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One-pot, atom and step economy (PASE) assembly of trifluoromethylated pyrimidines from CF_3-ynones

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Absract: Highly efficient synthesis of 6-trifluoromethylated pyrimidines based on reaction of CF_3 ynones with nitrogen 1,3-binucleophiles was developed. One-pot assembly of pyrimidine cor proceeds by the cascade route *via* aza-Michael addition – intramolecular cyclization – dehydratio sequence giving the target heterocycles in excellent yields (up to 97%). When acetamidine was used a a binucleophile, the unexpected addition of two equivalents of CF_3-ynone to acetamidine wa observed.

Keywords: pyrimidines / trifluoromethylated ynones / 1,3-binucleophiles

Introduction

A development of new methods for efficient and selective construction of biologically activ molecules is one of the most important challenges of modern organic chemistry. Nowadays, significant attention is paying to the study effective approaches to the fluorine-bearing organi compounds. The interest in the development of versatile methods of the synthesis of such type o derivatives is explained by unique properties provided by the presence of fluorinated fragment in molecule.[1] More than two hundreds of currently used drugs contain at least one fluorine atom in th structure.[2] Significant part of these drug molecules belongs to fluorinated aza-heterocycles which ar recognized as privileged pharmacophores.[3] For example, 5-fluorouracyl was the first synthet fluorinated medicine synthesized in 1957 by Heidelberger.[4] This simple and small molecule ha triggered huge impact of fluorinated molecules to our life. Remarkable progress has been achieved i the synthesis of perfluoroalkylated aza-heterocyclic compounds using selective methods o fluorination or perfluoroalkylation. However, the most efficient approach to the construction of such heterocyclic systems is based on the use of fluorinated building blocks. For example, recently we have demonstrated that fluorinated bromoenones can be used for the assembly of trifluoromethylated piperazinones,[5] bicyclic piperazines,[6] morpholines, oxazepanes and other heterocycles.[7]

Being a structural moiety of nucleic acids and drugs, pyrimidines occupy a distinct and unique place in bioorganic and medicinal chemistry, life-science and medicine.[8] Many pyrimidine derived

drugs are used mainly as anti-cancer, antiviral, anti-HIV, antibacterial, and antifungal agents (Figure 1).[9] A number of methods for their preparation has been described so far.[10] The most common approach to the non-fluorinated pyrimidines involves cyclocondensation of 1,3-dicarbonyl compounds or their equivalents with 1,3-binucleophiles bearing N-C-N moiety such as amidines, guanidines, ureas, and their derivatives. This procedure is known as the "principal synthesis" of pyrimidines. Until recently, only a very limited number of methods for the synthesis of trifluoromethylated pyrimidines based on easily accessible materials has been described.[11] Previously, the preparation of mono-, di-, and trifluoromethylated pyrimidines from fluorinated 1,3-diketones,[12] enones[13] and aminoenones,[14] β alkoxyvinyl(perfluoroalkyl)ketones,[15] perfluoroalkyl β-diketo phosphorus ylides,[16] and propargyli fluorides[17] was also reported.

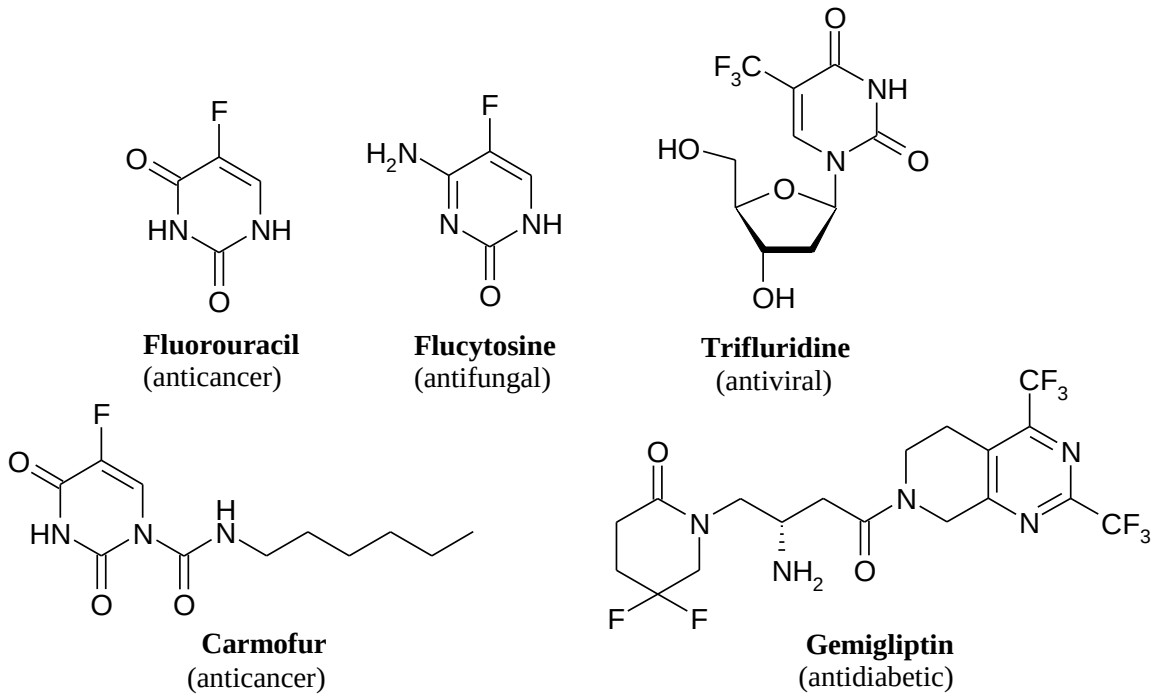


Figure 1. Examples of drugs derived from fluorinated pyrimidines.

While many sufficient methods for the pyrimidine synthesis were described, the developmen of new strategies for the preparation of these heterocycles remains an attractive area of the curren chemical research. The search for new pharmaceutical drugs possessing broad spectrum of activitie stimulates the search for novel reagents for the synthesis of pyrimidine derivatives. In continuation o our research program devoted to the synthesis of fluorinated aza-heterocycles, we decided to develop an alternative route for the assembly of fluorinated pyrimidine core based on the CF_3-ynones **1** and N-C-N nucleophiles. To the best of our knowledge, CF_3-ynones have never been used for the synthesis of trifluoromethylated pyrimidines.

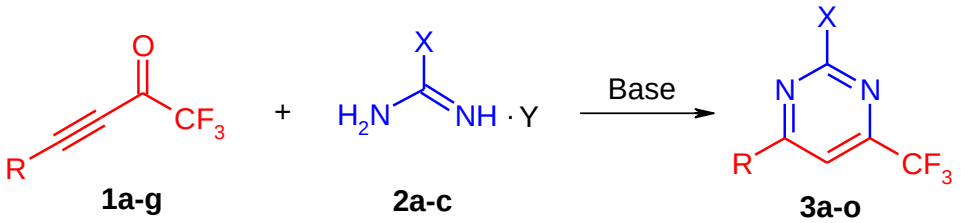
Trifluoromethyl alkynyl ketones **1** are valuable building blocks and key intermediates in the synthesis of a wide range of fluorinated aza-heterocycles. Recently, we have shown that five- and

seven-membered nitrogen-bearing heterocyclic compounds – pyrazoles[18] and diazepines[19] – can be successfully prepared from these building blocks. High polarity of the acetylenic bond and significant difference in electrophilicity of the triple bond and the carbonyl group of ynones **1** provides high selectivity in heterocyclic synthesis. Herein, we describe the efficient synthesis of trifluoromethylated pyrimidines based on these bielectrophiles.

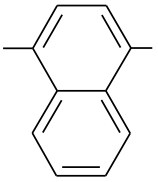
Results and Discussion

Firstly, we have examined the reaction of ynones **1a-g** with amidines **2a-c** (Table 1). We have found that aryl- and alkylsubstituted acetylenic ketones **1** react well with amidine acetate or hydrochloride **2a-c** in the presence of organic (alkali metal alkoxides, sodium acetate, DBU, or triethylamine) or mineral (Na_2CO_3) base to give the target pyrimidines **3a-p** in moderate to high yields. The reaction proceeds in the polar solvent (alcohols, acetonitrile) under reflux and is generally complete within 2-4 hours. The assembly of trifluoromethylated pyrimidine system occurs much faster than their non fluorinated analogs bearing even activated triple bond (see, for example, [12]). The best results were obtained when ketones **1** were treated with benzamidine **2b** (Table 1, entries 6-10).

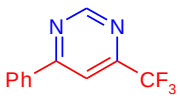
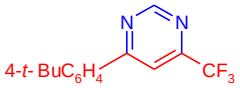
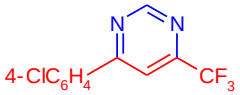
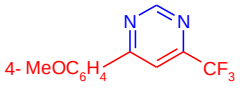
Table 1. Synthesis pyrimidines **3** from ynones **1a-g** and amidines **2a-c**.

