Tetrahedron 71 (2015) 1207–1214

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

One-pot synthesis of 4-aminated pyrrolo[2,3-*d*]pyrimidines from alkynylpyrimidines under metal-catalyst-free conditions

Vanessa Prieur [a,b], Nina Heindler [b], Jaime Rubio-Martínez [c], Gérald Guillaumet [a,*], M. Dolors Pujol [b,*]

[a] Institut de Chimie Organique et Analytique (ICOA), Université d'Orléans, UMR CNRS 7311, rue de Chartres, BP-6759, 45067 Orléans Cedex 2, France
[b] Laboratori de Química Farmacèutica (Unitat Associada al CSIC), Facultat de Farmàcia, Universitat de Barcelona, Av. Diagonal 643, 08028 Barcelona, Spain
[c] Laboratori de Química Física, Facultat de Química, Universitat de Barcelona, Av. Diagonal 647, 08028 Barcelona, Spain

ARTICLE INFO

Article history:
Received 25 November 2014
Received in revised form 7 January 2015
Accepted 8 January 2015
Available online 14 January 2015

Keywords:
Pyrrolo[2,3-*d*]pyrimidines
Cyclization
Alkynylpyrimidines
Microwave irradiation
One-pot procedure

ABSTRACT

A novel, general, and efficient one-pot sequential reaction toward a variety of 4-aminated-6-arylpyrrolo [2,3-*d*]pyrimidines from 5-alkynylpyrimidines has been developed. Microwave-assisted metal-free intramolecular cyclization and amination provided moderate to excellent yields of 4-aminated pyrrolo[2,3-*d*]pyrimidines in short reaction times. This method avoids the use of metal-catalyst and expensive additives and was shown to tolerate amines and anilines.

1. Introduction

A large number of heterocyclic compounds containing one or more nitrogen atoms, obtained from nature or by laboratory synthesis, have turned out to be potential therapeutic agents. Among the aromatic nitrogenated heterocycles, the pyrrolo[2,3-*d*]pyrimidine, also known as 7-deazapurine, is a highly important structural unit in a vast number of biologically active natural compounds,[1] synthetic drugs,[2] and industrial materials.[3] Pyrrolo[2,3-*d*]pyrimidines are also interesting intermediates in organic synthesis, often serving as scaffolds to provide access to other highly desirable structures.[4] However, compared to purines, pyrrolo[2,3-*d*]pyrimidines are under-explored and only a few methods have been published describing the synthesis of these interesting scaffolds based on the deazapurine skeleton.[5]

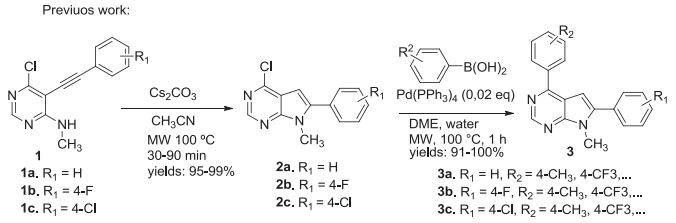
Our attention was directed toward the study of various synthetic analogous compounds possessing the pyrrolo[2,3-*d*]pyrimidine nuclei and the development of convenient synthetic strategies for their preparation. Described approaches to the preparation of 4-aminated pyrrolo[2,3-*d*]pyrimidines involve lengthy synthetic sequences and do not offer a general synthesis.[6] Amination of 4-halopyrrolopyrimidines can be carried out by conventional nucleophilic aromatic substitution under different conditions[3c,7] or by Pd-catalyzed cross-coupling conditions[8] but the direct preparation of 4-alkyl- or 4-aryl-aminopyrrolo[2,3-*d*]pyrimidines from substituted 5-alkynyl-6-chloro-4-methylaminopyrimidines in a single operation has not been described to date. Kubota et al. published the preparation of deazapurines from benzylalkynylpyrimidines under classical heating in two steps.[9] Compounds containing the 4-alkyl- or 4-aryl-aminopyrrolo[2,3-*d*]pyrimidine subunit were targeted as part of our program to provide targeted antitumor compounds with KRAS inhibition. Our aim was to provide general, efficient, and rapid access to these attractive structures from available starting material.

2. Results and discussion

In previous work,[10] we have shown that alkynylpyrimidines **1a**–**c** are cyclized to pyrrolo[2,3-*d*]pyrimidines **2** and arylated at C-4 in a two-step sequence to give the diarylated pyrrolopyrimidines **3a**–**c** in high yields (Scheme 1). In the present work, attempts were made to provide convenient and efficient synthetic routes using diverse conditions, ranging from rt to 140 °C or microwave heating,[11] to reduce the number of steps and shorten reaction times.

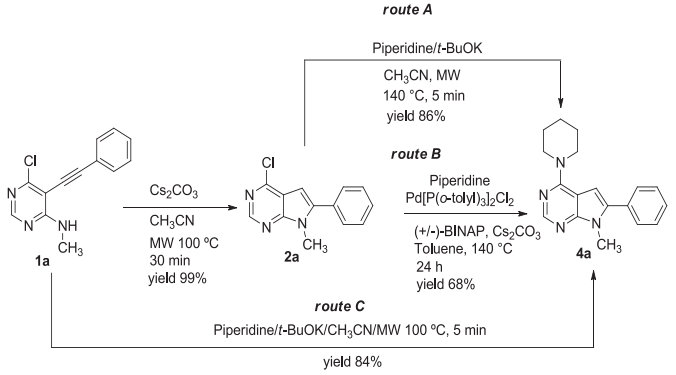
* Corresponding authors. E-mail addresses: gerald.guillaumet@univ-orleans.fr (G. Guillaumet), mdpujol@ub.edu (M.D. Pujol).

http://dx.doi.org/10.1016/j.tet.2015.01.012
0040-4020/



Scheme 1. Synthesis of substituted pyrrolopyrimidines in two steps.[10]

Treatment of **2a** with piperidine (2 equiv) under cross-coupling conditions using $Pd[P(o\text{-tolyl})_3]_2Cl_2$ as a catalyst, cesium carbonate, and BINAP at 140 °C for 24 h under thermal heating provided the pyrrolopyrimidine **4a** in 68% yield (Scheme 2, route B). Better results were obtained by treating **2a** with piperidine/*t*-BuOK at 100 °C (external temperature) assisted by microwave irradiation for 5 min (Scheme 2, route A).



Scheme 2. Preparation of 4-piperidinylpyrrolo[2,3-*d*]pyrimidine (**4a**).

Surprisingly, the direct addition of piperidine to alkynylpyrimidine **1a** and substitution of cesium carbonate by potassium *tert*-butoxide, after 5 min under microwave irradiation at 100 °C (external temperature), led to the aminated pyrrolopyrimidine **4a** in 84% yield in a one-pot reaction (Scheme 2, route C). To study the scope of this promising one-pot catalyst-free tandem reaction, different alkyl- or aryl-amines were added to the alkynylpyrimidines (**1**) and subjected to the same conditions. The results are illustrated in Tables 1 and 2.

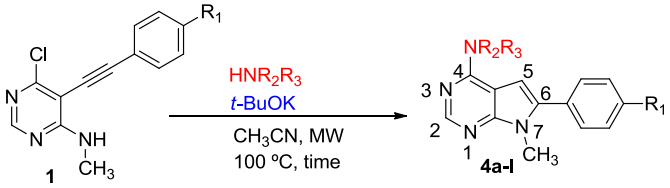
The tandem reaction consisted of cyclization and aromatic substitution without a metal-catalyst and gave rapid access to 4-aminated pyrrolopyrimidines. In this one-pot procedure reaction of the amine or aniline with an alkynylpyrimidine, employed as starting material gave the corresponding 4-aminated-6-arylpyrrolo[2,3-*d*]pyrimidines in moderate to excellent yields. The requisite alkynylpyrimidines (**1**) were readily prepared via a Sonogashira coupling reaction of 5-iodopyrimidines.[10]

Under conventional heating conditions, the alkynylpyrimidines (**1**) were converted to the pyrrolo[2,3-*d*]pyrimidines by treatment with alkylamines or anilines after 20–24 h of reaction with less than 20% (results not included in the tables). The use of microwave irradiation drastically reduced reaction times (from 20–24 h to 5–30 min) and gave a considerable increase in yield, which was attributed to a higher crude purity compared with conventional methods.

Increasing the reaction times under microwave assistance, did not modify the yield (Table 1, entry 1 vs 2). No significant changes were observed at temperatures lightly over 100 °C (external temperature) and similar results were obtained at >120 °C, whereas heating at 140 °C led to a slight decrease in yield due to the formation of secondary products (results not included in the tables).

