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Toward Pyrrolo[2,3-*d*]pyrimidine Scaffolds

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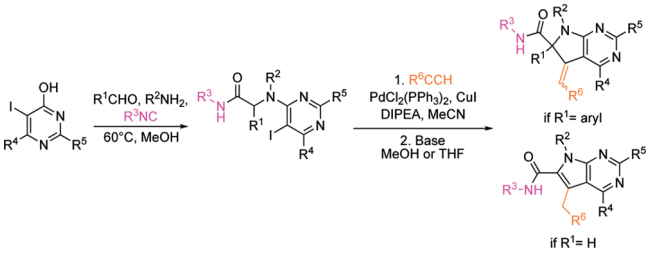
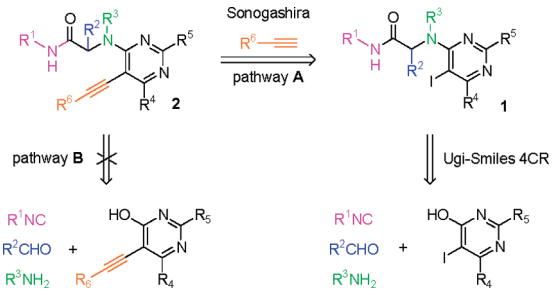


Herein, we present a new route to highly substituted pyrrolo[2,3-*d*]pyrimidines featuring a Ugi−Smiles/Sonogashira cascade followed by an efficient base-catalyzed intramolecular cyclization. When formaldehyde is chosen as input in the Ugi−Smiles step, aromatic fused systems are eventually obtained through the isomerization of an *exo*-alkylidene intermediate.

Multicomponent reactions (MCRs), in which three or more substrates react in a one-pot procedure, have become powerful tools to easily prepare large libraries of highly substituted molecules.[1] Over the past decades, the Ugi reaction has become the leading reaction of this field thanks to its great versatility. An even higher degree of diversity may be reached when these processes are coupled with postcondensation transformations, such cascades having been intensively explored by many research groups. We have recently disclosed a new Ugi-type reaction using electron-deficient phenols and heteroaromatic phenols (pyridines, pyrimidines) as the acidic partners.[2] Considering that phenols substituted by halogens at the *ortho* position are efficient partners in this coupling,[3] we developed this chemistry in association with palladium-catalyzed processes as previously featured in a one-pot, two-step formation of indoles.[4] Similarly, a Sonogashira coupling[5] could allow an easy access to acetylenic Ugi−Smiles adducts, providing us with some interesting opportunities for potential cyclizations. We report herein a new formation of fused pyrrolopyrimidine systems through a formal five-component coupling followed by a deprotonation alpha to the amide and a subsequent cyclization.

SCHEME 1. Ugi−Smiles Access to Pyrimidoalkyne Precursors



The Ugi-Smiles adducts **2** presenting an alkyne moiety can be prepared by a Ugi-Smiles reaction of *ortho* iodopyrimidin-4-ol derivatives followed by a Sonogashira coupling (Scheme 1, path A). The alternative path B starting with alkynepyrimidinol was unsuccessful due to its lack of reactivity in the Ugi−Smiles coupling step.

Several pyrimido alkynes **2** were prepared through modifications of the various partners of the couplings (Table 1) and following Hu's conditions for the Sonogashira step.[6] We had already exploited the acidity of aryl-substituted Ugi−Smiles adducts to trigger a palladium-induced cyclization.[7] The proposed mechanism for this previous study featured a stabilized anion formation in the α position of the amide. This intermediate cyclized onto a remote alkene activated by the palladium catalyst.

With these acetylenic pyrimidines **2** in hand, we next examined their behavior under basic conditions. In the case of the adducts **2**, we chose to first investigate aromatic aldehydes so that the stabilized anion can react with the alkyne to form the fused pyrrolidinopyrimidine derivatives. Indeed, a similar cyclization pattern was observed by Cacchi et al. when working on *N*-aryl-substituted glycine esters to form indole derivatives.[8]

The most acidic adducts **2a**−**g** were then submitted to different basic conditions as reported in Table 2. The first trials with the substrate **2a** (Table 2, entry 1) and various amounts of DBU in acetonitrile gave the compound **3a** as a mixture of two diastereomers. Both isomers can be selectively