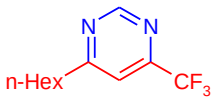
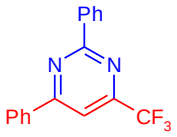
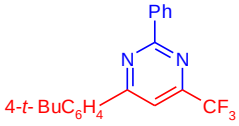
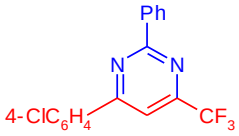
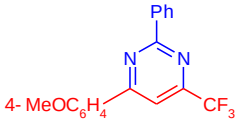
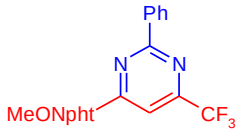
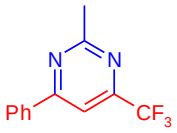
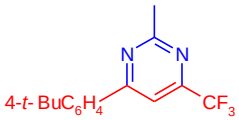
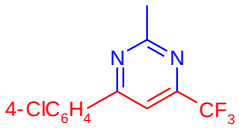
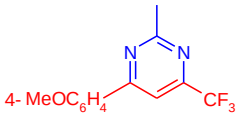
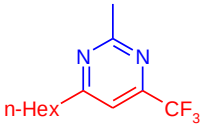
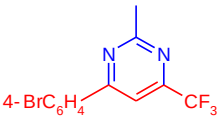


1a-g **2a-c** **3a-o**

1: R = Ph (**a**), 4-*t*-BuC_6H_4 (**b**), 4-ClC_6H_4 (**c**), 4-MeOC_6H_4 (**d**), *n*-Hex (**e**),  (**f**), 4-BrC_6H_4 (**g**)

2: X = H, Y = AcOH (**a**); X = Ph, Y = HCl (**b**); X = Me, Y = HCl (**c**)

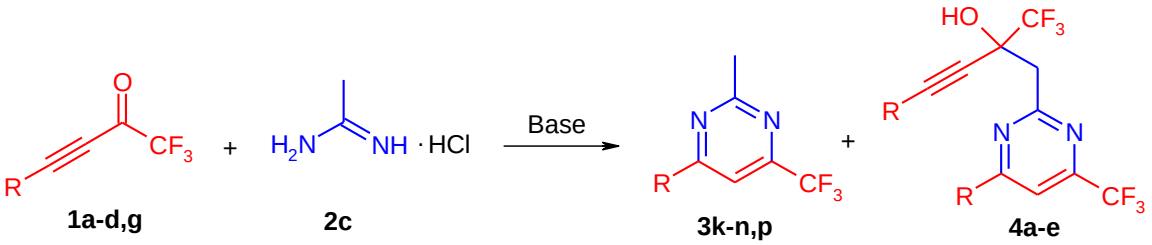
Entry	Initial reagents		Product		Conditions	Yield, %[a]
	1	**2**				
1	**1a**	**2a**		**3a**	*t*-BuOK, *t*-BuOH, 5 h	84
2	**1b**	**2a**		**3b**	*t*-BuOK, *t*-BuOH, 5 h	73
3	**1c**	**2a**		**3c**	*t*-BuOK, *t*-BuOH, 5 h	83
4	**1d**	**2a**		**3d**	*t*-BuOK, *t*-BuOH, 5 h	83

5	**1e**	**2a**		**3e**	*t*-BuOK, *t*-BuOH, 5 h	53
6	**1a**	**2b**		**3f**	EtONa, EtOH, 4 h	80
7	**1b**	**2b**		**3g**	EtONa, EtOH, 4 h	93
8	**1c**	**2b**		**3h**	EtONa, EtOH, 4 h	83
9	**1d**	**2b**		**3i**	EtONa, EtOH, 4 h	79
10	**1f**	**2b**		**3j**	EtONa, EtOH, 4 h	97
11	**1a**	**2c**		**3k**	EtONa, EtOH, 4 h	48[b]
12					Na_2CO_3, MeCN, 4 h	17
13					AcONa, *t*-BuOH, 4 h	37[c]
14	**1b**	**2c**		**3l**	Et_3N, *t*-BuOH, 3 h	57[b]
15	**1c**	**2c**		**3m**	DBU, *t*-BuOH, 4 h	18[c]
16					Et_3N, *t*-BuOH, 4 h	45[b]
17					MeONa, *t*-BuOH, 4 h	54 (63[c])
18					*t*-BuOK, *t*-BuOH, 4 h	65[c]
19	**1d**	**2c**		**3n**	MeONa, MeOH, 4 h	90
20					Et_3N, *t*-BuOH, 2 h	44[b]
21	**1e**	**2c**		**3o**	Na_2CO_3, MeCN, 3 h	31
22					MeONa, *t*-BuOH, 4 h	61[c]
23	**1g**	**2c**		**3p**	Na_2CO_3, MeCN, 4 h	49[b]

[a] Isolated yield; [b] Pyrimidines **4** were also isolated in the yield of 8 (entry 11), 20 (entry 14), 4% (entry 16), 16% (entry 20), and 15% (23); [c] According to ^{19}F NMR.

However, when the reaction with acetamidine hydrochloride **2c** was studied, the expected pyrimidines **3** were isolated in only moderate yield (Table 1, entries 11-23). All attempts to improve the yields of target heterocycles by varying the base or solvent failed. The nature of the base which was used for generation of acetamidine from its salt strongly influenced the pyrimidine yields. As a

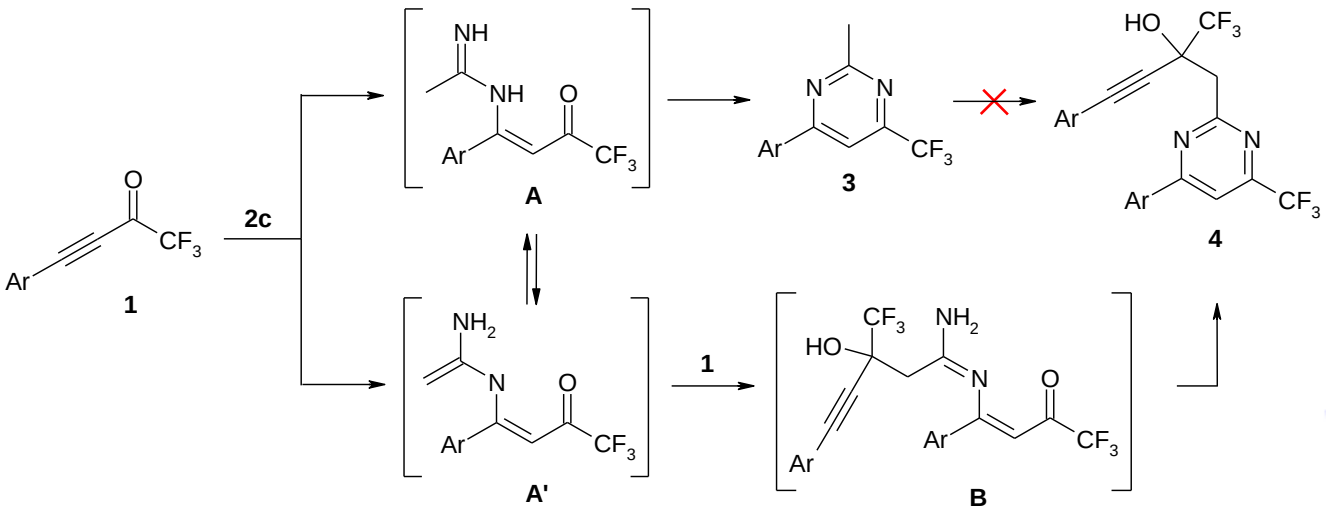
rule, when the reactions were performed in the presence of alkoxides, the target heterocycles were obtained in good yields. In contrast, the reaction was less efficient when DBU was used as a base. It was found that major byproducts formed during the reaction are compounds **4** derived from participation in the reaction of two molecules of ynone **1** with one molecule of acetamidine. Even in the case of low basic Na_2CO_3 or Et_3N pyrimidines **3k-n,p** were isolated in moderate yields together with adducts **4a-e** in yield up to 20% (Scheme 1, Table 1, entries 11, 14, 16, 20, 23). Such type of transformations has never been described for acetamidine in the literature.[20]



4: R = Ph (**a**), 4-*t*-BuC_6H_4 (**b**), 4-ClC_6H_4 (**c**), 4-MeOC_6H_4 (**d**), 4-BrC_6H_4 (**e**)

Scheme 1. Reaction of ynones **1** with acetamidine **2**.

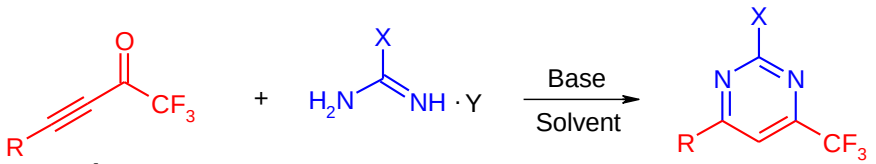
Trying to find the conditions for selective formation of both pyrimidine derivatives and to explain the mechanism of formation of adduct **4**, we assumed that pyrimidine **4** is the result of direc addition of 2-methylpyrimidine **3** as CH-acid to the second equivalent of ynone **1**. To proof thi sequence of transformations, we examined the reaction of pyrimidine **3k** with one equivalent of th ketone **1c** under the same conditions (Et_3N, MeCN, reflux, 4h). According to ^{19}F NMR spectrum o reaction mixture, the transformation of pyrimidine **3k** into corresponding adduct **4** did not occur: onl the signals of initial heterocycle **3k** and ketone **1a**, and some unidentified products were observed. Th same result was obtained when the reaction was performed under UV irradiation (no signal of th expected adduct **4** was observed in the ^{19}F NMR spectrum after irradiation of the reaction mixture at slightly elevated temperature for 6 hours) or in a superbasic medium (stirring of reaction mixture a room temperature in the system DMSO/KOH). Therefore, we proposed an alternative reactio pathway including a participation of methyl group of acetamidine as nucleophilic center. Mos probably the formation of adduct **4** occurs due to imine-enamine equilibrium for intermediate A formed after Michael addition. For example, sequence **1** → **A** → **A'** → **B** → **4** can explain formatio of products **4** (Scheme 2). The postulated intermediates should be quite reactive species formed in minor amounts. Our attempts to determine their structure were unsuccessful. Only low intensity signals (^{19}F NMR) of unidentified derivatives were registered during the reaction monitoring.



Scheme 2. Possible mechanism of formation of adduct **4**.