To further optimize reaction conditions, we tested solvents with different properties such as DMSO, methanol, DMF, and acetonitrile. The best results were obtained with DMF and acetonitrile, but acetonitrile was chosen since it favored the workup. Different amounts of a variety of bases were also studied, with the most efficient found to be *t*-BuOK.[12] When NaH or $NaNH_2$ was used no

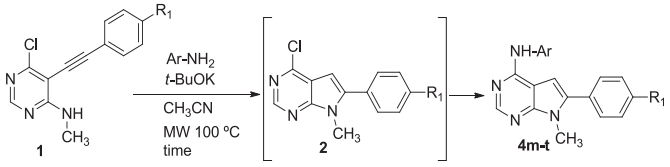
Table 1
Synthesis of substituted pyrrolo[2,3-*d*]pyrimidines (**4a**–**l**)



Entry	R_1	HNR_2R_3[a]	Time (min)	Yield%[b] (**4**)
1	H	Piperidine	60	85 (**4a**)
2	H	Piperidine	5	84 (**4a**)
3	H	Piperidine[c]	60	—
4	H	Piperidine[d]	60	—
5	H	Piperidine[e]	60	67 (**4a**)
6	F	Piperidine	5	76 (**4b**)
7	Cl	Piperidine	5	95 (**4c**)
8	NH_2	Piperidine	5	79 (**4d**)
9	H	4-Methylpiperidine	5	99 (**4e**)
10	F	4-Methylpiperidine	5	71 (**4f**)
11	Cl	4-Methylpiperidine	5	99 (**4g**)
12	H	Pyrrolidine	30	81 (**4h**)
13	H	Cyclohexylamine	30	76 (**4i**)
14	H	Diethylamine	60	33 (**4j**)
15	H	Diethylaminoethylamine	60	27 (**4k**)
16	H	*N*,*N*-Dimethylhydrazine	5	38 (**4l**)

[a] The reaction was conducted with 1 equiv of **1**, 1 equiv of *t*-BuOK, and 2 equiv of alkylamine or hydrazine.
[b] Isolated yields of **4**.
[c] With NaH.
[d] With $NaNH_2$.
[e] With Cs_2CO_3.

Table 2
Synthesis of 4-arylaminopyrrolo[2,3-*d*]pyrimidines (**4m**–**t**)



Entry	R_1	$Ar\text{–}NH_2$[a]	Time (min)	Yield[b] (**4**)	Yield[b] (**2**)
1	H	Aniline	5	17 (**4m**)	48
2	H	Aniline	20	35 (**4m**)	40
3	H	Aniline	60	33 (**4m**)	34
4	H	4-Methoxyaniline	5	—	49
5	H	4-Methoxyaniline	20	—	33
6	H	4-Methylaniline	5	—	63
7	H	4-Methylaniline	20	—	51
8	H	4-Fluoroaniline	5	22 (**4n**)	73
9	H	4-Fluoroaniline	20	27 (**4n**)	42
10	H	4-Bromoaniline	20	23 (**4o**)	72
11	H	4-Chloroaniline	20	31 (**4p**)	68
12	H	4-Nitroaniline	5	91 (**4q**)	—
13	F	4-Nitroaniline	5	55 (**4r**)	34
14	F	4-Nitroaniline	20	72 (**4r**)	—
15	Cl	4-Nitroaniline	5	82 (**4s**)	—
16	H	4-Cyanoaniline	5	40 (**4t**)	59
17	H	4-Cyanoaniline	20	46 (**4t**)	48

[a] The reaction was conducted with 1 equiv of **1**, 1 equiv of *t*-BuOK, and 2 equiv of aniline.
[b] Isolated yields of **2** and **4**.

intramolecular cyclization occurred, even with a prolonged reaction time (Table 1, entries 3 and 4).

Excess of Cs_2CO_3 led to mixtures of 4-aminated alkynylpyrimidines and 4-aminated pyrrolopyrimidines, while the best results were obtained with 1 equiv of *t*-BuOK. Increasing the concentration of the base had no noticeable effect on the overall yield of the reaction (Table 1, entry 5).

Thus, the best reaction conditions, consisted of using CH_3CN as the solvent and *t*-BuOK as the base, under microwave irradiation at 100 °C. In a parallel control experiment, the desired compounds **4** were not observed in the absence of base.

The nature of the substituent at C-6 of **4** had a moderate impact. Efficient pyrrolopyrimidine formation was observed with alkynylpyrimidines possessing phenyl, *p*-chloro-, *p*-fluoro- or *p*-aminophenyl groups. These results underline how the aryl moiety bonded to C-6 influences the reactivity. The phenyl and *p*-chlorophenyl gave far better yields than *p*-fluorophenyl and *p*-aminophenyl (Table 1, entries 2, 7, 9 and 11 vs 6, 8 and 10).

The 4-aminophenyl group of the alkynylpyrimidines was tolerated under the reaction conditions, and the corresponding pyrrolo[2,3-*d*]pyrimidine **4d** constitutes an interesting scaffold for accessing compounds with potential biological activity (Table 1, entry 8).

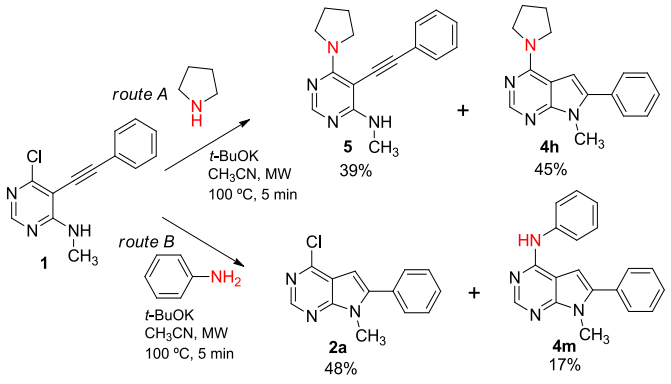
This one-pot protocol tolerated well the addition of secondary cycloalkylamines such as piperidine or pyrrolidine (Table 1, entries 1–12) and also primary amines such as cyclohexylamine (Table 1, entry 10), but non-cyclic amines such as diethylamine or diethylaminoethylamine gave only moderate yields (Table 1, entries 14 and 15). The conversion was high (TLC), but purification of the reaction was hampered by low solubility in organic solvents.

Another aminated reagent, alkylhydrazine, produced the expected substituted pyrrolopyrimidine (Table 1, entry 16) in 38% yield. Notably, in this case, a very polar product was obtained and its purification was difficult.

Anilines possessing halogens (Br, Cl or F) at *C*-4 gave a lower yield than free aniline (Table 2, entries 8–11 vs entry 2). The alkynylpyrimidine reacted with bromoaniline and *t*-BuOK giving the respective pyrrolopyrimidine (**4o**) in low yield (Table 2, entry 10), whereas other strong bases like NaH, $NaNH_2$ or Cs_2CO_3 were ineffective (results not included in Table 1). With 4-fluoro- or 4-chloroaniline the resulting pyrrolopyrimidines (**4n** and **4p**) were also obtained in a low yield and a significant amount of 4-chloropyrrolo[2,3-*d*]pyrimidine **2** was recovered (Table 2, entries 8–11). As in the case of amines (Table 1), the addition of anilines to alkynylpyrimidines **1** without a substituent or possessing chloro at *C*-4 of the phenyl group leads to better performances that the alkynylpyrimidines substituted by fluorine (Table 2, entries 12 and 15 vs 13).

Unfortunately, no formation of 4-aminated pyrrolo[2,3-*d*]pyrimidines (**4**) was observed using 4-methoxy- or 4-methylaniline and only the intermediate **2** was recovered, accompanied by minor by-products (Table 2, entries 4–7). The addition of transition metal-catalyst (CuI or $Pd[P(o\text{-tolyl})_3]_2Cl_2$) did not improve the results (tested with 4-bromoaniline and 4-methoxyaniline). The presence of donor substituents did not favor the reaction whereas the electron-withdrawing substituents activated the process considerably (Table 2, entries 12–15) or moderately (Table 2, entries 8–11 and 17). The basic conditions of the reaction facilitated the nucleophilic attack of the aniline-ion and the withdrawing substituents stabilized the formation of these anions.

The alkynylpyrimidines (**1**) reacted with amines or anilines and their behavior under basic conditions was examined in function of the intermediate isolated (Scheme 3). It is worth noting that under microwave assistance the reaction of alkynylpyrimidines with amines was nearly instantaneous, and could not be studied in detail. But in the case of the pyrrolidine, the reaction took place more



Scheme 3. Experimental sequential order for the reaction of alkynylpyrimidines with alkylamines (*route A*) or anilines (*route B*).

slowly providing a mixture of **4h** (45%) and the alkyne intermediate **5** (39%) (Scheme 3). This transformation was completed in 30 min of reaction with 81% of yield (Table 1, entry 12). The reaction with anilines was also slow, thus when anilines were added to the alkynylpyrimidines, using *t*-BuOK as the base after 5 min the intermediate 4-chloropyrrolopyrimidine **2** was isolated (Scheme 3 and Table 2, entries 1–11, 13, 16 and 17). Using a weak base such as Cs_2CO_3 instead of *t*-BuOK for 10 min (MW, 100 °C) the intermediate **2a** was isolated in 92% of yield. These conditions applied to the pyrrolidine drive to a mixture of **5** and **4h**.