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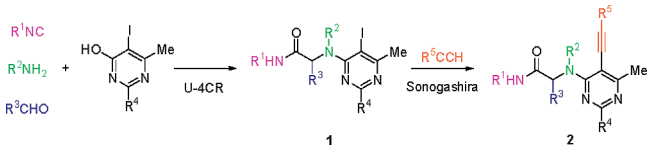
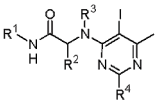
TABLE 1. Ugi-Smiles/Sonogashira Cascade Results

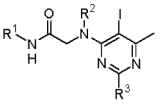


entry	Ugi−Smiles adduct (yield, %)	alkyne RCCH, R =	Sonogashira adduct (yield, %)
1	**1a** (65)	Ph	**2a** (62)
2	**1a**	*p*-MePh	**2b** (64)
3	**1a**	Bu	
4	**1b** (42)	*o*-CF_3Ph	**2c** (76)
5	**1c** (68)	Ph	**2d** (58)
6	**1d** (22)	*o*-CF_3Ph	**2e** (74)
7	**1d**	*p*-MeOPh	**2f** (70)
8	**1e** (59)	TMS	**2g**[a]
9	**1f** (50)	*o*-CF_3Ph	**2h** (61)
10	**1g** (64)	Ph	**2i** (74)
11	**1g**	*o*-CF_3Ph	**2j** (64)
12	**1h** (27)	Ph	**2k** (73)
13	**1i** (30)	*p*-MePh	**2l** (63)
14	**1j** (33)	Ph	**2m** (63)

[a] **2g** could not be isolated; the following cyclization was directly performed on the crude mixture.



1a R^1 = *p*-ClBn, R^2 = *p*-FPh, R^3 = *p*-ClBn, R^4 = *i*-Pr.
1b R^1 = *p*-ClBn, R^2 = *p*-ClPh, R^3 =$(CH_2)_2$OMe, R^4 = Ph.
1c R^1 = *p*-ClBn, R^2 = Ph, R^3 = *n*-Bu, R^4 = *i*-Pr.
1d R^1 = Cy, R^2 = *p*-FPh, R^3 = *p*-ClBn, R^4 = *i*-Pr.
1e R^1 = *p*-MeOBn, R^2 =*p*-FPh, R^3 = *p*-ClBn, R^4 = *i*-Pr.



1f R^1 = *p*-MeOBn, R^2 = *n*-Bu, R^3 = *i*-Pr.
1g R^1 = *p*-ClBn, R^2 = *p*-ClBn, R^3 = *i*-Pr.
1h R^1 = *t*-Bu, R^2 = *p*-ClBn, R^3 = *i*-Pr.
1i R^1 = Cy, R^2 = $(CH_2)_2$OMe, R^3 = *i*-Pr.
1j R^1 = homoveratryl, R^2 = *n*-Bu, R^3 = Ph.

formed using a catalytic amount of either DBU in refluxing methanol (conditions A) or potassium *tert*-butoxide in refluxing tetrahydrofuran (conditions B). For most starting alkynes, only one diastereomer can be isolated under conditions A, but the conditions B gave a mixture of both (the opposite is observed for trifluoropyrrolidinopyrimidine **3c** and **3e**). The diastereomers formed under conditions A show a 1 ppm ^{1}H NMR downfield shift of the methyl pyrimidine moiety compared to the major ones obtained under B. A NOESY experiment performed on both isomers of **3d** was consistent with a *Z* configuration of the alkene formed under condition A. All isomers could be separated, but some of these (Table 2, entries 3 and 5) appeared to be quite unstable and difficult to isolate as they can easily isomerize within a few days (a few hours in a $CDCl_3$ solution). In the case of the silyl-substituted alkyne **2g** (Table 1, entry 8, and Table 2, entry 7), it should be noted that the cyclization and the TMS deprotection occurred at the same time with potassium carbonate, giving a fused pyrrolidinopyrimidine bearing an *exo*-methylene.

More interestingly, a one-pot procedure can be performed for the Sonogashira/cyclization step by adding DBU in the mixture after the palladium-catalyzed step. Under these conditions, the substrate **2a** afforded both isomers **3a**(*Z*)/**3a**(*E*) in a 4:3 ratio in a 60% overall yield.