Next, we used other N-C-N binucleophiles for the assembly of pyrimidine core. We have found that the condensation of ketones **1a-e** with guanidine carbonate **2d** or hydrochloride **2e** under the same conditions afforded 2-aminopyrimidines **3q-u** in good yields (Scheme 3). This type of pyrimidines is especially important due to the fact that these heterocycles demonstrated a wide range of biological activity such as anti-inflammatory, analgesic, antitubercular, adenosine receptor antagonists, and protein kinases inhibitors.[21]

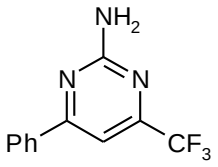
Finally, the reaction of CF_3-ynones **1** with isothiourea derivatives **2e,f** was studied (Scheme 3). When ketones **1a,e** were treated with ethyl isothiouronium salt **2e** in the presence of sodium acetate the target 2-ethylsulfanyl pyrimidines **3v,w** were obtained in good yields. Their benzylsulfanyl analogs **3x,y** were prepared by a similar procedure. Sulfanyl group is an important leaving group in pyrimidine chemistry because such derivatives can be used in reaction with some nucleophiles to construct 2-substituted pyrimidines. This fragment can be also oxidized to sulfones moiety to form even better nucleofuge.



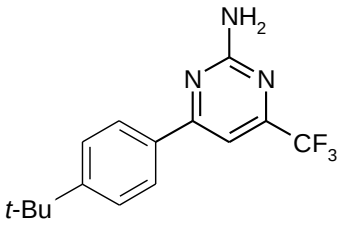
1a-e **2d-g** **3q-y**

1: R = Ph (**a**), 4-*t*-BuC_6H_4 (**b**), 4-ClC_6H_4 (**c**), 4-MeOC_6H_4 (**d**), *n*-Hex (**e**)

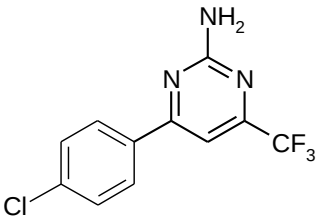
2: X = NH_2, Y = 0.5 H_2CO_3 (**d**); X = NH_2, Y = Cl (**e**);
X = SEt, Y = HBr (**f**); X = SBn, Y = HCl (**g**)



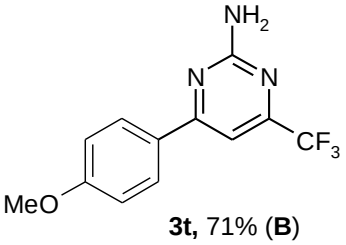
3q, 82% (**A**)



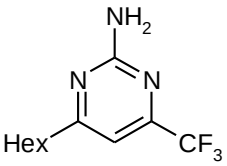
3r, 73% (**A**)



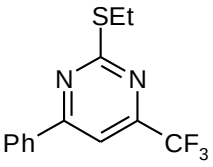
3s, 64% (**B**)



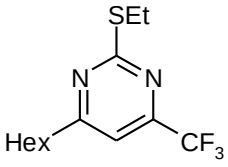
3t, 71% (**B**)



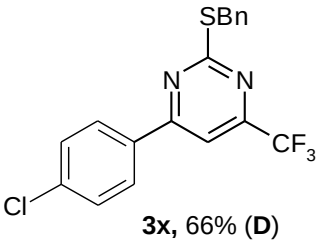
3u, 62% (**A**)



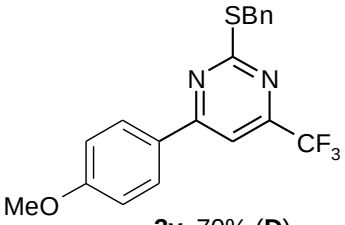
3v, 77% (**C**)



3w, 73% (**C**)



3x, 66% (**D**)



3y, 70% (**D**)

Conditions: **A**: *t*-BuOH; **B**: MeONa/MeOH; **C**: AcONa/*t*-BuOH; **D**: Et_3N/*t*-BuOH

Scheme 3. Synthesis of functionalized pyrimidines **3q-y** from ynones **1a-e** and guanidines **2d,e** or isothiourea derivatives **2f,g**.

The reactions of CF_3-ynones with guanidine and isothiourea derivatives proceed more quickly (3-5 times faster) than the similar reaction with non-fluorinated ynones. It should be noted that the product structure depends strongly on reaction conditions. Thus, when ketone **1d** was treated with guanidine hydrochloride **2e** in the presence of equimolar amounts of sodium methoxide in methanol the target pyrimidine **3t** was formed in good yield (Scheme 3, conditions B). However, when the same reaction was performed with EtONa obtained from ethanol containing little amount of water, only 4-methoxyphenylacetylene **5** was isolated in good yield. The similar cleavage of acetylenic ketones under the action of nitrogen nucleophiles was recently reported.[22]

In conclusion, the developed one-pot procedure can be regarded as an efficient alternative method for the synthesis of trifluoromethylated pyrimidines. One-pot, atom and step economy (PASE)[23] combination in the proposed protocol, easy accessibility of starting

trifluoromethyl(alkynyl)ketones as well as good and high yields of target heterocycles are the main advantages of this route to functionalized pyrimidines.

Experimental part

General Remarks ^{1}H (400.1 MHz), ^{13}C (100.6 MHz) ^{19}F (376.5 MHz), and ^{15}N (40.6 MHz) NMR spectra were recorded on Bruker AVANCE 400 MHz spectrometer. Chemical shifts (δ) are given in *ppm*; the coupling constants (*J*) are given in Hertz. The concerted application of ^{1}H-^{1}H 2D homonuclear experiments NOESY and COSY as well as ^{1}H-^{13}C 2D heteronuclear experiments HMBC and HSQC were used for the distinction of the carbon and proton resonances. The IR spectra were recorded with a Bruker Vertex 70 FT-IR spectrometer and with a portable Varian 3100 diamond ATR/FT-IR spectrometer. The GC/MS analyses were performed with a Shimadzu GCMS-QP5050A instrument (EI, 70 eV). HRMS spectra were measured at Orbitrap Elite instrument. The silica gel used for column chromatography was 230-400 Mesh. All reagents were of reagent grade and were used as such or distilled prior to use. All the solvents were dried according to standard procedures and freshly distilled prior to use. Ynones **1** were prepared as reported previously.[18]

General procedure for synthesis of pyrimidines 3.

A mixture of the appropriate base (0.75 mmol, Et_3N, DBU, AcONa, *t*-BuOK, EtONa, or MeONa; see main text) and binucleophile salt **2** (0.75 mmol) in the appropriate solvent (2 mL, *t*-BuOH, EtOH, MeOH, or MeCN; see main text) was stirred at r.t. for 0.5-2 h to generate the free binucleophile (in case of guanidinium carbonate **2d** no base was used). Next, ynone **1** (0.5 mmol) was added and the reaction mixture was refluxed for 2-4 h (TLC control). After being cooled the mixture was concentrated *in vacuo*, the residue was purified by column chromatography on silica gel or aluminium oxide (**3s**,**t**) using appropriate mixtures of hexane and CH_2Cl_2 (3:1-2:1, **3a-3e**, **3v, 3w**), $CHCl_3$ (**3f-3p**, **3s,t, 3x,y**), or mixture of CH_2Cl_2 and MeOH (100:1, **3q**, **3r**, **3u**).

4-(Trifluoromethyl)-6-phenylpyrimidine 3a. Pale yellow solid, mp 48-49 °C (lit.:[16] 31-33 °C), yield 94 mg (84%). R_f 0.24 (Hexane/CH_2Cl_2, 1:1) (UV). ^{1}H NMR ($CDCl_3$): 7.49-7.57 (m, 3H, Ar), 7.99 (s, 1H, C^5H), 8.10-8.13 (m, 2H, Ar), 9.35 (s, 1H, C^2H). ^{13}C NMR ($CDCl_3$): 112.5 (q, J = 1.9 Hz, C^5), 120.6 (q, J = 275.0 Hz, CF_3), 127.3, 129.2, 132.1, 135.2 (Ar), 156.1 (q, J = 36.1 Hz, $\underline{C}$-CF_3), 159.3 (C^2), 166.4 (C^6). ^{19}F NMR ($CDCl_3$): -71.1. HRMS (ESI): calcd for $C_{11}H_8F_3N_2^+$: $[M + H]^+$ 225.0634; found 225.0635. The NMR data are in agreement with those in the literature.[16]

4-(4-*tert*-Butylphenyl)-6-(trifluoromethyl)pyrimidine 3b. Pale yellow solid, mp 89-90 °C, yield 102 mg (73%). R_f 0.28 (Hexane/CH_2Cl_2, 1:1) (UV). ^{1}H NMR ($CDCl_3$): 1.37 (s, 9H, *t*-Bu), 7.56 (d, J = 8.6

Hz, 2H, Ar), 8.00 (s, 1H, C^5H), 8.08 (d, *J* = 8.6 Hz, 2H, Ar), 9.35 (s, 1H, C^2H). ^{13}C NMR ($CDCl_3$): 31.1 ($C(\underline{C}H_3)_3$), 35.0 ($\underline{C}(CH_3)_3$), 112.2 (q, *J* = 2.6 Hz, C^5), 120.7 (q, *J* = 275.0 Hz, CF_3), 126.3, 127.2, 132.5, 155.89 (Ar), 155.94 (q, *J* = 35.8 Hz, $\underline{C}$-CF_3), 159.4 (C^2), 166.4 (C^6). ^{19}F NMR ($CDCl_3$): -71.2. HRMS (ESI): calcd for $C_{15}H_{16}F_3N_2^+$: $[M + H]^+$ 281.126; found 281.1261.

