One-pot Synthesis of N^2-Aminoprotected 6-Substituted and Cycloalka[*d*] 4-Trifluoromethyl-2-acetylaminopyrimidines

Helio G. Bonacorso,* Adriana Ferla, Cleber A. Cechinel, Nilo Zanatta and Marcos A. P. Martins

Núcleo de Química de Heterociclos (NUQUIMHE), Departamento de Química, Universidade Federal de Santa Maria, 97105-900, Santa Maria, RS, Brasil. (E-mail: heliogb@base.ufsm.br)

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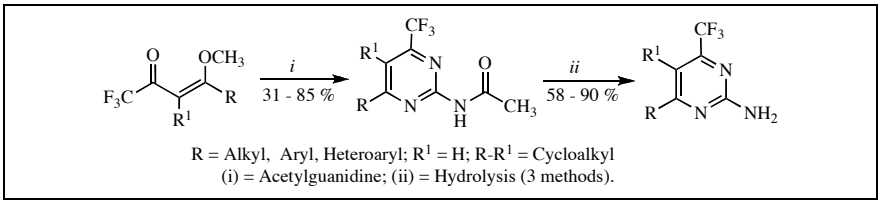

R = Alkyl, Aryl, Heteroaryl; R^1 = H; R-R^1 = Cycloalkyl
(i) = Acetylguanidine; (ii) = Hydrolysis (3 methods).

The one-pot synthesis of a novel series of amino-protected 6-alkyl-, 6-aryl-, 6-heteroaryl- and 5,6-fused-cycloalkane 4-trifluoromethyl-2-acetylaminopyrimidines, where alkyl = Me; aryl = Ph, 4-CH_3Ph, 4-FPh, 4-ClPh, 4-BrPh, 4-OCH_3Ph, 4-NO_2Ph, 4,4'-biphenyl, 1-naphthyl; heteroaryl = 2-thienyl, 2-furyl and cycloalkyl = *c*-C_6H_4, *c*-C_7H_5 from the reaction of substituted 4-methoxy-1,1,1-trifluoroalk-3-en-2-ones with 1-acetylguanidine in acetonitrile or propan-2-ol as solvent, is reported. The acetylamino group of 2-acetylaminopyrimidines was hydrolyzed under three different conditions to afford the corresponding free 2-aminopyrimidines.

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INTRODUCTION

Over the past 50 years numerous pyrimidines have been prepared and their pharmacology evaluated. Various 2-amino-4-substituted-5-alkylpyrimidines were reported to have diuretic activity and, in addition, numerous 2-amino-pyrimidines have exhibited bacteriostatic, fungicidal and antiviral activity [1].

The two problems in attempting to synthesize *N*-substituted pyrimidines are the regioselective introduction of the desired *N*-substituent and the unequivocal determination of the position of the substituent. The solution to these problems has been well explored by protection amines and has been documented successfully by many groups [2].

Although, the *N*-acetylation reaction of amino-pyrimidines is the most studied and widely used method [3], the pivaloyl group, an amine protecting group, has often been used during the synthesis of 2-amino-4(3*H*)-pyrimidinones and fused analogues such as 2-amino-4(3*H*)-quinazolinone or 2-amino-3*H*-pteridine derivatives. According to Bavetsias *et al.* [4] the pivaloyl group brings an additional benefit over other groups, such as acetyl, in that these amino protected compounds are more soluble in organic solvent and, therefore, easier to handle.

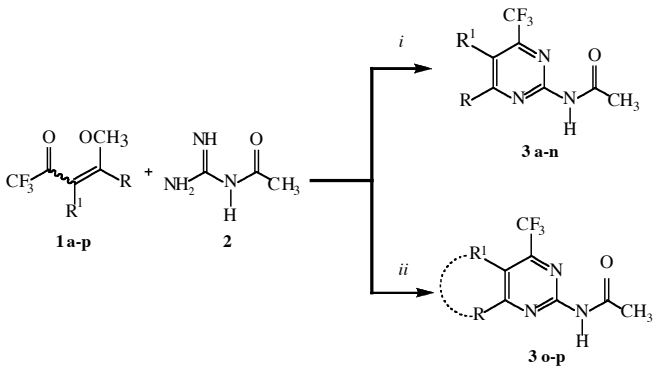
Moreover, since 2004, a simple methodology for pivalamide (trimethylacetamide) hydrolysis using $Fe(NO_3)_3.9H_2O$ in methanol at room temperature can be efficiently employed [4].

Of particular relevance to fluorine chemistry, a review of the literature has shown that the introduction of a trifluoromethyl group and higher homologue C_nF_{2n+1} substituents into a heterocycle frequently results in compounds, which display more potent activity than the parent, a fact which is probably due to the lipophilicity of the perfluoroalkyl substituents [5,6]. One of the better methods to introduce a trifluoromethyl group into heterocycles is based on the trifluoromethylated building block approach. This approach relies on the trifluoro-acetylation of enolethers or acetals to give, in an one-step and good yield, 4-alkoxy-1,1,1-trifluoroalk-3-en-2-ones (β-alkoxyvinyl trifluoromethyl ketones) which proved to be useful building blocks for the regiospecific synthesis of numerous heterocyclic compounds. Extensive studies have been devoted to the synthesis of pyrimidines and pyrimidinones from β-alkoxyvinyl trichloro(fluoro)-methyl ketones and their cyclocondensation reactions involving a variety of nitrogenated 1,3-dinucleophiles, since 1991. Studies about the regiochemistry of the reactions of these ketones with urea [7-9], *N*-methylurea [10], 2-methyl-2-thiopseudourea sulfate [11], guanidine hydrochloride [12], acetamidine and benzamidine hydrochloride [13] and *N*-methyl thiourea [14] have been developed in our research group. Recently, β-ethoxyvinyl trifluoromethyl ketone and their cycloalkane analogues, as building blocks to construct fluorine containing heterocycles, have been also widely studied and reviewed [15].