The methodology involves the direct amination with alkylamines of 4-chloropyrimidines possessing different alkynes followed by intramolecular hydroamination of the alkyne under relatively mild conditions. In contrast, when anilines were employed in this reaction, the *N*-arylation at C-4 competed with the intramolecular cyclization and occurred in second place (Scheme 3).

3. Conclusion

In conclusion, we have developed a new effective one-pot procedure for the transformation of alkynylpyrimidines to 4-alkylamino- or 4-arylamino-pyrrolopyrimidines. It is interesting to note that the nature of the amine determines the order of the reaction steps. When alkylamines were used the synthesis proceeded via chloro displacement followed by ring closure leading to pyrrolopyrimidines in moderate to excellent yields. On the other hand, when anilines were added instead of alkylamines, the intramolecular cyclization of **1** took place first (either using microwave or classical heating leads to the same results).

The new route demonstrates that cyclization and substitution of alkynylpyrimidines are possible without metal-catalytic assistance. Microwave assistance led to a notable reduction of reaction times and a substantial economic saving, since it obviated the need for metal-catalyst use. This procedure has the advantages of a simple one-pot reaction, mild reaction conditions, synthetically useful yield, product purity >99%, and except in some cases suitability for large-scale processes.

4. Experimental section

4.1. General methods

Microwave-assisted reactions were carried out in a Biotage Initiator Microwave synthesis instrument and the external temperature was measured by an IR sensor. The reactions were monitored by thin-layer chromatography (TLC) analysis using silica gel (60 F_{254}, Merck) plates. Compounds were visualized by UV irradiation. Column chromatography was performed with silica gel 60

(230–400 mesh, 0.040–0.063 mm). Melting points (Mp) were obtained on an MFB-595010M Gallenkamp apparatus with digital thermometer in open capillary tubes and are reported without correction. IR spectra were obtained using FTIR Perkin–Elmer 1600 Infrared Spectrophotometer. ^{1}H, and ^{13}C NMR spectra were recorded on a Bruker 250 MHz (^{13}C, 63 MHz), Varian Gemini-300 (75.5 MHz), Varian Gemini-400 (100 MHz), and Bruker 400 MHz (100 MHz). ^{19}F NMR spectra were recorded on a Bruker (376 MHz, $CDCl_3$) using C_6F_6 as an internal standard (δ 0 ppm). Chemical shifts are reported in parts per million (ppm) relative to the central peak of the solvent: $CDCl_3$ (δ 7.26 (H) and 77.16 (C)), CD_3OD (δ 3.31 (H) and 49.45 (C)), DMSO-d_6 (δ 2.49 (H) and 39.51 (C)) as internal standards. The following abbreviations are used for the proton spectra multiplicities: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet. Coupling constants (J) are reported in hertz (Hz). High-resolution mass spectra (HRMS) were performed on a Maxis Bruker 4G by the 'Federation de Recherche of University of Orleans (France)' ICOA/CBM (FR2708) platform or on an LC/MSD-TOF (2006) (Agilent technologies) by the 'Center spectrometry of masses' University of Barcelona (Spain). All reagents were of high quality or were purified before use. Organic solvents were of analytical grade or were purified by standard procedures.

4.2. General procedure A (Sonogashira coupling)

A mixture containing compound **3** (1.0 mmol), alkyne (2.0 mmol), $Pd(dba)_2$ (0.03 mmol), tri(2-furyl)phosphine (0.06 mmol) and CuI (0.04 mmol) in dry THF (1 mL), and dry triethylamine (3.5 mL) was transferred to a microwave tube and irradiated in a microwave oven at 100 °C (external temperature) for 15 min. The progress of the reaction was monitored by TLC. After cooling, the mixture was diluted with NH_4Cl (aqueous saturated solution, 15 mL) and the aqueous phase was extracted with ethyl acetate (3×20 mL). The combined organic phases were dried over Na_2SO_4 and filtered through Celite®. The evaporation of the solvent under reduced pressure gave the crude product, which was purified by silica gel column chromatography.

*4.2.1. 6-Chloro-N-methyl-5-(phenylethynyl)pyrimidin-4-amine (**1a**). General procedure A.* The reaction was carried out following the general procedure A as described in our previous work.[9]

*4.2.2. 6-Chloro-5-(2-(4-fluorophenyl)ethynyl)-N-methylpyrimidin-4-amine (**1b**). General procedure A.* The reaction was carried out following the general procedure A starting from 6-chloro-5-iodo-*N*-methylpyrimidin-4-amine (300 mg, 1.11 mmol) and 1-ethynyl-4-fluorobenzene (0.26 mL, 2.22 mmol). The crude product was purified by silica gel column chromatography (hexane/CH_2Cl_2/acetone 8:1:1) affording **1a** as off-white solid in 98% of yield (286 mg, 1.09 mmol). R_f (hexane/CH_2Cl_2/acetone 8:1:1)=0.15. Mp: 168–170 °C (ethyl acetate). IR (ATR diamond, cm^{-1}) ν: 3407, 1567, 1506, 1396, 1279, 1229, 1160, 1136, 1088, 906, 858, 837, 811, 778, 732, 658, 617. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.13 (d, J=5.0 Hz, 3H, NCH_3), 5.70 (s, 1H, NH), 7.09 (t, J=8.8 Hz, 2H, H–Ar), 7.54 (dd, J=8.8, 5.3 Hz, 2H, H–Ar), 8.36 (s, 1H, H_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.5 (CH_3), 79.3 (Cq), 100.7 (Cq), 101.1 (Cq), 116.0 (d, J=22 Hz, 2CH), 118.1 (d, J=3 Hz, Cq), 133.8 (d, J=9 Hz, 2CH), 156.3 (CH), 159.2 (Cq), 162.9 (Cq), 163.2 (d, J=251 Hz, Cq). ^{19}F NMR (376 MHz, $CDCl_3$) δ −108.89 (F). HRMS (ESI): calcd for $C_{13}H_{10}ClFN_3$ $[M+H]^+$: 262.0542, found 262.0545.

*4.2.3. 6-Chloro-5-(2-(4-chlorophenyl)ethynyl)-N-methylpyrimidin-4-amine (**1c**). General procedure A.* The reaction was carried out following the general procedure A starting from 6-chloro-5-iodo-*N*-methylpyrimidin-4-amine (300 mg, 1.11 mmol) and 1-chloro-4-ethynylbenzene (0.29 mL, 2.22 mmol). The crude product was purified by silica gel column chromatography (hexane/CH_2Cl_2/acetone 8:1:1) affording **1b** as beige solid in 90% of yield (279 mg, 1.00 mmol). R_f (hexane/CH_2Cl_2/acetone 8:1:1)=0.19. Mp: 167–169 °C (pentane). IR (ATR diamond, cm^{-1}) ν: 3413, 3050, 2922, 1568, 1489, 1395, 1348, 1279, 1233, 1199, 1137, 1086, 1017, 906, 848, 827, 801, 778, 698, 627. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.13 (d, J=5.0, 3H, NCH_3), 5.70 (s, 1H, NH), 7.37 (d, J=8.8 Hz, 2H, H–Ar), 7.48 (d, J=8.8 Hz, 2H, H–Ar), 8.36 (s, 1H, H_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.5 (CH_3), 80.6 (Cq), 100.6 (Cq), 101.0 (Cq), 120.5 (Cq), 129.0 (2CH), 132.9 (2CH), 135.6 (Cq), 156.4 (CH), 159.4 (Cq), 162.9 (Cq). HRMS (ESI): calcd for $C_{13}H_{10}Cl_2N_3$ $[M+H]^+$: 278.0246, found 278.0251.

*4.2.4. 5-(2-(4-Aminophenyl)ethynyl)-6-chloro-N-methylpyrimidin-4-amine (**1d**). General procedure A.* The reaction was carried out following the general procedure A starting from 6-chloro-5-iodo-*N*-methylpyrimidin-4-amine (100 mg, 0.37 mmol) and 4-ethynylaniline (86.9 mg, 0.74 mmol). The crude product was purified by silica gel column chromatography (hexane/CH_2Cl_2/acetone 8:1:1) affording **1c** as brown oil in 95% of yield (91 mg, 0.35 mmol). R_f (ethyl acetate/hexane 8:2)=0.53. IR (ATR diamond, cm^{-1}) ν: 3483, 3386, 3258, 2098, 1588, 1510, 1437, 1390, 1360, 1278, 1238, 1215, 1176, 1123, 1080, 1002, 957, 888, 856, 828, 762, 668, 645. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.09 (d, J=5.0, 3H, NCH_3), 3.96 (s, 2H, NH_2), 5.76 (s, 1H, NH), 6.63 (d, J=8.4 Hz, 2H, H–Ar), 7.33 (d, J=8.4 Hz, 2H, H–Ar), 8.31 (s, 1H, H_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.4 (CH_3), 77.4 (Cq), 101.6 (Cq), 103.5 (Cq), 110.7 (Cq), 114.6 (2CH), 133.1 (2CH), 147.8 (Cq), 155.5 (CH), 158.3 (Cq), 162.8 (Cq). HRMS (ESI): calcd for $C_{13}H_{12}ClN_4$ $[M+H]^+$: 259.0745, found 259.0740.