When formaldehyde was used in the Ugi−Smiles reaction, one would expect the resulting formation of less acidic adducts (Table 1, entries 9−14). Indeed, the treatment of **2h** with various amounts of DBU in methanol does not lead to any cyclization, nor do substoichiometric amounts of sodium hydride in DMF. However, the expected cyclization occurred at room temperature with 2 equiv of NaH, affording good yields for pyrrolo[2,3-*d*]pyrimidines (Table 3, entries 1−6). It is noteworthy that, in the case of *o*-trifluoromethylaryl alkynes **2h** and **2j** (Table 3, entries 1 and 3), the increased stability of the benzylic anion probably favors the oxidation of this position as the ketones **4h** and **4j** can be isolated.[9]

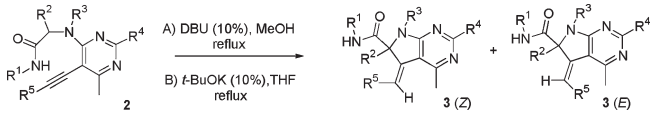
A plausible pathway starts with the deprotonation of the amide, forming a poorly reactive anion for a 7-*exo-dig* cyclization. The further addition of base results in the formation of a reactive dianion, prone to undergo a fast 5-*exo-dig* cyclization. Nevertheless, with an aromatic moiety as the aldehyde input, the acidities of the amide and the α-CH are quite similar, allowing an equilibrium between the two anionic sites so that the cyclization can be observed with a catalytic amount of base.

As already shown for aromatic derivatives, the whole process—Sonogashira coupling−cyclization−isomerization—can be performed according to a one-pot two-step procedure using acetonitrile as solvent. Under these conditions, the compound **3i** is obtained from **1g** in a 39% isolated yield, compared with 65% if the intermediate **2i** is separated (Table 1, entry 10, and Table 3, entry 2).

In conclusion, we have developed a new multicomponent synthesis of pyrrolopyrimidines, which are potentially relevant

(9) For a related oxidation, see: Bernini, R.; Cacchi, S.; Fabrizi, G.; Filisti, E.; Sferrazza, A. *Synlett* **2009**, 1245–1250.

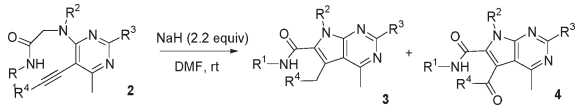
TABLE 2. Pyrrolidinopyrimidines from Pyrimidines 2a−g



entry	R^1	R^2	R^3	R^4	R^5	3	conditions (yield, %; ratio)
1	*p*-ClBn	*p*-FPh	*p*-ClPh	*i*-Pr	Ph	**3a**	A (91) B (100; 4:1)
2	*p*-ClBn	*p*-FPh	*p*-ClPh	*i*-Pr	*p*-MePh	**3b**	A (84) B (94; 4:1)
3	*p*-ClBn	*p*-ClPh	$(CH_2)_2OMe$	Ph	*o*-CF_3Ph	**3c**	A (87; 2:1)[a] B (72)
4	*p*-ClBn	Ph	*n*-Bu	*i*-Pr	Ph	**3d**	A (73) B (86; 3:1)
5	Cy	*p*-FPh	*p*-ClPh	*i*-Pr	*o*-CF_3Ph	**3e**	A (97; 2:1)[a] B (83)
6	Cy	*p*-FPh	*p*-ClPh	*i*-Pr	*p*-MeOPh	**3f**	A (66) B (75; 1.2:1)
7	*p*-MeOBn	*p*-FPh	*p*-ClPh	*i*-Pr	H	**3g**	(36)[b]

[a]Fast isomerization of both isomers after a few hours in $CDCl_3$ solutions. [b]Yield given directly from **1e** and cyclization performed using K_2CO_3.