4-(4-Chlorophenyl)-6-(trifluoromethyl)pyrimidine 3c. Pale yellow solid, mp 59-60 °C, yield 107 mg (83%). R_f 0.25 (Hexane/CH_2Cl_2, 1:1) (UV). ^1H NMR ($CDCl_3$): 7.49 (d, *J* = 8.6 Hz, 2H, Ar), 7.98 (s, 1H, C^5H), 8.08 (d, *J* = 8.6 Hz, 2H, Ar), 9.36 (s, 1H, C^2H). ^{13}C NMR ($CDCl_3$): 112.2 (q, *J* = 2.6 Hz C^5), 120.6 (q, *J* = 275.3 Hz, CF_3), 128.6, 129.5, 133.7, 138.6 (Ar), 156.3 (q, *J* = 36.1 Hz, $\underline{C}$-CF_3) 159.4 (C^2), 165.2 (C^6). ^{19}F NMR ($CDCl_3$): -71.1. HRMS (ESI): calcd for $C_{11}H_7ClF_3N_2^+$: $[M + H]$ 259.0250 (^{35}Cl), 261.0220 (^{37}Cl); found 259.0244 (^{35}Cl), 261.0214 (^{37}Cl).

4-(Trifluoromethyl)-6-(4-methoxyphenyl)pyrimidine 3d. Pale yellow solid, mp 58-60 °C, yield 10(mg (83%). R_f 0.29 (Hexane/CH_2Cl_2, 1:1) (UV). ^1H NMR ($CDCl_3$): 3.86 (s, 3H, OCH_3), 7.00 (d, *J* = 8.9 Hz, 2H, Ar), 7.91 (s, 1H, C^5H), 8.09 (d, *J* = 8.9 Hz, 2H, Ar), 9.27 (s, 1H, C^2H). ^{13}C NMR ($CDCl_3$) 55.4 (OCH_3), 111.5 (q, *J* = 1.8 Hz, C^5), 114.5, 120.7 (q, *J* = 275.0 Hz, CF_3), 127.6, 129.1, 155.7 (q, *J* = 35.8 Hz, $\underline{C}$-CF_3), 159.2 (C^2), 162.9, 165.8 (C^6). ^{19}F NMR ($CDCl_3$): -71.2. HRMS (ESI): calcd fo $C_{12}H_{10}F_3N_2O^+$: $[M + H]^+$ 255.074; found 255.0741.

4-(Trifluoromethyl)-6-hexylpyrimidine 3e. Pale yellow oil, yield 61 mg (53%). R_f 0.5 (CH_2Cl_2 (UV). ^1H NMR ($CDCl_3$): 0.85-0.89 (m, 3H, CH_3, Hex), 1.23-1.38, (m, 6H, $(CH_2)_3$, Hex), 1.71-1.79 (m 2H, CH_2, Hex), 2.86 (t, *J* = 7.8 Hz, 3H, C^7H_2), 7.49 (s, 1H, C^5H), 9.24 (s, 1H, C^2H). ^{13}C NMI ($CDCl_3$): 14.0, 22.5, 28.6, 28.9, 31.5, 38.1, 116.0 (q, *J* = 1.8 Hz, C^5), 120.6 (q, *J* = 275.3 Hz, CF_3) 155.2 (q, *J* = 36.5 Hz, $\underline{C}$-CF_3), 158.9 (C^2), 174.1 (C^6). ^{19}F NMR ($CDCl_3$): -71.2. HRMS (ESI): calc for $C_{11}H_{16}F_3N_2^+$: $[M + H]^+$ 233.126; found 233.1260.

2,4-Diphenyl-6-trifluoromethylpyrimidine 3f

White solid, mp 84-86 °C (lit.:[16] 77-79 °C), yield 120 mg (80%). ^1H NMR ($CDCl_3$): 7.48-7.60 (m, 6H Ph), 7.86 (s, 1H, C^5H), 8.20-8.28 (m, 2H, Ph), 8.59-8.68 (m, 2H, Ph). ^{13}C NMR ($CDCl_3$): 110.0 (C^5), 121.0 (q, *J* = 275.3 Hz, CF_3), 127.5, 128.7, 128.8, 129.2, 131.6, 131.9, 136.0, 136.6 (Ph), 156.8 (q, *J* = 35.6 Hz, C^6), 165.4 (C^4), 166.5 (C^2). ^{19}F NMR ($CDCl_3$): -70.3. ^{15}N NMR ($CDCl_3$): -96.1 (N^3), -110.9 (N^1). IR (KBr, cm^{-1}): *v* 1140, 1184 (C-F), 1550 (C^2=N-C^4=C^5), 1587 (C^6=N). MS (EI) *m/z* (relative intensity, %): 300 (100, M^+), 197 (18), 128 (80), 104 (37), 103 (33), 102 (18), 101 (10), 77 (31), 76 (18), 51 (18). HRMS (ESI): calcd for $C_{17}H_{11}F_3N_2H^+$: $[M + H]^+$ 301.0947; found 301.0948. The NMR data are in agreement with those in the literature.[16]

4-(4-*tert*-Butylphenyl)-2-phenyl-6-trifluoromethylpyrimidine 3g

Pale yellow solid, mp 59-61 °C, yield 165 mg (93%). ^{1}H NMR ($CDCl_3$): 1.41 (s, 9H, CH_3, *t*-Bu), 7.52-7.57 (m, 3H, Ph), 7.59 (d, *J* = 8.2 Hz, 2H, Ar), 7.86 (s, 1H, C^5H), 8.20 (d, *J* = 8.2 Hz, 2H, Ar), 8.63-8.69 (m, 2H, Ph). ^{13}C NMR ($CDCl_3$): 31.3 ($C(\underline{C}H_3)_3$), 35.2 ($\underline{C}(CH_3)_3$), 109.8 (C^5), 121.2 (q, *J* = 275.3 Hz, CF_3), 126.3, 127.4, 133.3, 155.7 (Ar), 128.8, 128.9, 131.6, 136.8 (Ph), 156.7 (q, *J* = 35.5 Hz, C^6), 165.4 (C^4), 166.5 (C^2). ^{19}F NMR ($CDCl_3$): -70.3. IR (film, cm^{-1}): *v* 1152, 1179 (C-F), 1544 (C^2=N-C^4=C^5), 1582 (C^6=N). MS (EI) *m/z* (relative intensity, %): 356 (48, M^+), 342 (43), 341 (100), 313 (29), 171 (19), 157 (46), 128 (13), 122 (12), 115 (10), 103 (11), 77 (10). Calcd for $C_{21}H_{19}F_3N_2$: C 70.77; H 5.37; N 7.86. Found: C 70.91; H 5.44; N 7.95.

4-(4-Chlorophenyl)-2-phenyl-6-trifluoromethylpyrimidine 3h

Pale yellow solid, mp 128-130 °C, yield 138 mg (83%). ^{1}H NMR ($CDCl_3$): 7.45-7.57 (m, 5H, Ph, Ar), 7.81 (s, 1H, C^5H), 8.17 (d, *J* = 8.2 Hz, 2H, Ar), 8.54-8.63 (m, 2H, Ph). ^{13}C NMR ($CDCl_3$): 109.8 (C^5), 121.0 (q, *J* = 275.3 Hz, CF_3), 128.9 (3 C), 129.6, 134.5, 136.5, 138.4 (Ph, Ar), 157.1 (q, *J* = 35.6 Hz, C^6), 165.4 (C^4), 165.6 (C^2). ^{19}F NMR ($CDCl_3$): -70.3. ^{15}N NMR ($CDCl_3$): -96.1 (N^3), -109.4 (N^1). IR (KBr, cm^{-1}): *v* 1148, 1179 (C-F), 1543 (C^2=N-C^4=C^5), 1584 (C^6=N). MS (EI) *m/z* (relative intensity, %): 336 (34, M^++2), 335 (20, M^++1), 334 (100, M^+), 230 (14), 164 (15), 162 (55), 139 (11), 127 (15), 126 (12), 104 (35), 103 (27), 77 (12), 76 (13), 75 (12), 51 (13). Calcd for $C_{17}H_{10}ClF_3N_2$: C 61.00; H 3.01; N 8.37. Found: C 60.89; H 2.87; N 8.43.

4-(4-Methoxyphenyl)-2-phenyl-6-trifluoromethylpyrimidine 3i

Yellowish solid, mp 119-120 °C (lit.:[13] 120-121 °C), yield 131 mg (79%). ^{1}H NMR ($CDCl_3$): 3.87 (s, 3H, CH_3), 7.02 (d, *J* = 8.8 Hz, 2H, Ar), 7.48-7.56 (m, 3H, Ph), 7.76 (s, 1H, C^5H), 8.19 (d, *J* = 8.8 Hz, 2H, Ar), 8.57-8.63 (m, 2H, Ph). ^{13}C NMR ($CDCl_3$): 55.6 (CH_3), 109.1 (C^5), 121.2 (q, *J* = 275.2 Hz, CF_3), 114.6, 128.5, 128.8, 128.9, 129.3, 131.6, 136.9, 163.0 (Ph, Ar), 156.5 (q, *J* = 35.3 Hz, C^6), 165.3 (C^4), 165.9 (C^2). ^{19}F NMR ($CDCl_3$): -70.3. IR (KBr, cm^{-1}): *v* 1143, 1182 (C-F), 1545 (C^2=N-C^4=C^5), 1587 (C^6=N). MS (EI) *m/z* (relative intensity, %): 330 (100, M^+), 227 (21), 165 (12), 158 (68), 132 (11), 132 (20), 103 (22), 77 (15). HRMS (ESI): calcd for $C_{18}H_{13}F_3N_2OH^+$: $[M + H]^+$ 331.1053; found 331.1054. The NMR data are in agreement with those in the literature.[16]