4.3. General procedure B (cyclization)

A solution of the alkynes **1a–d** (1.0 mmol), the amine (2.0 mmol), and potassium *tert*-butoxide (1.0 mmol) in acetonitrile (10 mL) was transferred to a microwave reaction tube and irradiated in a microwave oven at 100 °C (external temperature) for a time between 5 and 60 min. The progress of the reaction was monitored by TLC. After cooling, the solvent was removed under vacuo. A mixture of ethyl acetate and diethylether (30 mL, 1:1) was added to the mixture and the crude of reaction mixture was washed with water (3×10 mL) and brine (10 mL). The evaporation of the solvent under reduced pressure gave the crude product, which was directly purified by silica gel column chromatography.

*4.3.1. 7-Methyl-6-phenyl-4-(piperidin-1-yl)-7H-pyrrolo[2,3-d]pyrimidine (**4a**). General procedure B.* The reaction was carried out following the general procedure B starting from the alkyne **1a** (50 mg, 0.21 mmol) and piperidine (41 μL, 0.41 mmol). The reaction mixture was irradiated for 5 min. The crude product was purified by flash chromatography (hexane/ethyl acetate) affording **4a** as light brown solid in 83% of yield (51.0 mg, 0.17 mmol). R_f (hexane/ethyl acetate 6:4)=0.19. Mp: 102–105 °C (ethyl acetate). IR (ATR diamond, cm^{-1}) ν: 2939, 2851, 1562, 1543, 1459, 1444, 1385, 1337, 1314, 1274, 1257, 1135, 1078, 1016, 994, 950, 914, 853, 825, 787, 764, 730, 697, 627. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62–1.79 (m, 6H, $3CH_2$), 3.77 (s, 3H, CH_3), 3.87–3.97 (m, 4H, $2CH_2$), 6.51 (s, 1H, H_5), 7.30–7.53 (m, 5H, H–Ar), 8.37 (s, 1H, H_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9 (CH_2), 26.1 ($2CH_2$), 30.1 (CH_3), 47.2 ($2CH_2$), 100.1 (CH), 103.3 (Cq), 128.2 (CH), 128.7 (2CH), 129.1 (2CH), 132.2 (Cq), 137.2 (Cq), 151.3 (CH), 152.9 (Cq), 156.8 (Cq). HRMS (ESI): calcd for $C_{18}H_{21}N_4$ $[M+H]^+$: 293.1761, found 293.1764.

*4.3.2. 6-(4-Fluorophenyl)-7-methyl-4-(piperidin-1-yl)-7H-pyrrolo[2,3-d]pyrimidine (**4b**). General procedure B.* The reaction was carried out following the general procedure B starting from the alkyne **1b** (50 mg, 0.19 mmol) and piperidine (38 μL, 0.38 mmol). The

reaction mixture was irradiated for 5 min. The crude product was purified by flash chromatography (hexane/ethyl acetate) affording **4b** as off-white solid in 76% of yield (45.0 mg, 0.15 mmol). R_f (hexane/ethyl acetate 6:4)=0.22. Mp: 136–139 °C (ethyl acetate). IR (ATR diamond, cm^{-1}) ν: 2939, 2854, 1562, 1542, 1494, 1460, 1444, 1385, 1336, 1314, 1271, 1256, 1219, 1159, 1136, 1098, 1076, 1011, 993, 947, 912, 838, 814, 785, 744, 726, 624. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.65–1.77 (m, 6H, $3CH_2$), 3.73 (s, 3H, CH_3), 3.84–3.95 (m, 4H, $2CH_2$), 6.47 (s, 1H, H_5), 7.07–7.19 (m, 2H, H–Ar), 7.38–7.49 (m, 2H, H–Ar), 8.36 (s, 1H, H_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9 (CH_2), 26.1 ($2CH_2$), 30.0 (CH_3), 47.2 ($2CH_2$), 100.8 (CH), 103.2 (Cq), 115.8 (d, J=22 Hz, 2CH), 128.3 (d, J=3 Hz, Cq), 130.9 (d, J=8 Hz, 2CH), 136.1 (Cq), 151.4 (CH), 152.8 (Cq), 156.8 (Cq), 162.8 (d, J=248 Hz, Cq). ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.24 (F). HRMS (ESI): calcd for $C_{18}H_{20}FN_4$ $[M+H]^+$: 311.1667, found 311.1669.

*4.3.3. 6-(4-Chlorophenyl)-7-methyl-4-(piperidin-1-yl)-7H-pyrrolo [2,3-d]pyrimidine (**4c**). General procedure B.* The reaction was carried out following the general procedure B starting from the alkyne **1c** (50 mg, 0.18 mmol) and piperidine (40 μL, 0.36 mmol). The reaction mixture was irradiated for 5 min. The crude product was purified by flash chromatography (hexane/ethyl acetate) affording **4c** as beige solid in 95% of yield (56.0 mg, 0.17 mmol). R_f (hexane/ethyl acetate 6:4)=0.24. Mp: 115–118 °C (ethyl acetate). IR (ATR diamond, cm^{-1}) ν: 2924, 2850, 1559, 1476, 1442, 1384, 1315, 1274, 1255, 1088, 1012, 992, 913, 838, 764, 736, 684, 622. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62–1.74 (m, 6H, $3CH_2$), 3.75 (s, 3H, CH_3), 3.88–3.94 (m, 4H, $2CH_2$), 6.50 (s, 1H, H_5), 7.43 (s, 4H, H–Ar), 8.36 (s, 1H, H_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9 (CH_2), 26.1 ($2CH_2$), 30.2 (CH_3), 47.2 ($2CH_2$), 101.1 (CH), 103.3 (Cq), 129.0 (2CH), 130.3 (2CH), 130.6 (Cq), 134.4 (Cq), 135.9 (Cq), 151.5 (CH), 153.0 (Cq), 156.8 (Cq). HRMS (ESI): calcd for $C_{18}H_{20}ClN_4$ $[M+H]^+$: 327.1371, found 327.1374.

*4.3.4. 4-(7-Methyl-4-(piperidin-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)aniline (**4d**). General procedure B.* The reaction was carried out following the general procedure B starting from the alkyne **1d** (50 mg, 0.19 mmol) and piperidine (38 μL, 0.39 mmol). The reaction mixture was irradiated for 5 min. The crude product was purified by flash chromatography (hexane/ethyl acetate) affording **4d** as beige solid in 79% of yield (47.0 mg, 0.15 mmol). R_f (hexane/ethyl acetate 2:8)=0.29. Mp: 208–212 °C (ethyl acetate). IR (ATR diamond, cm^{-1}) ν: 3437, 3326, 3210, 2920, 2848, 1647, 1612, 1562, 1493, 1457, 1444, 1390, 1358, 1335, 1314, 1266, 1175, 1063, 1024, 988, 916, 853, 824, 790, 756, 719, 687. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.66–1.78 (m, 6H, $3CH_2$), 3.75 (s, 3H, CH_3), 3.86 (s, 2H, NH_2), 3.89–3.94 (m, 4H, $2CH_2$), 6.42 (s, 1H, H_5), 6.77 (d, J=8.6 Hz, 2H, H–Ar), 7.29 (d, J=8.6 Hz, 2H, H–Ar), 8.37 (s, 1H, H_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.0 (CH_2), 26.1 ($2CH_2$), 30.0 (CH_3), 47.2 ($2CH_2$), 99.5 (CH), 103.4 (Cq), 115.1 (2CH), 122.1 (Cq), 130.3 (2CH), 137.7 (Cq), 146.7 (Cq), 150.9 (CH), 152.6 (Cq), 156.6 (Cq). HRMS (ESI): calcd for $C_{18}H_{22}N_5$ $[M+H]^+$: 308.1870, found 308.1873.