TABLE 3. Pyrrolopyrimidines from Pyrimidines 2h−m



entry	R^1	R^2	R^3	R^4	3 (yield, %) (A/B)
1	*p*-MeOPh	*n*-Bu	*i*-Pr	*o*-CF_3Ph	**4h** (88)
2	*p*-ClPh	*p*-ClPh	*i*-Pr	Ph	**3i** (90)
3	*p*-ClPh	*p*-ClPh	*i*-Pr	*o*-CF_3Ph	**4j** (57)
4	*t*-Bu	*p*-ClPh	*i*-Pr	Ph	**3k** (82)
5	Cy	$(CH_2)_2OMe$	*i*-Pr	*p*-MePh	**3l** (69)
6	$ArCH_2CH_2$[a]	*n*-Bu	Ph	Ph	**3m** (75)

[a]Ar = 3,4-dimethoxyphenyl.

scaffolds for use in the pharmaceutical industry.[10] More interestingly, this study underlines the potential of Ugi adducts in the alkylation of amide enolates and the necessity to address the relative acidities of the N−H and C−H protons. Several studies by Marcaccini et al. have already shown a possible control of the cyclization paths by a proper selection of the Ugi starting partners.[11] We are further studying the behavior of such Ugi−Smiles adducts under basic conditions.

Experimental Section

General Procedure for Pyrimidine-Induced Ugi-4CR. To a 1 M solution of pyrimidine in methanol were successively added 1.0 equiv of aldehyde, 1.0 equiv of amine, and 1.0 equiv of isocyanide under inert atmosphere. The resulting mixture was stirred at 60 °C for 3 days. It was then concentrated under reduced pressure, and the crude product was purified by flash chromatography on silica gel.

***N*-(4-Chlorobenzyl)-2-[(4-chlorobenzyl)(5-iodo-2-isopropyl-6-methylpyrimidin-4-yl)amino]-2-(4-fluorophenyl)acetamide (1a).** General procedure for this Ugi−Smiles adduct using *p*-fluorobenzaldehyde (110 μL, 1.0 mmol), *p*-chlorobenzylamine (120 μL, 1.0 mmol), *p*-chlorobenzyl isocyanide (130 μL, 1.0 mmol), and 5-iodo-2-isopropyl-6-methylpyrimidin-4-ol (280 mg, 1.0 mmol): Purification by flash chromatography (petroleum ether−diethyl ether, 70:30) afforded **1a** as a colorless oil: yield 65% (440 mg); R_f 0.3 (70:30 petroleum ether/diethyl ether); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32 (dd, $J_{H-H,\,H-F}$ = 8.6, 5.3 Hz, 2H), 7.22 (d, *J* = 8.3 Hz, 2H), 7.13 (d, *J* = 8.3 Hz, 2H), 7.04 (t, *J* = 8.6 Hz, 2H), 6.98−6.89 (m, 3H), 6.75 (d, *J* = 8.3 Hz, 2H), 5.27 (s, 1H), 4.50−4.42 (m, 2H), 4.27 (d, *J* = 15.2 Hz, 1H), 4.16 (dd, *J* = 14.7, 4.8 Hz, 1H), 2.90 (sept, *J* = 6.8 Hz, 1H), 2.68 (s, 3H), 1.11 (d, *J* = 6.8 Hz, 3H), 1.10 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 173.6, 171.3, 170.3, 167.7, 163.0 (d, *J* = 248.9 Hz), 136.8, 134.8, 133.8, 133.7, 131.5 (d, *J* = 2.9 Hz), 130.9 (d, *J* = 8.1 Hz), 130.3, 129.4, 129.2, 128.7, 116.0 (d, *J* = 21.2 Hz), 89.4, 68.4, 53.8, 43.1, 37.0, 30.4, 22.0, 21.7; IR (ATR) 1670, 1541, 1508, 1490 cm^{-1}; HRMS calcd for [$C_{30}H_{28}Cl_2FIN_4O$ − C_8H_7ClNO] 508.0453, found 508.0460.

2-[Butyl-(5-iodo-2-isopropyl-6-methylpyrimidin-4-yl)amino]-*N*-(4-methoxybenzyl)acetamide (1f). General procedure for this Ugi−Smiles adduct using formaldehyde (180 μL, 2.0 mmol), butylamine (200 μL, 2.0 mmol), *p*-methoxybenzylisocyanide (300 μL, 2.0 mmol), and 5-iodo-2-isopropyl-6-methylpyrimidin-4-ol (560 mg, 2.0 mmol): Purification by flash chromatography (petroleum ether−diethyl ether, 50:50) afforded **1f** as a colorless oil: yield 50% (510 mg); R_f 0.3 (50:50 petroleum ether/diethyl ether); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.16−7.10 (m, 3H), 6.83 (d, *J* = 8.3 Hz, 2H), 4.39 (d, *J* = 5.6 Hz, 2H), 4.17 (s, 2H), 3.80 (s, 3H), 3.41−3.35 (m, 2H), 2.97 (sept, *J* = 6.8 Hz), 2.66 (s, 3H), 1.65−1.55 (m, 2H), 1.33−1.25 (m, 2H), 1.23 (d, *J* = 6.8 Hz, 6H), 0.90 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 173.4, 171.2, 170.4, 167.0, 159.4, 130.5, 129.5, 114.4, 84.0, 55.7, 54.8, 53.5, 43.2, 37.0, 30.8, 30.2, 22.0, 20.5, 14.3; IR (ATR) 1668, 1539, 1513, 1490 cm^{-1}; HRMS calcd for $C_{22}H_{31}IN_4O_2$ 510.1492, found 510.1510.