4-(4-Methoxynaphtalen-1-yl)-2-phenyl-6-trifluoromethylpyrimidine 3j

Yellowish solid, mp 149-151 °C, yield 185 mg (97%). ^{1}H NMR ($CDCl_3$): 4.08 (s, 3H, CH_3), 6.93 (d, *J* = 8.1 Hz, 2H, Ar), 7.48-7.65 (m, 5H, Ar, Ph), 7.73-7.80 (m, 1H, Ar), 7.76 (s, 1H, C^5H), 8.35-8.47 (m,

2H, Ar), 8.58-8.68 (m, 2H, Ph). ^{13}C NMR ($CDCl_3$): 55.9 (CH_3), 103.5 (C^5), 121.2 (q, J = 275.3 Hz, CF_3), 114.7, 122.8, 124.8, 126.0, 126.2, 127.7, 128.1, 128.9, 128.9, 130.0, 131.7, 136.8, 157.8 (Ph, Ar), 156.3 (q, J = 35.3 Hz, C^6), 165.2 (C^4), 169.4 (C^2). ^{19}F NMR ($CDCl_3$): -70.2. IR (KBr, cm^{-1}): v 1147, 1177 (C-F), 1540 (C^2=N-C^4=C^5), 1571 (C^6=N). MS (EI) *m/z* (relative intensity, %): 380 (100, M^+), 379 (81), 365 (25), 364 (26), 312 (15), 311 (65), 296 (21), 180 (21), 164 (12), 138 (12), 77 (10). Calcd for $C_{22}H_{15}F_3N_2O$: C 69.47; H 3.97; N 7.36. Found: C 69.32; H 3.96; N 6.97.

2-Methyl-4-phenyl-6-trifluoromethylpyrimidine 3k

Yellow oil, yield 115 mg (48%). ^{1}H NMR ($CDCl_3$): 2.85 (s, 3H, CH_3), 7.45-7.55, 8.05-8.15 (m, 5H Ph), 7.78 (s, 1H, C^5H). ^{13}C NMR ($CDCl_3$): 26.2 (CH_3), 109.6 (C^5), 120.9 (q, J = 275.2 Hz, CF_3), 127.5 129.3, 131.9, 135.9 (Ph), 156.3 (q, J = 35.3 Hz, C^6), 166.6 (C^4), 169.7 (C^2). ^{19}F NMR ($CDCl_3$): -69.8 ^{15}N NMR ($CDCl_3$): -87.5, -104.5. IR (KBr, cm^{-1}): v 1142, 1174 (C-F), 1554 (C^2=N-C^4=C^5), 1577 (Ph) 1595 (C^6=N). MS (EI) *m/z* (relative intensity, %): 238 (100, M^+), 197 (38), 177 (15), 128 (72), 10 (21). Calcd for $C_{12}H_9F_3N_2$: C 60.51; H 3.81; N 11.76. Found: C 60.17; H 3.83; N 11.46. The NMI data are in agreement with those in the literature.[16]

2-Methyl-4-(4-*tert*-butylphenyl)-6-trifluoromethylpyrimidine 3l

Pale yellow solid, mp 73-75 °C, yield 84 mg (57%). ^{1}H NMR ($CDCl_3$): 1.35 (s, 9H, CH_3, *t*-Bu), 2.8 (s, 3H, CH_3), 7.53 (d, J = 8.5 Hz, 2H, Ar), 7.78 (s, 1H, C^5H), 8.04 (d, J = 8.5 Hz, 2H, Ar). ^{13}C NMI ($CDCl_3$): 26.4 (CH_3), 31.3 (C(<u>C</u>H_3)$_3$), 35.2 (<u>C</u>(CH_3)$_3$), 109.4 (C^5), 121.0 (q, J = 275.1 Hz, CF_3), 126.3 127.4, 133.2, 155.7 (Ar), 156.3 (q, J = 35.2 Hz, C^6), 166.7 (C^4), 169.7 (C^2). ^{19}F NMR ($CDCl_3$): -70.3 IR (film, cm^{-1}): v 1150, 1199 (C-F), 1549 (C^2=N-C^4=C^5), 1590 (C^6=N). MS (EI) *m/z* (relativ intensity, %): 294 (14, M^+), 280 (18), 279 (100), 251 (22), 91 (11). HRMS (ESI): calcd fo $C_{16}H_{17}F_3N_2H^+$: $[M + H]^+$ 295.1417; found 295.1418.

4-(4-Chlorophenyl)-2-methyl-6-trifluoromethylpyrimidine 3m

Pale yellow solid, mp 50-51 °C, yield 111 mg (41%). ^{1}H NMR ($CDCl_3$): 2.85 (s, 3H, CH_3), 7.48 (d, = 8.2 Hz, 2H, Ar), 7.77 (s, 1H, C^5H), 8.07 (d, J = 8.2 Hz, 2H, Ar). ^{13}C NMR ($CDCl_3$): 26.3 (CH_3) 109.4 (C^5), 120.9 (q, J = 275.3 Hz, CF_3), 128.9, 129.6, 134.3, 138.4 (Ar), 156.6 (q, J = 35.4 Hz, C^6) 165.4 (C^4), 169.9 (C^2). ^{19}F NMR ($CDCl_3$): -70.3. IR (KBr, cm^{-1}): v 1151, 1201 (C-F), 1551 (C^2=N-C^4=C^5), 1590 (C^6=N). MS (EI) *m/z* (relative intensity, %): 274 (31, M^++2), 272 (100, M^+), 233 (12), 231 (37), 211 (16), 164 (21), 162 (66), 138 (10), 136 (28), 127 (17), 126 (16), 75 (24), 66 (28), 50 (12). HRMS (ESI): calcd for $C_{12}H_8ClF_3N_2H^+$: $[M + H]^+$ 273.0401 (^{35}Cl), 275.0372 (^{37}Cl); found 273.0403 (^{35}Cl), 275.0368 (^{37}Cl).

4-(4-Methoxyphenyl)-2-methyl-6-trifluoromethylpyrimidine 3n

Pale yellow solid, mp 79-81 °C, yield 121 mg (90%). ^{1}H NMR ($CDCl_3$): 2.81 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 6.99 (d, *J* = 7.4 Hz, 2H, Ar), 7.71 (s, 1H, C^5H), 8.08 (d, *J* = 7.4 Hz, 2H, Ar). ^{13}C NMR ($CDCl_3$): 26.3 (CH_3), 55.6 (OCH_3), 108.7 (C^5), 121.0 (q, *J* = 274.8 Hz, CF_3), 114.6, 128.3, 129.2, 162.9 (Ar), 156.0 (q, *J* = 34.9 Hz, C^6), 166.0 (C^4), 169.5 (C^2). ^{19}F NMR ($CDCl_3$): -70.4. IR (KBr, cm^{-1}): *v* 1135, 1179 (C-F), 1549 (C^2=N-C^4=C^5), 1591 (C^6=N). MS (EI) *m/z* (relative intensity, %): 268 (100, M^+), 227 (15), 225 (14), 158 (26), 132 (22), 66 (14), 63 (11). HRMS (ESI): calcd for $C_{13}H_{11}F_3N_2OH^+$: $[M + H]^+$ 269.0896; found 269.0901.

4-Hexyl-2-methyl-6-trifluoromethylpyrimidine 3o

Yellow oil, yield 115 mg (31%). ^{1}H NMR ($CDCl_3$): 0.75-0.92 (m, 3H, CH_3, Hex), 1.20-1.40, 1.65-1.78 (m, 8H, $(CH_2)_4$, Hex), 2.76 (s, 3H, C^7H_3), 2.77-2.83 (m, 2H, CH_2), 7.26 (s, 1H, C^5H). ^{13}C NMR ($CDCl_3$): 14.2, 22.7, 26.2, 29.0, 29.2, 31.7, 38.5 (Hex, C^7H_3), 112.7 (C^5), 120.9 (q, *J* = 275.1 Hz, CF_3), 155.6 (q, *J* = 35.3 Hz, C^6), 169.2 (C^4), 174.1 (C^2). ^{19}F NMR ($CDCl_3$): -70.0. ^{15}N NMR ($CDCl_3$): -81.1, -106.1. IR (film, cm^{-1}): 1152, 1181 (C-F), 1563 (C^2=N-C^4=C^5), 1596 (C^6=N). MS (EI) *m/z* (relative intensity, %): 246 (2, M^+), 203 (15), 189 (26), 176 (100). Calcd for $C_{12}H_{17}F_3N_2$: C 58.52; H 6.96; N 11.37. Found: C 58.53; H 6.87; N 11.10.

4-(4-Bromophenyl)-2-methyl-6-trifluoromethylpyrimidine 3p

Pale yellow solid, mp 49-51 °C, yield 78 mg (49%). ^{1}H NMR ($CDCl_3$): 2.85 (s, 3H, CH_3), 7.65 (d, *J* = 8.5 Hz, 2H, Ar), 7.77 (s, 1H, C^5H), 8.00 (d, *J* = 8.5 Hz, 2H, Ar). ^{13}C NMR ($CDCl_3$): 26.3 (CH_3), 109.4 (C^5), 120.9 (q, *J* = 275.3 Hz, CF_3), 126.9, 129.1, 132.6, 134.9 (Ar), 156.7 (q, *J* = 35.5 Hz, C^6), 165.5 (C^4), 169.9 (C^2). ^{19}F NMR ($CDCl_3$): -70.3. IR (KBr, cm^{-1}): *v* 1147 (C-F), 1549 (C^2=N-C^4=C^5), 1588 (C^6=N). MS (EI) *m/z* (relative intensity, %): 318 (98, M^++1), 317 (17, M^+), 316 (100, M^+-1), 277 (25), 275 (25), 208 (38), 206 (40), 182 (12), 180 (13), 127 (34), 101 (10), 76 (11), 75 (19), 66 (17), 50 (12). Calcd for $C_{12}H_8BrF_3N_2$: C 45.45; H 2.54; N 8.83. Found: C 45.82; H 2.41; N 8.89.