*4.3.5. 7-Methyl-4-(4-methylpiperidin-1-yl)-6-phenyl-7H-pyrrolo [2,3-d]pyrimidine (**4e**). General procedure B.* The reaction was carried out following the general procedure B starting from the alkyne **1a** (50 mg, 0.21 mmol) and 4-methylpiperidine (49 μL, 0.41 mmol). The reaction mixture was irradiated for 5 min. The crude product was purified by flash chromatography (hexane/ethyl acetate) affording **4e** as beige oil in 99% of yield (62.2 mg, 0.21 mmol). R_f (hexane/ethyl acetate 6:4)=0.28. IR (ATR diamond, cm^{-1}) ν: 2917, 2848, 2189, 1562, 1484, 1452, 1388, 1306, 1253, 1216, 1072, 1015, 971, 913, 849, 777, 748, 729, 698, 627. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (d, J=6.4 Hz, 3H, CH_3), 1.24–1.32 (m, 2H, CH_2), 1.66–1.73 (m, 1H, CH), 1.77–1.79 (m, 2H, CH_2), 3.08 (t, J=13.2 Hz, 2H, CH_2), 3.76 (s, 3H, CH_3), 4.75 (d, J=13.2 Hz, 2H, CH_2), 6.51 (s, 1H, H_5), 7.36–7.51 (m, 5H, H–Ar), 8.36 (s, 1H, H_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0 (CH_3), 30.1 (CH_3), 31.4 (CH), 34.3 ($2CH_2$), 46.5 ($2CH_2$), 100.7 (CH), 103.4 (Cq), 128.2 (CH), 128.7 (2CH), 129.1 (2CH), 132.1 (Cq), 137.2 (Cq), 151.3 (CH), 152.9 (Cq), 156.8 (Cq). HRMS (ESI): calcd for $C_{19}H_{23}N_4$ $[M+H]^+$: 307.1917, found 307.1922.

*4.3.6. 6-(4-Fluorophenyl)-7-methyl-4-(4-methylpiperidin-1-yl)-7H-pyrrolo[2,3-d]pyrimidine (**4f**). General procedure B.* The reaction was carried out following the general procedure B starting from the alkyne **1b** (50 mg, 0.19 mmol) and 4-methylpiperidine (45 μL, 0.38 mmol). The reaction mixture was irradiated for 5 min. The crude product was purified by silica gel column chromatography (CH_2Cl_2/acetone 9:1) affording **4f** as green oil in 71% of yield (44.1 mg, 0.14 mmol). R_f (CH_2Cl_2/acetone 9:1)=0.35. IR (ATR diamond, cm^{-1}) ν: 2920, 2849, 1564, 1493, 1454, 1377, 1336, 1308, 1254, 1223, 1158, 1071, 971, 913, 839, 818, 763. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (d, J=6.4 Hz, 3H, CH_3), 1.28–1.34 (m, 2H, CH_2), 1.66–1.72 (m, 1H, CH), 1.74–1.80 (m, 2H, CH_2), 3.08 (t, J=13.4 Hz, 2H, CH_2), 3.74 (s, 3H, CH_3), 4.75 (d, J=13.4 Hz, 2H, CH_2), 6.48 (s, 1H, H_5), 7.15 (t, J=8.7 Hz, 2H, H–Ar), 7.46 (t, J=8.7 Hz, 2H, H–Ar), 8.36 (s, 1H, H_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0 (CH_3), 30.0 (CH_3), 31.4 (CH), 34.3 ($2CH_2$), 46.5 ($2CH_2$), 100.8 (CH), 103.3 (Cq), 115.9 (d, J=22 Hz, 2CH), 128.3 (d, J=4 Hz, Cq), 130.9 (d, J=8 Hz, 2CH), 136.1 (Cq), 151.4 (CH), 152.9 (Cq), 156.8 (Cq), 162.8 (d, J=249 Hz, Cq). ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.26 (F). HRMS (ESI): calcd for $C_{19}H_{22}FN_4$ $[M+H]^+$: 325.1823, found 325.1828.

*4.3.7. 6-(4-Chlorophenyl)-7-methyl-4-(4-methylpiperidin-1-yl)-7H-pyrrolo[2,3-d]pyrimidine (**4g**). General procedure B.* The reaction was carried out following the general procedure B starting from the alkyne **1c** (50 mg, 0.18 mmol) and 4-methylpiperidine (43 μL, 0.36 mmol). The reaction mixture was irradiated for 5 min. The crude product was purified by silica gel column chromatography (CH_2Cl_2/acetone from 98:2 to 8:2) affording **4g** as brown oil in 99% of yield (61.0 mg, 0.21 mmol). R_f (CH_2Cl_2/acetone 9:1)=0.38. IR (ATR diamond, cm^{-1}) ν: 2952, 2919, 2849, 1563, 1480, 1454, 1308, 1254, 1091, 971, 833, 762. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (d, J=6.4 Hz, 3H, CH_3), 1.26–1.30 (m, 2H, CH_2), 1.66–1.71 (m, 1H, CH), 1.74–1.79 (m, 2H, CH_2), 3.08 (t, J=13.2 Hz, 2H, CH_2), 3.74 (s, 3H, CH_3), 4.74 (d, J=13.2 Hz, 2H, CH_2), 6.50 (s, 1H, H_5), 7.42 (s, 4H, H–Ar), 8.36 (s, 1H, H_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0 (CH_3), 30.1 (CH), 31.4 (CH_3), 34.3 ($2CH_2$), 46.5 ($2CH_2$), 101.1 (CH), 103.3 (Cq), 129.0 (2CH), 130.2 (2CH), 130.6 (Cq), 134.3 (Cq), 135.9 (Cq), 151.5 (CH), 153.1 (Cq), 156.8 (Cq). HRMS (ESI): calcd for $C_{19}H_{22}ClN_4$ $[M+H]^+$: 341.1528, found 341.1532.

*4.3.8. 7-Methyl-6-phenyl-4-(pyrrolidin-1-yl)-7H-pyrrolo[2,3-d]pyrimidine (**4h**). General procedure B.* The reaction was carried out following the general procedure B starting from the alkyne **1a** (50 mg, 0.21 mmol) and pyrrolidine (34 μL, 0.41 mmol). The reaction mixture was irradiated for 30 min. The crude product was purified by silica gel column chromatography (ethyl acetate) affording **4h** as white solid in 81% of yield (46.5 mg, 0.17 mmol). R_f (ethyl acetate)=0.20. Mp: 125–127 °C (ethyl acetate). IR (ATR diamond, cm^{-1}) ν: 2964, 2922, 2874, 1571, 1548, 1505, 1479, 1455, 1385, 1344, 1330, 1307, 1257, 1223, 1126, 1074, 1028, 1014, 950, 926, 840, 777, 751, 738. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.00–2.07 (m, 4H, $2CH_2$), 3.78 (s, 3H, CH_3), 3.81–3.87 (m, 4H, $2CH_2$), 6.58 (s, 1H, H_5), 7.35–7.51 (m, 5H, H–Ar), 8.36 (s, 1H, H_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.5 ($2CH_2$), 30.1 (CH_3), 48.0 ($2CH_2$), 100.8 (CH), 103.7 (Cq), 128.1 (CH), 128.8 (2CH), 129.0 (2CH), 132.4 (Cq), 136.8 (Cq), 151.9 (CH), 152.0 (Cq), 155.2 (Cq). HRMS (ESI): calcd for $C_{17}H_{19}N_4$ $[M+H]^+$: 279.1604, found 279.1603.

*4.3.9. N-Cyclohexyl-7-methyl-6-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine (**4i**). General procedure B.* The reaction was carried out

following the general procedure B starting from the alkyne **1a** (50 mg, 0.21 mmol) and cyclohexylamine (47 μL, 0.41 mmol). The reaction mixture was irradiated for 20 min. The crude product was purified by flash chromatography (ethyl acetate/methanol) affording **4i** as yellow solid in 76% of yield (49.0 mg, 0.16 mmol). R_f (ethyl acetate)=0.14. Mp: 210–212 °C (ethyl acetate). IR (ATR diamond, cm^{-1}) ν: 3247, 3192, 3165, 3114, 3034, 2925, 2850, 1602, 1566, 1546, 1523, 1505, 1470, 1443, 1404, 1383, 1357, 1337, 1310, 1250, 1207, 1110, 1072, 1012, 907, 896, 769, 740. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20–1.33 (m, 3H, H_{ax}), 1.40–1.54 (m, 2H, H_{ax}), 1.62–1.72 (m, 1H, H_{eq}), 1.74–1.84 (m, 2H, H_{eq}), 2.10–2.18 (m, 2H, H_{eq}), 3.78 (s, 3H, CH_3), 4.06–4.21 (m, 1H, CH_{alk}), 4.84–5.00 (m, 1H, NH), 6.36 (s, 1H, H_5), 7.38–7.53 (s, 5H, H–Ar), 8.37 (s, 1H, H_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.1 ($2CH_2$), 25.8 (CH_2), 30.1 (CH_3), 33.9 ($2CH_2$), 49.8 (CH), 97.3 (CH), 103.0 (Cq), 128.3 (CH), 128.8 (2CH), 129.1 (2CH), 132.2 (Cq), 138.1 (Cq), 151.7 (CH), 152.1 (Cq), 155.6 (Cq). HRMS (ESI): calcd for $C_{19}H_{23}N_4$ $[M+H]^+$: 307.1917, found 307.1914.