General Procedure for Sonogashira Adducts. To a 0.1 M solution of Smiles adduct in acetonitrile were successively added 1.2 equiv of alkyne, 5 mol % of dichlorobis(triphenylphosphine)-palladium, 5 mol % of CuI, and 1 equiv of a diisopropylethylamine. The resulting mixture was stirred at 70 °C overnight. The solution was filtered under reduced pressure, and the filtrate was washed with methanol. The solvent was removed afterward under reduced pressure to afford Ugi−Smiles products after purification by flash chromatography on silica gel.

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***N*-(4-Chlorobenzyl)-2-[(4-chlorobenzyl)-(2-isopropyl-6-methyl-5-phenylethynylpyrimidin-4-yl)amino]-2-(4-fluorophenyl)acetamide (2a).** General procedure for this Sonogashira adduct using **1a** (615 mg, 0.91 mmol), phenylacetylene (120 μL, 1.09 mmol), dichlorobis(triphenylphosphine)palladium (32 mg, 0.05 mmol), CuI (9 mg, 0.05 mmol), and diisopropylethylamine (160 μL, 0.91 mmol): Purification by flash chromatography (petroleum ether−diethyl ether, 60:40) afforded **2a** as a yellow oil: yield 65% (385 mg); R_f 0.3 (60:40 petroleum ether/diethyl ether); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32−7.23 (m, 6H), 7.17−7.15 (m, 4H), 7.10 (d, J = 8.3 Hz, 2H), 6.99−6.91 (m, 6H), 5.91 (s, 1H), 5.29 (d, J = 16.9 Hz, 1H), 4.93 (d, J = 16.9 Hz, 1H), 4.43 (dd, J = 14.7, 5.8 Hz, 1H), 4.36 (dd, J = 14.7, 5.7 Hz, 1H), 2.90 (sept, J = 6.9 Hz, 1H), 2.66 (s, 3H), 1.12 (d, J = 6.9 Hz, 3H), 1.08 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 171.7, 171.2, 170.5, 162.9, 162.8 (d, J = 248.1 Hz), 137.5, 136.8, 133.8, 133.0, 131.4 (d, J = 8.1 Hz) 131.4 (d, J = 2.9 Hz), 131.2, 129.6, 129.2, 129.1, 129.0, 128.7, 128.7, 123.0, 115.8 (d, J = 22.0 Hz), 102.3, 100.5, 84.3, 66.6, 52.4, 43.5, 37.8, 24.5, 21.8, 21.6; IR (ATR) 1664, 1528, 1491, 1430 cm^{-1}; HRMS calcd for $C_{38}H_{33}Cl_2FN_4O$ 650.2015, found 650.2024.

