2CH$_2$Ar); ^{13}C NMR (90.6 MHz, $CDCl_3$) 163.6 (C), 161.6 (C), 161.3 (C), 138.5 (C), 129.6 (CH), 128.2 (2× CH), 127.7 (2× CH), 109.9 (C), 32.1 (CH_2), 22.4 (CH_2), 22.3 (2× CH_2); HRMS (ES) exact mass calcd for $C_{14}H_{16}N_3$ $[M+H]^+$: 226.1339, found: 226.1335.

*4.3.2. 2-(4-Trifluoromethylphenyl)-5,6,7,8-tetrahydroquinazolin-4-ylamine (**10b**).* The title compound was prepared according to general procedure B using pimelonitrile (251 μL, 1.95 mmol) and 4-(trifluoromethyl)benzonitrile (222 mg, 1.30 mmol) and purified by flash chromatography (0% EtOAc/cyclohexane→100% EtOAc/cyclohexane) to give a white solid (218 mg, 57%). Mp 152–154 °C; IR (film) 3496, 3298 (NH), 3183, 2936, 2863, 1624, 1566, 1456, 1332, 1158, 1126, 785 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44–8.42 (2H, m, Ar*H*), 7.69–7.67 (2H, m, Ar*H*), 4.87 (2H, br s, NH_2), 2.84–2.81 (2H, m, CH_2Ar), 2.44–2.41 (2H, m, CH_2Ar), 1.93–1.87 (4H, m, CH_2CH_2CH$_2$Ar); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 163.9 (C), 161.6 (C), 159.9 (C), 141.9 (C), 131.2 (C, q, J_F=33.2 Hz), 128.0 (2× CH), 125.1 (2× CH, q, J_F=3.7 Hz), 124.3 (C, q, J=272.6 Hz), 110.7 (C), 32.1 (CH_2), 22.5 (CH_2), 22.3 (CH_2), 22.2 (CH_2); HRMS (ES) exact mass calcd for $C_{15}H_{15}N_3F_3$ $[M+H]^+$: 294.1218, found: 294.1215.

*4.3.3. 6-Methyl-2-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamine (**10c**).* The title compound was prepared according to general procedure B using 3-[(2-cyanoethyl)methylamino]propionitrile (206 mg, 1.95 mmol) and benzonitrile (133 μL, 1.30 mmol) and purified by flash chromatography (0% EtOAc/cyclohexane→100% EtOAc/cyclohexane→20% MeOH/CH_2Cl_2) to give a white solid (280 mg, 90%). Mp 118–119 °C; IR (film) 3332 (NH), 3188, 2937, 2787, 1627, 1590, 1558, 1450, 1400, 1375, 758, 700 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32–8.23 (2H, m, Ar*H*), 7.49–7.38 (3H, m, Ar*H*), 6.64 (2H, br s, NH_2), 3.29–3.21 (2H, m, NCH_2Ar), 2.75–2.72 (2H, m, NCH$_2$CH_2), 2.66–2.64 (2H, m, NCH_2CH$_2$), 2.39 (3H, s, NCH_3); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 160.4 (C), 160.1 (C), 159.7 (C), 138.3 (C), 129.6 (CH), 128.1 (2× CH), 127.3 (2× CH), 108.3 (C), 51.9 (CH_2), 51.6 (CH_2), 45.7 (CH_3), 31.8 (CH_2); HRMS (ES) exact mass calcd for $C_{14}H_{17}N_4$ $[M+H]^+$: 241.1453, found: 241.1452.