*4.3.10. N,N-Diethyl-7-methyl-6-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine (**4j**). General procedure B.* The reaction was carried out following the general procedure B starting from the alkyne **1a** (50 mg, 0.21 mmol) and diethylamine (42 μL, 0.41 mmol). The reaction mixture was irradiated for 60 min. The crude product was purified by flash chromatography (hexane/ethyl acetate) affording **4j** as brown oil in 33% of yield (19.0 mg, 0.07 mmol). R_f (hexane/ethyl acetate 6:4)=0.24. IR (ATR diamond, cm^{-1}) ν: 2973, 2928, 1566, 1507, 1487, 1447, 1376, 1360, 1315, 1294, 1247, 1135, 1075, 1048, 1016, 909, 845, 778, 750, 728, 699, 639, 628. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (t, J=7.1 Hz, 6H, $2CH_3$), 3.77 (s, 3H, CH_3), 3.78 (q, J=7.1 Hz, 4H, $2CH_2$), 6.47 (s, 1H, H_5), 7.39–7.52 (m, 5H, H–Ar), 8.36 (s, 1H, H_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8 ($2CH_3$), 30.2 (CH_3), 43.5 ($2CH_2$), 101.1 (CH), 102.4 (Cq), 128.2 (CH), 128.7 (2CH), 129.2 (2CH), 132.3 (Cq), 137.1 (Cq), 151.5 (CH), 152.5 (Cq), 155.9 (Cq). HRMS (ESI): calcd for $C_{17}H_{21}N_4$ $[M+H]^+$: 281.1761, found 281.1766.

*4.3.11. N^1,N^1-Diethyl-N^2-(7-methyl-6-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)ethane-1,2-diamine (**4k**). General procedure B.* The reaction was carried out following the general procedure B starting from the alkyne **1a** (50 mg, 0.21 mmol) and *N*,*N*-diethylethylenediamine (58 μL, 0.41 mmol). The reaction mixture was irradiated for 60 min. The crude product was purified by flash chromatography (hexane/ethyl acetate) affording **4k** as brown oil in 27% of yield (18.0 mg, 0.06 mmol). R_f (hexane/ethyl acetate 6:4)=0.22. IR (ATR diamond, cm^{-1}) ν: 3287, 2965, 2925, 1595, 1562, 1468, 1380, 1340, 1304, 1211, 1113, 1071, 1013, 915, 758, 699, 632. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (t, J=7.1 Hz, 6H, $2CH_3$), 2.62 (q, J=7.1 Hz, 4H, $2CH_2$), 2.77 (t, J=5.7 Hz, 2H, CH_2), 3.67 (q, J=5.7 Hz, 2H, CH_2), 3.78 (s, 3H, CH_3), 5.97 (s, 1H, NH), 6.42 (s, 1H, H_5), 7.37–7.54 (m, 5H, H–Ar), 8.38 (s, 1H, H_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8 ($2CH_3$), 29.8 (CH_2), 30.1 (CH_3), 46.9 ($2CH_2$), 51.7 (CH_2), 97.4 (CH), 103.5 (Cq), 128.2 (CH), 128.8 (2CH), 129.1 (2CH), 132.3 (Cq), 138.0 (Cq), 152.1 (CH), 156.1 (Cq), 156.3 (Cq). HRMS (ESI): calcd for $C_{19}H_{26}N_5$ $[M+H]^+$: 324.2183, found 324.2185.

*4.3.12. 4-(2,2-Dimethylhydrazinyl)-7-methyl-6-phenyl-7H-pyrrolo[2,3-d]pyrimidine (**4l**). General procedure B.* The reaction was carried out following the general procedure B starting from the alkyne **1a** (50 mg, 0.21 mmol) and *N*,*N*-dimethylhydrazine (31.2 μL, 0.41 mmol). The reaction mixture was irradiated for 5 min. The crude product was purified by silica gel column chromatography (ethyl acetate/methanol 95:5) affording **4l** as light yellow solid in 38% of yield (21.2 mg, 0.08 mmol). R_f (ethyl acetate/methanol 95:5)=0.23. Mp: 181–183 °C (ethyl acetate). IR (ATR diamond, cm^{-1}) ν: 3188, 3045, 2954, 2918, 2855, 1584, 1488, 1446, 1434, 1341, 1302, 1159, 1009, 909, 876, 785, 760, 742, 701. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.67 (s, 6H, $2CH_3$), 3.80 (s, 3H, CH_3), 5.98 (s, 1H, NH), 6.89 (s, 1H, H_5), 7.41–7.55 (m, 5H, H–Ar), 8.31 (s, 1H, H_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.1 (CH_3), 48.5 ($2CH_3$), 101.2 (CH), 102.5 (Cq), 128.2 (CH), 128.8 (2CH), 129.2 (2CH), 132.4 (Cq), 138.2 (Cq), 151.5 (CH), 153.0 (Cq), 156.8 (Cq). HRMS (ESI): calcd for $C_{15}H_{18}N_5$ $[M+H]^+$: 268.1557, found 268.1553.

*4.3.13. 7-Methyl-N,6-diphenyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine (**4m**). General procedure B.* The reaction was carried out following the general procedure B starting from the alkyne **1a** (50 mg, 0.21 mmol) and aniline (37.4 μL, 0.41 mmol). The reaction mixture was irradiated for 20 min. The crude product was purified by silica gel column chromatography (CH_2Cl_2/acetone from 98:2 to 9:1) affording **4m** as beige solid in 35% of yield (22.0 mg, 0.07 mmol). R_f (CH_2Cl_2/acetone 9:1)=0.15. Mp: 212–214 °C (ethyl acetate). IR (ATR diamond, cm^{-1}) ν: 2918, 2849, 1600, 1581, 1563, 1537, 1491, 1469, 1450, 1434, 1404, 1352, 1341, 1306, 1244, 1222, 1212, 1074, 1012, 920, 801, 780, 755, 735. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 3H, CH_3), 6.16 (s, 1H, H_5), 7.09 (m, 1H, NH), 7.14–7.18 (m, 1H, H–Ar), 7.35–7.48 (m, 7H, H–Ar), 7.57–7.64 (m, 2H, H–Ar), 8.50 (s, 1H, H_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.2 (CH_3), 97.8 (CH), 104.0 (Cq), 122.4 (2CH), 124.4 (CH), 128.5 (CH), 128.8 (2CH), 129.1 (2CH), 129.2 (2CH), 131.9 (Cq), 138.9 (Cq), 139.1 (Cq), 151.6 (CH), 152.5 (Cq), 154.0 (Cq). HRMS (ESI): calcd for $C_{19}H_{17}N_4$ $[M+H]^+$: 301.1448, found 301.1446.

*4.3.14. 7-Methyl-N-(4-fluorophenyl)-6-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine (**4n**). General procedure B.* The reaction was carried out following the general procedure B starting from the alkyne **1a** (50 mg, 0.21 mmol) and 4-fluoroaniline (38.9 μL, 0.41 mmol). The reaction mixture was irradiated for 20 min. The crude product was purified by silica gel column chromatography (CH_2Cl_2/acetone from 98:2 to 9:1) affording **4n** as off-white solid in 27% of yield (65.3 mg, 0.19 mmol). R_f (CH_2Cl_2/acetone 9:1)=0.17. Mp: 201–203 °C (ethyl acetate). IR (ATR diamond, cm^{-1}) ν: 3152, 2911, 2873, 1603, 1569, 1538, 1504, 1491, 1434, 1404, 1352, 1339, 1304, 1240, 1215, 1152, 1091, 1012, 918, 838, 796, 778, 755, 741, 711. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H, CH_3), 6.08 (s, 1H, H_5), 7.08 (t, J=8.6 Hz, 2H, H–Ar), 7.37–7.50 (m, 5H, H–Ar), 7.54 (dd, J=8.6, 4.8 Hz, 2H, H–Ar), 7.55 (s, 1H, NH), 8.47 (s, 1H, H_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.2 (CH_3), 97.7 (CH), 103.7 (Cq), 115.9 (d, J=23 Hz, 2CH), 124.8 (d, J=8 Hz, 2CH), 128.5 (CH), 128.9 (2CH), 129.2 (2CH), 131.8 (Cq), 135.1 (d, J=3 Hz, Cq), 139.0 (Cq), 151.5 (CH), 152.5 (Cq), 154.2 (Cq), 160.0 (d, J=244 Hz, Cq). ^{19}F NMR (376 MHz, $CDCl_3$) δ −117.85 (F). HRMS (ESI): calcd for $C_{19}H_{16}FN_4$ $[M+H]^+$: 319.1354, found 319.1352.