2-[Butyl[2-isopropyl-6-methyl-5-(2-trifluoromethylphenylethynyl)-pyrimidin-4-yl]amino]-*N*-(4-methoxybenzyl)acetamide (2h). General procedure for this Sonogashira adduct using **1f** (490 mg, 0.96 mmol), 1-ethynyl-2-trifluoromethylbenzene (160 μL, 1.2 mmol), dichlorobis(triphenylphosphine)palladium (34 mg, 0.05 mmol), CuI (10 mg, 0.05 mmol), and diisopropylethylamine (170 μL, 0.96 mmol): Purification by flash chromatography (petroleum ether−diethyl ether, 50:50) afforded **2h** as a colorless oil: yield 51% (270 mg); R_f 0.3 (50:50 petroleum ether/diethyl ether); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70 (d, J = 7.8 Hz, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.55 (t, J = 7.8 Hz, 1H), 7.45 (t, J = 7.8 Hz, 1H), 7.12 (d, J = 8.3 Hz, 2H), 6.84−6.76 (m, 3H), 4.45 (s, 2H), 4.36 (d, J = 5.8 Hz, 2H), 3.87−3.79 (m, 2H), 3.77 (s, 3H), 2.95 (sept, J = 6.8 Hz, 1H), 2.60 (s, 3H), 1.68 (m, 2H), 1.32−1.23 (m, 2H), 1.21 (d, J = 6.8 Hz, 6H), 0.85 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 172.7, 171.6, 170.3, 161.9, 159.4, 134.0, 132.1, 131.0 (q, J = 30.7 Hz), 130.4, 129.5, 128.6, 126.3 (q, J = 5.1 Hz), 124.0 (q, J = 273.7 Hz), 121.6 (q, J = 2.9 Hz), 114.4, 97.6, 96.4, 90.5, 55.6, 54.5, 51.4, 43.3, 37.8, 30.5, 24.4, 21.8, 20.4, 14.2; IR (ATR) 1663, 1537, 1515, 1409 cm^{-1}; HRMS calcd for $C_{31}H_{35}F_3N_4O_2$ 552.2712, found 552.2723.

General Procedure for 5-Benzylidene-6,7-dihydro-5*H*-pyrrolo-[2,3-*d*]pyrimidine Derivatives. Conditions A. To a 0.3 M solution of Sonogashira adduct in methanol was added 0.1 equiv of DBU. The resulting mixture was stirred until TLC showed no trace of the starting materials. The solvent was then removed under reduced pressure to afford 5-benzylidene-6,7-dihydro-5*H*-pyrrolo-[2,3-*d*]pyrimidines after purification by flash column chromatography on silica gel.

5-Benzylidene-7-(4-chlorobenzyl)-6-(4-fluorophenyl)-2-isopropyl-4-methyl-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxylic Acid 4-Chlorobenzylamide (3a-*Z*-Isomer). General procedure for this benzylidene-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine using Sonogashira adduct **2a** (110 mg, 0.17 mmol) and DBU (one drop, 0.02 mmol): Purification by flash chromatography (petroleum ether−diethyl ether, 50:50) afforded ***Z*-3a** as a colorless oil: yield 91% (100 mg); R_f 0.2 (50:50 petroleum ether/diethyl ether); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.48 (dd, $J_{H-H,\ H-F}$ = 8.8, 5.6 Hz, 2H), 7.19 (d, J = 8.4 Hz, 2H), 7.16 (s, 1H), 7.12−7.08 (m, 5H), 7.06 (d, J = 7.8 Hz, 2H), 6.91 (d, J = 7.8 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 6.78 (t, J = 8.8 Hz, 2H), 6.39 (t, J = 6.1 Hz, 1H), 4.66 (d, J = 15.6 Hz, 1H), 4.46 (d, J = 15.6 Hz, 1H), 4.26 (dd, J = 14.8, 6.6 Hz, 1H), 3.87 (dd, J = 14.8, 5.0 Hz, 1H), 3.04 (sept, J = 6.8 Hz, 1H), 2.66 (s, 3H), 1.32 (d, J = 6.8 Hz, 3H), 1.30 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 175.8, 167.8, 165.5, 162.7 (d, J = 248.8 Hz), 157.6, 139.1, 136.9, 136.1, 134.9, 133.8, 133.1, 132.8 (d, J = 3.7 Hz), 131.6 (d, J = 8.1 Hz), 130.5, 129.5, 129.2, 128.7, 128.4, 128.4, 128.3, 115.2 (d, J = 20.5 Hz), 112.6, 76.0, 44.8, 43.6, 38.0, 24.1, 22.2, 22.1.

Condition B. To a 0.3 M solution of Sonogashira adduct in THF was added 0.1 equiv of *t*-BuOK. The resulting mixture was stirred until TLC showed no trace of the starting materials. The solvent was then removed under reduced pressure to afford 5-benzylidene-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidines after purification by flash column chromatography on silica gel.