2-Amino-4-phenyl-6-trifluoromethylpyrimidine 3q. Pale yellow solid, mp 124-125 °C (lit.:[16] 128-129 °C), yield 98 mg (82%). R_f 0.30 (CH_2Cl_2) (UV). ^{1}H NMR ($CDCl_3$): 5.90 (br.s., 2H, NH_2), 7.31 (s, 1H, C^5H), 7.46-7.54 (m, 3H, Ar), 8.00-8.03 (m, 2H, Ar). ^{13}C NMR ($CDCl_3$): 102.8 (q, *J* = 3.0 Hz, C^5), 120.7 (q, *J* = 275.3 Hz, CF_3), 127.2, 128.9, 131.5, 136.1 (Ar), 157.1 (q, *J* = 35.4 Hz, C^6), 163.5 (C^4), 168.2 (C^2). ^{19}F NMR ($CDCl_3$): -71.8. The NMR data are in agreement with those in the literature.[16]

2-Amino-4-(4-*tert*-butylphenyl)-6-trifluoromethylpyrimidine 3r. Pale yellow solid, mp 134-136 °C, yield 107 mg (73%). R_f 0.32 (CH_2Cl_2) (UV). ^{1}H NMR ($CDCl_3$): 1.36 (s, 9H, *t*-Bu), 5.96 (br.s., 2H,

NH_2), 7.30 (s, 1H, C^5H), 7.51 (d, J = 8.4 Hz, 2H, Ar), 7.95 (d, J = 8.4 Hz, 2H, Ar). ^{13}C NMR ($CDCl_3$): 31.1 ($C(\underline{C}H_3)_3$), 34.9 ($\underline{C}(CH_3)_3$), 102.6 (q, J = 2.6 Hz, C^5), 120.8 (q, J = 275.0 Hz, CF_3), 125.9, 127.0, 133.3, 155.1 (Ar), 156.9 (q, J = 34.6 Hz, C^6), 163.5 (C^4), 168.1 (C^2). ^{19}F NMR ($CDCl_3$): -71.7. HRMS (ESI): calcd for $C_{15}H_{17}F_3N_3^+$: $[M + H]^+$ 296.1369; found 296.1369.

2-Amino-4-(4-chlorophenyl)-6-trifluoromethylpyrimidine 3s

Pale yellow solid, mp 192-194 °C (lit.:[24] 202-203 °C), yield 88 mg (64%). ^1H NMR (DMSO-d_6): 7.39 (br.s., 2H, NH_2), 7.54 (s, 1H, C^5H), 7.58 (d, J = 8.3 Hz, 2H, Ar), 8.20 (d, J = 8.3 Hz, 2H, Ar). ^{13}C NMR (DMSO-d_6): 100.8 (C^5), 120.8 (q, J = 275.4 Hz, CF_3), 128.9, 129.0, 134.7, 136.3 (Ar), 156.2 (q, J = 34.2 Hz, C^6), 163.8 (C^4), 165.7 (C^2). ^{19}F NMR (DMSO-d_6): -69.5. IR (KBr, cm^{-1}): ν 1137, 1184 (C-F), 1551 (C^2=N-C^4=C^5), 1591 (C^6=N). MS (EI) *m/z* (relative intensity, %): 275 (30, M^++2), 274 (29, M^++1), 273 (100, M^+), 272 (58, M^+-1), 252 (16), 162 (21), 136 (16), 127 (16), 126 (12), 75 (27), 51 (12), 50 (15). HRMS (ESI): calcd for $C_{12}H_{10}F_3N_3OH^+$: $[M + H]^+$ 274.0354 (^{35}Cl), 276.0324 (^{37}Cl) found 274.0356 (^{35}Cl), 276.0320 (^{37}Cl). The NMR data are in agreement with those in the literature.[24]

2-Amino-4-(4-methoxyphenyl)-6-trifluoromethylpyrimidine 3t

Pale yellow solid, mp 184-187 °C (lit.:[24] 193-194 °C), yield 95 mg (71%). ^1H NMR (DMSO-d_6): 3.83 (s, 3H, OCH_3), 7.05 (d, J = 8.6 Hz, 2H, Ar), 7.25 (br.s., 2H, NH_2), 7.44 (s, 1H, C^5H), 8.15 (d, J = 8.6 Hz, 2H, Ar). ^{13}C NMR (DMSO-d_6): 55.3 (OCH_3), 100.0 (C^5), 121.0 (q, J = 275.3 Hz, CF_3), 114.2, 128.1, 128.9, 162.0 (Ar), 155.8 (q, J = 33.9 Hz, C^6), 163.8 (C^4), 166.4 (C^2). ^{19}F NMR (DMSO-d_6): 69.6. ^{15}N NMR (DMSO-d_6): -132.9 (N^3), -150.7 (N^1), -293.6 (NH_2). IR (KBr, cm^{-1}): ν 1137, 1188 (C-F), 1553 (C^2=N-C^4=C^5), 1594 (C^6=N). MS (EI) *m/z* (relative intensity, %): 269 (100, M^+), 268 (38), 254 (10), 206 (13). HRMS (ESI): calcd for $C_{12}H_{10}F_3N_3OH^+$: $[M + H]^+$ 270.0849; found 270.0851. The NMR data are in agreement with those in the literature.[24]

2-Amino-4-hexyl-6-trifluoromethylpyrimidine 3u. Pale yellow oil, yield 76 mg (62%). R_f 0.35 (CH_2Cl_2) (UV). ^1H NMR ($CDCl_3$): 0.83-0.90 (m, 3H, CH_3), 1.24-1.37 (m, 6H, $(CH_2)_3$, Hex), 1.62-1.70 (m, 2H, CH_2), 1.62-1.70 (m, 2H, CH_2), 2.62 (t, J = 7.8 Hz, 2H, CH_2-Het), 5.69 (br.s., 2H, NH_2), 6.70 (s, 1H, C^5H). ^{13}C NMR ($CDCl_3$): 14.0, 22.5, 28.5, 28.9, 31.5, 38.1, 105.7 (q, J = 2.6 Hz, C^5), 120.6 (q, J = 275.3 Hz, CF_3), 156.2 (q, J = 35.0 Hz, C^6), 163.1 (C^4), 175.4 (C^2). ^{19}F NMR ($CDCl_3$): -71.8. HRMS (ESI): calcd for $C_{11}H_{17}F_3N_3^+$: $[M + H]^+$ 248.1369; found 248.1371.

2-Ethylsulfanyl-4-phenyl-6-trifluoromethylpyrimidine 3v. Pale yellow solid, mp 51-52 °C, yield 109 mg (77%). ^1H NMR ($CDCl_3$): 1.47 (t, J = 7.3 Hz, CH_3), 3.26 (q, J = 7.3 Hz, CH_2), 7.48-7.56 (m, 3H, Ar), 7.62 (s, 1H, C^5H), 8.09-8.11 (m, 2H, Ar). ^{13}C NMR ($CDCl_3$): 14.2, 25.6, 107.2 (q, J = 2.6 Hz,

C^5), 120.5 (q, *J* = 275.7 Hz, CF_3), 127.3, 129.0, 132.0, 135.3 (Ar), 156.3 (q, *J* = 35.8 Hz, C^6), 166.2 (C^4), 174.0 (C^2). ^{19}F NMR ($CDCl_3$): -71.4. ^{15}N NMR ($CDCl_3$): -100.7, -115.4. HRMS (ESI): calcd for $C_{13}H_{12}F_3N_2S^+$: $[M + H]^+$ 285.0668; found 285.0672.

2-Ethylsulfanyl-4-hexyl-6-trifluoromethylpyrimidine 3w. Pale yellow oil, yield 107 mg (73%). R_f 0.35 (CH_2Cl_2) (UV). ^1H NMR ($CDCl_3$): 0.84-0.89 (m, 3H, CH_3, Hex), 1.25-1.40 (m, 9H, $(CH_2)_3$, Hex, $SCH_2\underline{CH_3}$), 1.68-1.75 (m, 2H, CH_2), 2.75 (t, *J* = 7.8 Hz, 2H, CH_2-Het), 3.16 (q, *J* = 7.3 Hz, CH_2), 7.07 (s, 1H, C^5H). ^{13}C NMR ($CDCl_3$): 14.0, 14.2, 22.4, 25.4, 28.4, 28.9, 31.5, 38.0, 110.7 (q, *J* = 2.6 Hz C^5), 120.5 (q, *J* = 275.3 Hz, CF_3), 155.4 (q, *J* = 36.1 Hz, C^6), 173.5 (C^4), 174.0 (C^2). ^{19}F NMR ($CDCl_3$): -71.5. HRMS (ESI): calcd for $C_{13}H_{20}F_3N_2S^+$: $[M + H]^+$ 293.1294; found 293.1299.