*4.3.15. N-(4-Bromophenyl)-7-methyl-6-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine (**4o**). General procedure B.* The reaction was carried out following the general procedure B starting from the alkyne **1a** (50 mg, 0.21 mmol) and 4-bromoaniline (70.6 mg, 0.41 mmol). The reaction mixture was irradiated for 20 min. The crude product was purified by silica gel column chromatography (CH_2Cl_2/acetone from 98:2 to 8:2) affording **4o** as white solid in 23% of yield (17.9 mg, 0.05 mmol). R_f (hexane/ethyl acetate 6:4)=0.38. Mp: 230–232 °C (ethyl acetate). IR (ATR diamond, cm^{-1}) ν: 3172, 3100, 3059, 2997, 2915, 1621, 1575, 1561, 1546, 1524, 1487, 1455, 1443, 1379, 1356, 1335, 1302, 1243, 1223, 1073, 1031, 1009, 909, 820, 807, 795, 772, 712, 700. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 3H, CH_3), 6.26 (s, 1H, H_5), 6.95 (s, 1H, NH), 7.41–7.51 (m, 7H, H–Ar), 7.55 (d, J=8.6 Hz, 2H, H–Ar), 8.51 (s, 1H, H_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.2 (CH_3), 97.3 (CH), 104.2 (Cq), 116.6 (Cq), 123.2 (2CH), 128.7 (CH), 128.9 (2CH), 129.2 (2CH), 131.8 (Cq), 132.1 (2CH), 138.4 (Cq), 139.4 (Cq), 151.4 (CH), 152.5 (Cq), 153.4 (Cq). HRMS (ESI): calcd for $C_{19}H_{16}BrN_4$ $[M+H]^+$: 379.0553, found 379.0555.

*4.3.16. 7-Methyl-N-(4-chlorophenyl)-6-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine (**4p**). General procedure B.* The reaction was

carried out following the general procedure B starting from the alkyne **1a** (50 mg, 0.21 mmol) and 4-chloroaniline (52.3 mg, 0.41 mmol). The reaction mixture was irradiated for 20 min. The crude product was purified by silica gel column chromatography (CH_2Cl_2/acetone from 98:2 to 8:2) affording **4p** as yellow solid in 31% of yield (21.5 mg, 0.06 mmol). R_f (CH_2Cl_2/acetone 9:1)=0.23. Mp: 211–213 °C (ethyl acetate). IR (ATR diamond, cm^{-1}) ν: 2919, 2850, 1619, 1578, 1563, 1548, 1490, 1470, 1456, 1443, 1380, 1356, 1337, 1304, 1243, 1223, 1099, 1085, 1030, 1012, 909, 823, 808, 797, 779, 701. ^1H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 3H, CH_3), 6.24 (s, 1H, NH), 7.04 (s, 1H, H_5), 7.33 (d, J=8.6 Hz, 2H, H–Ar), 7.42–7.49 (m, 5H, H–Ar), 7.59 (d, J=8.6 Hz, 2H, H–Ar), 8.50 (s, 1H, H_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.2 (CH_3), 97.4 (CH), 116.6 (Cq), 123.1 (2CH), 128.7 (CH), 128.9 (2CH), 129.1 (Cq), 129.2 (2CH), 129.2 (2CH), 131.8 (Cq), 137.8 (Cq), 139.3 (Cq), 151.4 (CH), 152.5 (Cq), 153.5 (Cq). HRMS (ESI): calcd for $C_{19}H_{16}ClN_4$ $[M+H]^+$: 335.1058, found 335.1055.

*4.3.17. 7-Methyl-N-(4-nitrophenyl)-6-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine (**4q**). General procedure B.* The reaction was carried out following the general procedure B starting from the alkyne **1a** (50 mg, 0.21 mmol) and 4-nitroaniline (56.7 mg, 0.41 mmol). The reaction mixture was irradiated for 5 min. The crude product was purified by silica gel column chromatography (CH_2Cl_2/acetone from 98:2 to 8:2) affording **4q** as yellow solid in 91% of yield (65.3 mg, 0.19 mmol). R_f (CH_2Cl_2/acetone 98:2)=0.22. Mp: 240–242 °C (ethyl acetate). IR (ATR diamond, cm^{-1}) ν: 3119, 2922, 2852, 1628, 1590, 1563, 1493, 1469, 1416, 1382, 1311, 1298, 1254, 1226, 1181, 1113, 1079, 1026, 1005, 946, 914, 848, 810, 773, 742, 694, 660, 652, 614. ^1H NMR (400 MHz, DMSO-d_6) δ 3.80 (s, 3H, CH_3), 7.03 (s, 1H, H_5), 7.47–7.52 (m, 1H, H–Ar), 7.54–7.59 (m, 2H, H–Ar), 7.65–7.69 (m, 2H, H–Ar), 8.25 (s, 4H, H–Ar), 8.52 (s, 1H, H_2), 10.08 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 29.7 (CH_3), 98.0 (CH), 105.0 (Cq), 118.7 (2CH), 124.9 (2CH), 128.5 (CH), 128.7 (2CH), 128.9 (2CH), 131.3 (Cq), 138.9 (Cq), 140.7 (Cq), 147.0 (Cq), 150.5 (CH), 151.8 (Cq), 152.1 (Cq). HRMS (ESI): calcd for $C_{19}H_{16}N_5O_2$ $[M+H]^+$: 346.1299, found 346.1304.

*4.3.18. 6-(4-Fluorophenyl)-7-methyl-N-(4-nitrophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (**4r**). General procedure B.* The reaction was carried out following the general procedure B starting from the alkyne **1b** (50 mg, 0.19 mmol) and 4-nitroaniline (52.8 mg, 0.38 mmol). The reaction mixture was irradiated for 5 min. The crude product was purified by silica gel column chromatography (CH_2Cl_2/acetone from 98:2 to 9:1) affording **4r** as yellow solid in 50% of yield (35.1 mg, 0.10 mmol). R_f (CH_2Cl_2/acetone 98:2)=0.19. Mp: 265–267 °C (ethyl acetate). IR (ATR diamond, cm^{-1}) ν: 3119, 2920, 2851, 1628, 1590, 1564, 1495, 1467, 1413, 1382, 1312, 1224, 1181, 1165, 1113, 1019, 948, 913, 838, 812, 763, 749, 688, 647, 624. ^1H NMR (400 MHz, DMSO-d_6) δ 3.78 (s, 3H, CH_3), 7.01 (s, 1H, H_5), 7.37–7.43 (m, 2H, H–Ar), 7.69–7.74 (m, 2H, H–Ar), 8.25 (s, 4H, H–Ar), 8.52 (s, 1H, H_2), 10.08 (s, 1H, NH). ^{13}C NMR^{13}C NMR (100 MHz, DMSO-d_6) δ 30.2 (CH_3), 98.7 (CH), 105.4 (Cq), 116.4 (d, J=22 Hz, 2CH), 119.2 (2CH), 125.4 (2CH), 128.2 (d, J=3 Hz, 2CH), 131.4 (d, J=8 Hz, 2CH), 132.1 (Cq), 139.8 (d, J=284 Hz, Cq), 147.5 (Cq), 151.0 (CH), 152.2 (Cq), 152.6 (Cq). ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.07 (F). HRMS (ESI): calcd for $C_{19}H_{15}FN_5O_2$ $[M+H]^+$: 364.1204, found 364.1209.

*4.3.19. 6-(4-Chlorophenyl)-7-methyl-N-(4-nitrophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (**4s**). General procedure B.* The reaction was carried out following the general procedure B starting from the alkyne **1c** (50 mg, 0.18 mmol) and 4-nitroaniline (49.7 mg, 0.36 mmol). The reaction mixture was irradiated for 5 min. The crude product was purified silica gel column chromatography (CH_2Cl_2/acetone from 98:2 to 9:1) affording **4s** as orange solid in 82% of yield (56.0 mg, 0.15 mmol). R_f (CH_2Cl_2/acetone 98:2)=0.23. Mp: 295–297 °C (ethyl acetate). IR (ATR diamond, cm^{-1}) ν: 3377, 2920, 2850, 1737, 1621, 1593, 1559, 1504, 1465, 1402, 1375, 1350, 1312, 1260, 1178, 1111, 1090, 1017, 1008, 907, 859, 847, 830, 772, 751, 726, 713, 689, 640. ^1H NMR (400 MHz, DMSO-d_6) δ 3.80 (s, 3H, CH_3), 7.05 (s, 1H, H_5), 7.60–7.64 (m, 2H, H–Ar), 7.68–7.72 (m, 2H, H–Ar), 8.22–8.28 (m, 4H, H–Ar), 8.52 (s, 1H, H_2), 10.10 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 29.9 (CH_3), 98.5 (CH), 105.0 (Cq), 118.7 (2CH), 125.0 (2CH), 129.0 (2CH), 130.2 (Cq), 130.5 (2CH), 133.4 (Cq), 137.6 (Cq), 140.8 (Cq), 147.0 (Cq), 150.7 (CH), 151.9 (Cq), 152.2 (Cq). HRMS (ESI): calcd for $C_{19}H_{15}ClN_5O_2$ $[M+H]^+$: 380.0909, found 380.0910.