5-Benzylidene-7-(4-chlorobenzyl)-6-(4-fluorophenyl)-2-isopropyl-4-methyl-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxylic Acid 4-Chlorobenzylamide (3a-*E*-Isomer). General procedure for this benzylidene-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine using Sonogashira adduct **2a** (90 mg, 0.14 mmol) and *t*-BuOK (2 mg, 0.02 mmol): Purification by flash chromatography (petroleum ether−diethyl ether, 60:40) afforded ***E*-3a** as a colorless oil, yield 80% (72 mg). ***Z*-3a** was also isolated in a 20% yield: R_f 0.4 (50:50 petroleum ether/diethyl ether); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40 (dd, $J_{H-H,\ H-F}$ = 8.6, 5.6 Hz, 2H), 7.37−7.29 (m, 3H), 7.21−7.13 (m, 8H), 7.04 (t, J = 8.6 Hz, 2H), 6.94 (d, J = 8.3 Hz, 2H), 6.77 (s, 1H), 6.43 (t, J = 5.9 Hz, 1H), 4.64 (d, J = 15.3 Hz, 1H), 4.36 (dd, J = 14.9, 6.3 Hz, 1H), 4.26 (d, J = 15.3 Hz, 1H), 4.13 (dd, J = 14.9, 5.9 Hz, 1H), 3.05 (sept, J = 6.8 Hz, 1H), 1.74 (s, 3H), 1.37 (d, J = 6.8 Hz, 3H), 1.34 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 175.9, 170.5, 168.5, 163.0 (d, J = 249.6 Hz), 158.7, 138.8, 137.8, 137.2, 136.4, 135.2 (d, J = 2.9 Hz), 133.8, 133.7, 132.0 (d, J = 8.1 Hz), 130.5, 129.2, 129.2, 129.0, 128.9, 128.8, 128.3, 115.9 (d, J = 20.5 Hz), 111.3, 80.8, 46.0, 43.6, 37.9, 25.6, 22.2, 22.0; IR (ATR) 1670, 1569, 1541, 1506, 1492 cm^{-1}; HRMS calcd for $C_{38}H_{33}Cl_2FN_4O$ 650.2015, found 650.1991.

General Procedure for Pyrrolo[2,3-*d*]pyrimidines. To a 0.2 M solution of Sonogashira adduct in DMF was added 2.2 equiv of NaH (95%). The resulting mixture was stirred overnight at room temperature. The solvent was then removed by extraction, and the organic phases were collected and concentrated in vacuo to afford pyrrolo[2,3-*d*]pyrimidines after purification by flash column chromatography on silica gel.

7-Butyl-2-isopropyl-4-methyl-5-(2-trifluoromethylbenzoyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxylic Acid 4-Methoxybenzylamide (3h). General procedure for this pyrrolo[2,3-*d*]pyrimidine using Sonogashira adduct **2h** (100 mg, 0.18 mmol) and sodium hydride (10 mg, 0.40 mmol): Purification by flash chromatography (petroleum ether−diethyl ether, 50:50) afforded **3h** as a colorless oil: yield 88% (88 mg); R_f 0.3 (50:50 petroleum ether/diethyl ether); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.87 (d, J = 7.6 Hz, 1H), 7.67 (dd, J = 7.6, 7.4 Hz, 1H), 7.59 (dd, J = 7.6, 7.4 Hz, 1H), 7.54 (d, J = 7.4 Hz, 1H), 7.14 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.5 Hz, 2H), 6.75 (t, J = 5.1 Hz, 1H), 4.08 (br s, 2H), 4.49 (t, J = 7.3 Hz, 2H), 3.80 (s, 3H), 3.26 (sept, J = 6.8 Hz, 1H), 2.58 (s, 3H), 1.76−1.66 (m, 2H), 1.39 (d, J = 6.8 Hz, 6H), 1.32−1.21 (m, 2H), 0.90 (t, J = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 190.6, 171.1, 162.9, 160.8, 159.6, 152.2, 139.5, 138.7, 132.2, 132.1, 131.8, 129.8, 128.9 (q, J = 32.2 Hz), 127.8 (q, J = 5.1 Hz), 124.2 (q, J = 273.7 Hz), 121.6 (q, J = 2.9 Hz), 114.5, 113.1, 55.7, 43.8, 43.5, 37.8, 32.6, 24.9, 22.4, 20.3, 14.0; IR (ATR) 1650, 1548, 1514, 1400 cm^{-1}; HRMS calcd for $C_{31}H_{33}F_3N_4O_3$ 566.2505, found 566.2500.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.