2-Benzylsulfanyl-4-(4-chlorophenyl)-6-trifluoromethylpyrimidine 3x

Pale yellow solid, mp 89-92 °C, yield 84 mg (66%). ^1H NMR ($CDCl_3$): 4.41 (s, 2H, CH_2), 7.10-7.29 (m, 3H, Ph), 7.37-7.44 (m, 4H, Ph, Ar), 7.52 (s, 1H, C^5H), 7.95 (d, *J* = 8.7 Hz, 2H, Ar). ^{13}C NMR ($CDCl_3$): 35.8 (CH_2), 107.6 (C^5), 120.7 (q, *J* = 275.6 Hz, CF_3), 127.5, 128.7, 128.9, 129.3, 129.6, 133.8, 137.3, 138.7 (Ph, Ar), 156.6 (q, *J* = 36.0 Hz, C^6), 165.4 (C^4), 173.9 (C^2). ^{19}F NMR ($CDCl_3$): -70.4. IR (KBr, cm^{-1}): *v* 1152, 1191 (C-F), 1532 (C^2=N-C^4=C^5), 1586 (C^6=N). MS (EI) *m/z* (relative intensity, %): 382 (10, M^++2), 380 (28, M^+), 349 (11), 347 (36), 91 (100), 65 (26). HRMS (ESI): calcd for $C_{18}H_{12}ClF_3N_2SH^+$: $[M + H]^+$ 381.0435 (^{35}Cl), 383.0406 (^{37}Cl); found 381.0439 (^{35}Cl), 383.0405 (^{37}Cl).

2-Benzylsulfanyl-4-(4-methoxyphenyl)-6-trifluoromethylpyrimidine 3y

Yellow solid, mp 92-94 °C, yield 131 mg (70%). ^1H NMR ($CDCl_3$): 3.85 (s, 3H, CH_3), 4.47 (s, 2H CH_2), 6.97 (d, *J* = 8.7 Hz, 2H, Ar), 7.15-7.35 (m, 3H, Ph), 7.43-7.51 (m, 2H, Ph), 7.53 (s, 1H, C^5H) 8.04 (d, *J* = 8.7 Hz, 2H, Ar). ^{13}C NMR ($CDCl_3$): 35.7 (CH_2), 55.6 (CH_3), 106.9 (C^5), 120.8 (q, *J* = 275.4 Hz, CF_3), 127.4, 127.8, 128.7, 129.3, 129.4, 137.6, 163.1 (Ph, Ar), 156.1 (q, *J* = 35.7 Hz, C^6) 166.0 (C^4), 173.3 (C^2). ^{19}F NMR ($CDCl_3$): -70.5. ^{15}N NMR ($CDCl_3$): -100.7 (N^3), -115.4 (N^1). IR (KBr, cm^{-1}): *v* 1137, 1177 (C-F), 1532 (C^2=N-C^4=C^5), 1579 (C^6=N). MS (EI) *m/z* (relative intensity, %): 376 (51, M^+), 344 (12), 343 (54), 299 (12), 298 (13), 254 (12), 92 (12), 91 (100), 65 (28). HRMS (ESI): calcd for $C_{19}H_{15}F_3N_2OSH^+$: $[M + H]^+$ 377.0930; found 377.0933.

1,1,1-trifluoro-4-phenyl-2-{[4-phenyl-6-(trifluoromethyl)pyrimidin-2-yl]methyl}but-3-yn-2-ol 4a

Pale yellow oil, yield 17 mg (8%). ^1H NMR ($CDCl_3$): 3.77 (s, 2H, CH_2), 6.63 (b.s., 1H, OH), 7.17-7.64 (m, 8H, Ph), 7.98 (s, 1H, C^5H), 8.07-8.13 (m, 2H, Ph). ^{13}C NMR ($CDCl_3$): 43.4 (CH_2), 71.5 (q, *J* =

32.6 Hz, C(OH)), 83.7 (C≡CPh), 87.2 (C≡CPh), 111.5 (q, J = 2.7 Hz, C^5), 120.5 (q, J = 275.3 Hz, C^6CF_3), 123.6 (q, J = 284.1 Hz, C(OH)CF_3), 121.3, 127.8, 128.4, 129.3, 129.7, 132.1, 132.9, 134.8 (Ph), 156.5 (q, J = 36.2 Hz, C^6), 167.0 (C^4), 167.4 (C^2). ^{19}F NMR ($CDCl_3$): -70.0, -81.2. IR (film, cm^{-1}): ν 1155, 1181 (C-F), 1551 (C^2=N-C^4=C^5), 1597 (C^6=N), 2239 (C≡C), 3343 (OH). MS (EI) *m/z* (relative intensity, %): 436 (27, M^+), 435 (100), 417 (12), 365 (11), 349 (25), 129 (23). Calcd for $C_{22}H_{14}F_6N_2O$: C 60.56; H 3.23; N 6.42. Found: C 60.78; H 3.54; N 6.22.

4-(4-*tert*-Butylphenyl)-2-{[4-(4-*tert*-butylphenyl)-6-(trifluoromethyl)pyrimidin-2-yl]methyl}-1,1,1-trifluorobut-3-yn-2-ol 4b

Yellow oil, yield 27 mg (20%). ^{1}H NMR ($CDCl_3$): 1.24 (s, 9H, CH_3, *t*-Bu), 1.35 (s, 9H, CH_3, *t*-Bu) 3.74 (s, 2H, CH_2), 6.74 (b.s., 1H, OH), 7.19-7.25 (m, 4H, Ar), 8.07-8.13 (d, J = 8.4 Hz, 2H, Ar), 7.9 (s, 1H, C^5H), 8.02 (d, J = 8.4 Hz, 2H, Ar). ^{19}F NMR ($CDCl_3$): -70.3, -81.5. IR (film, cm^{-1}): ν 1183 (C F), 1546 (C^2=N-C^4=C^5), 1595 (C^6=N), 2237 (C≡C), 3364 (OH). MS (EI) *m/z* (relative intensity, %) 548 (48, M^+), 547 (35), 533 (14), 531 (11), 492 (31), 491 (100), 260 (10), 259 (38), 245 (11), 161 (17) 155 (10), 115 (10), 57 (30). HRMS (ESI): calcd for $C_{30}H_{30}F_6N_2OH^+$: $[M + H]^+$ 549.2335; found 549.2338.

4-(4-Chlorophenyl)-2-{[4-(4-chlorophenyl)-6-(trifluoromethyl)pyrimidin-2-yl]methyl}-1,1,1-trifluorobut-3-yn-2-ol 4c

Yellow oil, yield 11 mg (4%). ^{1}H NMR ($CDCl_3$): 3.79 (s, 2H, CH_2), 6.41 (s, 1H, OH), 7.21-7.30 (m 4H, Ar), 7.56 (d, J = 6.9 Hz, 2H, Ar), 7.98 (s, 1H, C^5H), 8.09 (d, J = 6.9 Hz, 2H, Ar). ^{13}C ^{19}F NMR ($CDCl_3$): -70.3, -81.4. IR (film, cm^{-1}): ν 1159, 1182 (C-F), 1548 (C^2=N-C^4=C^5), 1594 (C^6=N), 2240 (C≡C), 3370 (OH). MS (EI) *m/z* (relative intensity, %): 506 (18, M^++2), 505 (63, M^++1), 504 (28, M^+) 503 (100), 419 (15), 417 (26), 272 (11), 217 (12), 165 (21), 163 (62), 137 (13), 135 (12), 101 (14), 9 (16), 75 (17). HRMS (ESI): calcd for $C_{22}H_{10}Cl_2F_6N_2OH^+$: $[M - H]^+$ 503.0148 (^{35}Cl), 505.0118 (^{37}Cl) found 503.0159 (^{35}Cl), 505.0128 (^{37}Cl).

1,1,1-Trifluoro-4-(4-methoxyphenyl)-2-{[4-(4-methoxyphenyl)-6-(trifluoromethyl)pyrimidin-2-yl]methyl}-but-3-yn-2-ol 4d

Yellow oil, yield 39 mg (16%). ^{1}H NMR ($CDCl_3$): 3.71 (s, 2H, CH_2), 3.74 (s, 3H, CH_3), 3.88 (s, 3H, CH_3), 6.73 (d, J = 8.5 Hz, 2H, Ar), 6.74 (b.s., 1H, OH), 7.02 (d, J = 8.6 Hz, 2H, Ar), 7.21 (d, J = 8.5 Hz, 2H, Ar), 7.87 (s, 1H, C^5H), 8.08 (d, J = 8.6 Hz, 2H, Ar). ^{19}F NMR ($CDCl_3$): -70.4, -81.5. IR (film, cm^{-1}): ν 1181 (C-F), 1547 (C^2=N-C^4=C^5), 1597 (C^6=N), 2234 (C≡C), 3341 (OH). MS (EI) *m/z* (relative intensity, %): 496 (36, M^+), 495 (100), 481 (17), 409 (13), 248 (10), 159 (18). HRMS (ESI): calcd for $C_{24}H_{18}F_6N_2O_3H^+$: $[M + H]^+$ 497.1294; found 497.1299.

4-(4-Bromophenyl)-2-{[4-(4-bromophenyl)-6-(trifluoromethyl)pyrimidin-2-yl]methyl}-1,1,1-trifluorobut-3-yn-2-ol 4e

Light yellow oil, yield 23 mg (15%). ^{1}H NMR ($CDCl_3$): 3.75 (s, 2H, CH_2), 6.34 (s, 1H, OH), 7.13 (d, *J* = 8.3 Hz, 2H, Ar), 7.36 (d, *J* = 8.3 Hz, 2H, Ar), 7.68 (d, *J* = 8.4 Hz, 2H, Ar), 7.94 (s, 1H, C^5H), 7.98 (d, *J* = 8.4 Hz, 2H, Ar). ^{13}C NMR ($CDCl_3$): 43.4 (CH_2), 71.5 (q, *J* = 32.6 Hz, C(OH)), 84.8 (C≡CAr), 86.3 (C≡CAr), 111.2 (C^5), 120.5 (q, *J* = 275.5 Hz, C^6CF_3), 123.5 (q, *J* = 284.4 Hz, C(OH)CF_3), 120.2, 123.9, 128.1, 129.2, 131.8, 133.0, 133.5, 133.7 (Ar), 156.8 (q, *J* = 36.6 Hz, C^6), 166.1 (C^4), 167.4 (C^2) ^{19}F NMR ($CDCl_3$): -70.3, -81.4. IR (film, cm^{-1}): *v* 1186 (C-F), 1549 (C^2=N-C^4=C^5), 1591 (C^6=N) 2239 (C≡C), 3363 (OH). MS (EI) *m/z* (relative intensity, %): 506 (18, M^++2), 505 (63, M^++1), 504 (28, M^+), 503 (100), 419 (15), 417 (26), 272 (11), 217 (12), 165 (21), 163 (62), 137 (13), 135 (12), 101 (14), 99 (16), 75 (17). Calcd for $C_{22}H_{12}Br_2F_6N_2O$: C 44.47; H 2.04. Found C 44.76; H 2.18.