*4.3.20. 4-((7-Methyl-6-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)benzonitrile (**4t**). General procedure B.* The reaction was carried out following the general procedure B starting from the alkyne **1a** (50 mg, 0.21 mmol) and 4-aminobenzonitrile (48.5 mg, 0.41 mmol). The reaction mixture was irradiated for 10 min. The crude product was purified by silica gel column chromatography (CH_2Cl_2/acetone from 98:2 to 8:2) affording **4t** as yellow solid in 63% of yield (42.3 mg, 0.13 mmol). R_f (CH_2Cl_2/acetone 98:2)=0.16. Mp: 251–253 °C (ethyl acetate). IR (ATR diamond, cm^{-1}) ν: 3362, 2215, 1617, 1602, 1559, 1543, 1518, 1505, 1461, 1446, 1414, 1374, 1355, 1343, 1316, 1279, 1253, 1226, 1173, 1024, 904, 837, 778, 756, 703. ^1H NMR (400 MHz, $CDCl_3$) δ 3.85 (s, 3H, CH_3), 6.46 (s, 1H, H_5), 7.11 (s, 1H, NH), 7.43–7.54 (m, 5H, H–Ar), 7.64 (d, J=8.7 Hz, 2H, H–Ar), 7.90 (d, J=8.7 Hz, 2H, H–Ar), 8.58 (s, 1H, H_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.3 (CH_3), 96.5 (CH), 105.1 (Cq), 105.4 (Cq), 119.5 (Cq), 119.8 (2CH), 128.9 (CH), 129.0 (2CH), 129.2 (2CH), 131.5 (Cq), 133.4 (2CH), 140.3 (Cq), 143.7 (Cq), 151.1 (CH), 152.3 (Cq), 152.5 (Cq). HRMS (ESI): calcd for $C_{20}H_{16}N_5$ $[M+H]^+$: 326.1400, found 326.1398.

Acknowledgements

Financial support of this research by the Minister of Science and Innovation of Spain (CTQ2011-29285) is gratefully acknowledged.

Supplementary data

^1H NMR, ^{13}C NMR and ^{19}F NMR spectra for all new compounds. This material is available free of charge via the internet. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2015.01.012.

References and notes

1. Battaglia, U.; Long, J. E.; Searle, M. S.; Moody, C. J. *Org. Biomol. Chem.* **2011**, *9*, 2227–2232.
2. (a) Ding, S.; Wu, T. Y. H.; Brinker, A.; Peters, E. C.; Hur, W.; Gray, N. S.; Schultz, P. G. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 7632–7637; (b) Jiao, X. Y.; Kopecky, D. J.; Liu, J. S.; Liu, J. Q.; Jaen, J. C.; Cardozo, M. G.; Sharma, R.; Walker, N.; Wesche, H.; Li, S.; Farrelly, E.; Xiao, S. H.; Wang, Z.; Kayser, F. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 6212–6217; (c) Chakka, N.; Bregman, H.; Du, B.; Nguyen, H. N.; Buchanan, J. L.; Feric, E.; Ligutti, J.; Liu, D.; McDermott, J. S.; Zou, A.; McDo-nough, S. I.; DiMauro, E. F. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2052–2062.
3. (a) Tumkevicius, S.; Dodonova, J.; Kazlauskas, K.; Masevicius, V.; Skardziute, L.; Jursenas, S. *Tetrahedron Lett.* **2010**, *51*, 3902–3906; (b) Tumkevicius, S.; Dodonova, J. *Synlett* **2011**, 1705–1708; (c) Vrábel, M.; Pohl, R.; Votruba, I.; Sajadi, M.; Kovalenko, S. A.; Ernsting, N. P.; Hocek, M. *Org. Biomol. Chem.* **2008**, *6*, 2852–2860; (d) Dodonova, J.; Skardziute, L.; Kazlauskas, K.; Jursenas, S.; Tumkevicius, S. *Tetrahedron* **2012**, *68*, 329–339.
4. (a) Kumar, V. P.; Frey, K. M.; Wang, Y.; Jain, H. K.; Gangjee, A.; Anderson, K. S. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 5426–5428; (b) Gangjee, A.; Zaware, N.; Raghavan, S.; Yang, J.; Thorpe, J. E.; Ihnat, M. A. *Bioorg. Med. Chem.* **2012**, *20*, 2444–2454; (c) Wang, L.; Cherian, C.; Desmoulin, S. K.; Mitchell-Ryan, S.; Hou, Z.; Matherly, L. H.; Gangjee, A. *J. Med. Chem.* **2012**, *55*, 1758–1770.
5. (a) Taylor, E. C.; Liu, B. *J. Org. Chem.* **2003**, *68*, 9938–9947; (b) Liu, Y.; Fang, J.; Cai, J. H.; Xiao, F.; Ding, K.; Hu, Y. *Bioorg. Med. Chem.* **2012**, *20*, 5473–5482; (c) Amarnath, V.; Madhav, R. *Synthesis* **1974**, 837–859; (d) Legreverend, M. *Tetrahedron* **2008**, *64*, 8585–8603.
6. Jung, M.-H.; Kim, H.; Choi, W.-K.; El-Gamal, M.; Park, T. B.; Sim, K. H. Y.; Lee, S. H.; Baek, D.; Hah, J.-M.; Cho, J.-H.; Oh, C.-Y. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6538–6543.
7. (a) Galatsis, P.; Hayward, M. M.; Kormos, B. L.; Wager, T. T.; Zhang, L.; Stepan, A. F.; Henderson, J. L.; Kurumbail, R. G.; Verhoest, P. R. U.S. Pat. Appl. Publ. US 20,140,005,183 A1 20,140,102, 2014; (b) Gangjee, A.; Kurup, S.; Ihnat, M. A.;

Thorpe, J. E.; Shenoy, S. S. *Bioorg. Med. Chem.* **2010**, *18*, 3575–3587; (c) Tumkevicius, S.; Dodonova, J. *Chem. Heterocycl. Compd.* **2012**, *48*, 258–279; (d) Kaspersen, S. J.; Sundby, E.; Charnock, C.; Hoff, B. H. *Bioorg. Chem.* **2012**, *44*, 35–44; (e) Lee, J. H.; Lim, H.-S. *Org. Biomol. Chem.* **2012**, *10*, 4229–4235.

8. Henderson, J. L.; McDermott, S. M.; Buchwald, S. L. *Org. Lett.* **2010**, *12*, 4438–4441.
9. Kubota, K.; Takada, T.; Asano, S. S.; Isobe, Y. PCT Int. Appl. WO 2009107767 A1 20090903, 2009.
10. Prieur, V.; Rubio-Martínez, J.; Font-Bardia, M.; Guillaumet, G.; Pujol, M. D. *Eur. J. Org. Chem.* **2014**, 1514–1524.
11. For general microwave-reactions information to see: (a) He, H.; Wu, Y. J. *Tetrahedron Lett.* **2003**, *44*, 3445–3446; (b) Perreux, L.; Loupu, A. *Tetrahedron* **2001**, *57*, 9199–9223; (c) Lidström, P.; Tierney, J.; Wathey, B.; Westmen, J. *Tetrahedron* **2001**, *57*, 9223–9283; (d) Chaouchi, M.; Loupy, A.; Marque, S.; Petit, A. *Eur. J. Org. Chem.* **2002**, 1278–1283; (e) Buxaderas, E.; Alonso, D. A.; Nájera, C. *Eur. J. Org. Chem.* **2013**, 5864–5870; (f) Broggini, G.; Barbera, V.; Beccalli, E. M.; Chiacchio, U.; Fasana, A.; Galli, S.; Gazzola, S. *Adv. Synth. Catal.* **2013**, *355*, 1640–1648; (g) Nguyen, H. H.; Kurth, M. J. *Org. Lett.* **2013**, *15*, 362–365; (h) Qian, W.; Zhang, L.; Sun, H.; Jiang, H.; Liu, H. *Adv. Synth. Catal.* **2012**, *354*, 3231–3236; (i) Baghbanzadeh, M.; Pilger, C.; Kappe, C. O. *J. Org. Chem.* **2011**, *76*, 8138–8142; (j) Cívicos, J. F.; Alonso, D. A.; Nájera, C. *Adv. Synth. Catal.* **2011**, *353*, 1683–1687; (k) Beccalli, E. M.; Bernasconi, A.; Borsini, E.; Broggini, G.; Rigamonti, M.; Zecchi, G. *J. Org. Chem.* **2010**, *75*, 6923–6932; (l) Miljanuic, O. S.; Volhard, K. P. C.; Whitener, G. D. *Synlett* **2003**, 29–34; (m) Sarkate, P.; Bahekar, S. S.; Wadhai, V. M.; Ghandge, G. N.; Wakte, P. S.; Shinde, D. B. *Synlett* **2013**, 1513–1516; (n) Nücher, M.; Ondruschka, B.; Bonrath, W.; Gum, A. *Green Chem.* **2004**, *6*, 128–141.
12. *t*-BuOK has interesting basic properties: (a) Rodriguez, A. L.; Koradin, C.; Dohle, W.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 2488–2490; (b) Schlosser, M.; Rauchschwable, G. *J. Am. Chem. Soc.* **1978**, *100*, 3258–3260; (c) Schlosser, M. *Pure Appl. Chem.* **1988**, *60*, 1627–1634; (d) Schlosser, M.; Hartmann, J. *J. Am. Chem. Soc.* **1976**, *98*, 4674–4676.