*4.3.4. 2-(4-Bromophenyl)-6-methyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-ylamine (**10d**).* The title compound was prepared according to general procedure B using 3-[(2-cyanoethyl)methylamino]propionitrile (206 mg, 1.95 mmol) and 4-bromobenzonitrile (182 mg, 1.30 mmol) and purified by flash chromatography (0% EtOAc/cyclohexane→100% EtOAc/cyclohexane→20% MeOH/CH_2Cl_2) to give a white solid (293 mg, 92%). Mp 169–171 °C; IR (film) 3317 (NH), 3181, 2942, 2792, 1629, 1557, 1583, 1453, 1420, 1401, 1377, 785, 730 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21–8.18 (2H, m, Ar*H*), 7.64–7.62 (2H, m, Ar*H*), 6.70 (2H, br s, NH_2), 3.26–3.20 (2H, m, NCH_2Ar), 2.74–2.71 (2H, m, NCH$_2$CH_2), 2.68–2.61 (2H, m, NCH_2CH$_2$), 2.38 (3H, s, NCH_3); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 160.4 (C), 159.7 (C), 159.2 (C), 137.5 (C), 131.1 (2× CH), 129.3 (2× CH), 123.3 (C), 108.6 (C), 51.9 (CH_2), 51.5 (CH_2), 45.7 (CH_3), 31.7 (CH_2); HRMS (ES) exact mass calcd for $C_{14}H_{16}N_4Br$ $[M+H]^+$: 319.0558, found: 319.0560.

*4.3.5. 2-Phenyl-9H-indeno[2,1-d]pyrimidin-4-ylamine (**10e**).* The title compound was prepared according to a modification of general procedure B in that *t*-BuOK (29.2 mg, 0.26 mmol) was used, using 1,2-phenylenediacetonitrile (305 mg, 1.95 mmol) and benzonitrile (133 μL, 1.30 mmol). Purification was carried out by flash chromatography (0% EtOAc/cyclohexane→50% EtOAc/cyclohexane) to give

a violet solid (128 mg, 38%). Mp 196–198 °C; IR (film) 3308 (NH), 3169, 2923, 1588, 1548, 1451, 1390, 1265, 905, 729, 713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.52–8.38 (2H, m, Ar*H*), 7.64–7.60 (1H, m, Ar*H*), 7.58–7.40 (5H, m, Ar*H*), 7.41–7.31 (1H, m, Ar*H*), 5.33 (2H, br s, NH_2), 4.02 (2H, s, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.0 (C), 162.6 (C), 157.4 (C), 139.9 (C), 138.1 (C), 137.6 (C), 130.1 (CH), 128.4 (2× CH), 128.2 (2× CH), 127.2 (CH), 126.4 (CH), 125.2 (CH), 120.8 (CH), 114.4 (C), 39.3 (CH_2); HRMS (ES) exact mass calcd for $C_{17}H_{14}N_3$ $[M+H]^+$: 260.1188, found: 260.1188.

*4.3.6. 2-(4-tert-Butylphenyl)-9H-indeno[2,1-d]pyrimidin-4-ylamine (**10f**).* The title compound was prepared according to a modification general procedure B in that *t*-BuOK (29.2 mg, 0.26 mmol) was used, using 1,2-phenylenediacetonitrile (305 mg, 1.95 mmol) and 4-*tert*-butylbenzonitrile (220 μL, 1.30 mmol). Purification was carried out by flash chromatography (0% EtOAc/cyclohexane→50% EtOAc/cyclohexane) to give a yellow solid (163 mg, 40%). Mp 207–209 °C; IR (film) 3306 (NH), 3177, 2962, 1618, 1581, 1548, 1460, 1396, 797, 734, 715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.38–8.36 (2H, m, Ar*H*), 7.58 (1H, d, *J*=7.3 Hz, Ar*H*), 7.51 (2H, d, *J*=8.6 Hz, Ar*H*), 7.49–7.45 (1H, m, Ar*H*), 7.40 (1H, t, *J*=7.3 Hz, Ar*H*), 7.35–7.29 (1H, m, Ar*H*), 5.41 (2H, br s, NH_2), 3.99 (2H, s, CH_2), 1.39 (9H, s, C(CH_3)$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.9 (C), 162.6 (C), 157.4 (C), 153.3 (C), 139.8 (C), 137.7 (C), 135.3 (C), 127.9 (2× CH), 127.1 (CH), 126.2 (CH), 125.3 (2× CH), 125.1 (CH), 120.6 (CH), 114.1 (C), 39.2 (CH_2), 34.8 (C), 31.2 (3× CH_3); HRMS (ES) exact mass calcd for $C_{21}H_{22}N_3$ $[M+H]^+$: 316.1814, found: 316.1817.

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Supplementary data

Copies of ^1H and ^{13}C NMR spectra for new compounds. Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2011.03.098.

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