1-Ethynyl-4-methtoxybenzene 5

^{1}H NMR ($CDCl_3$): 2.98 (s, 1H, C≡CH), 3.79 (s, 3H, CH_3), 6.83 (d, *J* = 8.7 Hz, 2H, Ar), 7.42 (d, *J* = 8.7 Hz, 2H, Ar). ^{13}C NMR ($CDCl_3$): 55.4 (CH_3), 76.0 (C≡CAr), 83.8 (C≡CAr), 114.1, 114.4, 133.8, 160.1 (Ar). The NMR data are in agreement with those in the literature.[25]

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References

1. For recent reviews, see: (a) *Modern Synthesis Processes and Reactivity of Fluorinated Compounds. Progress in Fluorine Science*, 1st Edition, eds. H. Groult, F. R. Leroux and A. Tressaud Academic Press, London, **2017**, 760 pp.; (b) V. Gouverneur, K. Seppelt. *Chem. Rev*. **2015**, *115*, 563-565; (c) M. Shimizu, T. Hiyama, *Angew. Chem. Int. Ed*. **2005**, *44*, 214-231.

2. A. Togni, *Adv. Synth. Catal*. **2010**, *352*, 2689-2690.

3. (a) A. Yu. Rulev, A. R. Romanov. *RSC Adv*. **2016**, *6*, 1984-1998; (b) *Fluorine in Heterocyclic Chemistry*, ed. V. G. Nenajdenko, Springer, **2014**, V.1, 681 pp; V.2, 760 pp.; (c) *Fluorinated Heterocyclic Compounds: Synthesis, Chemistry, and Applications*, ed. V. A. Petrov, Wiley: New

Jersey, **2009**, 515 pp.; (d) *Fluorinated Heterocycles*, eds. A. A. Gakh, K. L. Kirk, ACS Symposium Series, Oxford University Press/American Chemical Society, Washington, DC, **2009**, 360 pp.

4. C. Heidelberger, N. K. Chaudhuri, P. Danneberg, D. Mooren, L. Griesbach, R. Duschinsky, R. J. Schnitzer, E. Pleven, J. Scheiner. *Nature* **1957**, *179*, 663-666.

5. (a) A. Yu. Rulev, V. M. Muzalevskiy, E. V. Kondrashov, I. A. Ushakov, A. R. Romanov, V. N. Khrustalev, V. G. Nenajdenko. *Org. Lett.* **2013**, *15*, 2726-2729; (b) V. M. Muzalevskiy, Yu. A. Ustynyuk, I. P. Gloriozov, V. A. Chertkov, A. Yu. Rulev, E. V. Kondrashov, A. R. Romanov, I. A. Ushakov, V. G. Nenajdenko. *Chem. Eur. J.* **2015**, *21*, 16982-16989; (c) I. P. Gloriosov, V. M Muzalevskiy, A. Yu. Rulev, E. V. Kondrashov, V. G. Nenajdenko, Yu. A. Ustynyuk. *Russ. J. Org Chem.* **2016**, *55*, 1108-1121.

6. V. M. Muzalevskiy, A. Yu. Rulev, E. V. Kondrashov, A. R. Romanov, I. A. Ushakov, V. A Chertkov, V. G. Nenajdenko. *Eur. J. Org. Chem.* **2016**, *2016*, 1612-1618.

7. A. Yu. Rulev, A. R. Romanov, E. V. Kondrashov, I. A. Ushakov, A. V. Vaschenko, V. M Muzalevskiy, V. G. Nenajdenko. *J. Org. Chem.* **2016**, *81*, 10029-10034.

8. For selected recent reviews, see: (a) T. P. Selvam, C. R. James, P. V. Dniandev, S. K. Valzita. *Res Pharm.* **2012**, *2*, 1-9; (b) V. Yerragunta, P. Patil, V. Anusha, T. KumaraSwamy, D. Suman, T Samhitha. *PharmaTutor*, **2013**, *1*, 39-44; (c) R. Meguru, S. Garimella, D. Balla, K. Sambaru. *Int. J PharmTech. Res*. **2015**, *8*, 88-93.

9. J. P. Bégué, D. Bonnet-Delpon, In: *Bioorganic and Medicinal Chemistry of Fluorine*, John Wiley & Sons, Hoboken, **2008**, 366 pp.

10. For a recent review on the strategies for the pyrimidine synthesis, see: M. D. Hill, M Mavossaghi. *Chem. Eur. J.* **2008**, *14*, 6836-6844, and references therein.

11. A. Kotljarov, R. A. Irgashev, V. O. Iaroshenko, D. V. Sevenard, V. Ya. Sosnovskikh. *Synthesis* **2009**, 3233-3242.

12. I. L. Dalinger, I. A. Vatsadse, S. A. Shevelev, A. V. Ivachtchenko. *J. Comb. Chem*. **2005**, *7*, 236 245.

13. K. Funabiki, H. Nakamura, M. Matsui, K. Shibata. *Synlett* **1999**, 756-758.

14. M. Kawase, M. Hirabayashi, S. Saito, K. Yamamoto. *Tetrahedron Lett*. **1999**, *40*, 2541-2544.

15. H. G. Bonacorso, G. P. Bortolotto, J. Navarini, L. M. F. Porte, C. W. Wiethan, N. Zanatta, M. A. P. Martins, A. F. C. Flores. *J. Fluorine Chem.* **2010**, *131*, 1297-1301.

16. R. Saijo, G. Watanabe, K. Kurihara, M. Kawase. *Heterocycles* **2014**, *89*, 2334-2345.

17. P. Bannwarth, A. Valleix, D. Grée, R. Grée. *J. Org. Chem.* **2009**, *74*, 4646-4649.

18. V. M. Muzalevskiy, A. Yu. Rulev, A. R. Romanov, E. V. Kondrashov, I. A. Ushakov, V. A. Chertkov, V. G. Nenajdenko. *J. Org. Chem.* **2017**, *82*, in press.

19. A. R. Romanov, A. Yu. Rulev, I. A. Ushakov, V. M. Muzalevskiy, V. G. Nenajdenko. *Mendeleev Comm*. **2014**, *24*, 269-271.

20. M. C. Bagley, D. D. Hughes, P. H. Taylor. *Synlett* **2003**, 259-261.

21. E. Yu. Schmidt, I. V. Tatarinova, N. I. Protsuk, I. A. Ushakov, B. A. Trofimov. *J. Org. Chem* **2017**, *82*, 119-125.

22. a) S. F. Vasilevsky, M. P. Davydova, V. I. Mamatuyk, N. V. Pleshkova, D. S. Fadeev, I. V Alabugin. *Mendeleev Comm*. **2015**, *25*, 377-379; b) M. P. Davydova, S. F. Vasilevsky, V.G Nenajdenko. *J. Fluor. Chem.* **2016**, 190, 61-67.

23. P. A. Clarke, S. Santos, W. H. C. Martin. *Green Chem*. **2007**, *9*, 438-440.

24. C. Liu, Z. Cui, X. Yan, Z. Qi, M. Ji, X. Li. *Molecules* **2016**, *21*, 828/1-828/16.

25. A. Rosiak, W. Frey, J. Christoffers. *Eur. J. Org. Chem.* **2006**, *2006*, 4044–4054.

10.1002/ejoc.201700727

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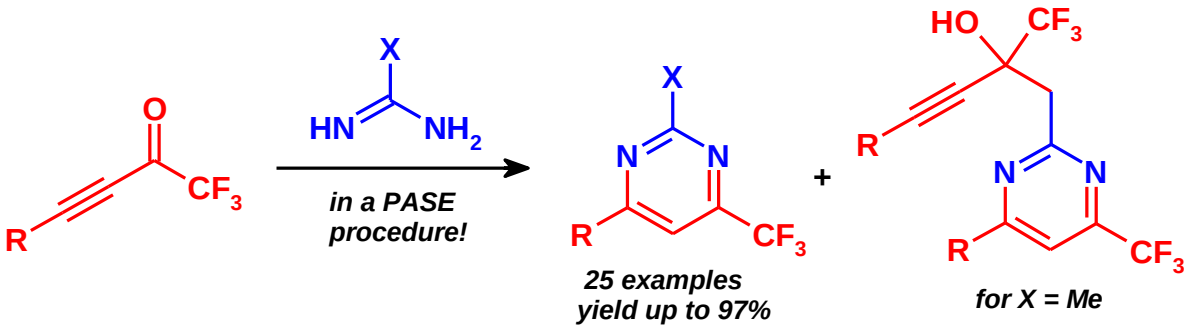

The use of CF_3-ynones as fluorine-containing building blocks is shown to be a convenient approach to fluorinated pyrimidines. The PASE methodology of their assembly proved to be efficient, simple, and applicable to a variety of acetylenic ketones and 1,3-binucleophiles.

Key topic

Nitrogen heterocycles