Striving for future biological evaluations, and as an extension of these findings we are now investigating the possibility of obtaining a novel series of 6-alkyl-, 6-aryl-, 6-heteroaryl- and 5,6-fused-cycloalkyl-substituted 4-trifluoromethyl-2-acetylaminopyrimidine **3** (N^2-amino-

protected pyrimidines), in a one-pot reaction using the trifluoromethylated ketones **1** and 1-acetylguanidine (**2**) in a building block approach.

Scheme I



1-4	a	b	c	d	e	f	g
R	Me	Ph	4-MePh	4-FPh	4-ClPh	4-BrPh	4-OMePh
R^1	H	H	H	H	H	H	H

1-4	h	i	j	k	l
R	4-NO_2Ph	4-ClPh	4-OMePh	4-Biphenyl	1-Naphthyl
R^1	H	Me	Me	H	H

1-4	m	n	o	p
R	2-Thienyl	2-Furyl	$-(CH_2)_4-$	$-(CH_2)_5-$
R^1	H	H		

(i) = CH_3CN, 80-85 °C, 24 h, (31-85%); (ii) = $BF_3.OEt_2$, *i*-PrOH, 80-85 °C, 20 h, (42-62%).

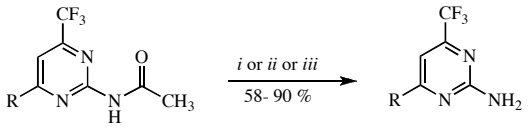
RESULTS AND DISCUSSION

The 4-alkoxy-1,1,1-trifluoroalk-3-en-2-ones (**1a-h**) were synthesized from the trifluoroacetylation reaction of the respective enolethers (**1a, 1o-p**) or acetals (**1b-n**) with trifluoroacetic anhydride according to previous publications [16,17]. The best reaction conditions, selected physical and spectral data for compounds **3** and **4** are presented in the experimental part.

The cyclocondensation reactions of compounds **1** with 1-acetylguanidine were carried out in acetonitrile (for **3a-n)** or in propan-2-ol in the presence of a catalytic amount of boron trifluoride diethyl etherate (for **3o-p**) by a procedure described in the literature [18] for similar molecules (Scheme I). The reactions were monitored by TLC and the optimal reaction time and temperature is 24 hours at 80 - 85 °C for the synthesis of **3a-n** and 20 hours at 80 – 85 ºC for **3o-p**.

An investigation of the literature demonstrated that the attainment of some acetylaminopyrimidines has been carried out in the presence of acetic anhydride under reflux conditions for approximately 2 hours. Baker *et al.* [19] carried out the *N*-acetylation reaction of 2-methylmercapto-4-amino-6-dimethylaminopyrimidine utilizing the above described reaction condition, isolating 2-methylmercapto-4-acetylamino-6-dimethylaminopyrimidine in yields of 90 %. The methodology described by Baker *et al.* [19] was used in an attempt to obtain 2-acetylaminopyrimidines **3** from 2-aminopyrimidines **4**, as described in our work. Specifically for the *N*-acetylation reaction of **4b**, the respective 2-acetylamino derivative **3b** was obtained only in a yield of 30 %. On the other hand, our results demonstrated that 2-acetylamino-4(3*H*)-pyrimidine **3b** can be obtained in a yield of 80 %, in a single reaction step from the cyclocondensation reaction of 1-acetylguanidine and 4-methoxy-4-phenyl-1,1,1-trifluorobut-3-en-2-one (**1b**).

Scheme II



3,4	a	b	e	g
R	Me	Ph	4-ClPh	4-OMePh

(i): $Fe(NO_3)_3 . 9H_2O$, MeOH, 40 °C, 24 h (58 - 90 %); (ii): NaOH 1M, EtOH, reflux, 20 h (70 - 85 %); (iii): HCl conc., EtOH, reflux, 20 h (66 - 80 %).

Since it is known that numerous 2-aminopyrimidines exhibit bacteriostatic, fungicidal, antiviral and diuretic activities [1], we attempted to perform the hydrolysis of the acetamide group of some compounds **3** using a procedure similar to that described by Bavetsias *et al.* [4]. We found that upon treatment with $Fe(NO_3)_3 \bullet 9H_2O$ in methanol for 24 h at 40 ºC, 2-acetylaminopyrimidines derivatives, **3a, 3b, 3e** and **3g**, gave the corresponding 2-aminopyrimidines, **4a, 4b**, **4e** and **4g**, in satisfactory yields (58 – 90 %). Subsequently, to obtain the above cited compounds **4**, alkaline conditions [20] [aqueous sol. of sodium hydroxide 1 *M* in ethanol (7:3) at 100 ºC for 20 hours] or acidic conditions [21] [concentrated HCl in ethanol, heating at reflux for 20 hours] were also successfully utilized for the acetamide hydrolysis, furnishing yields of 70 – 85 % and 66 – 80%, respectively. However, the hydrolysis conditions using $Fe(NO_3)_3 \bullet 9H_2O$ are milder and the work-up of these reactions was also simple and efficient (Scheme II).

NMR Spectroscopy. The unambiguous ^1H and ^{13}C NMR chemical shift assignments of pyrimidines **3** and pyrimidinones **4**, in DMSO-d_6 as solvent, were made with the help of homo- and heteronuclear 2D NMR experiments and by comparison with NMR data of other 2-pyrazolines formerly synthesized in our laboratory.

The trifluoromethylated heterocycles **3a-p** present the typical ^1H chemical shifts of pyrimidine ring protons at δ 7.56 – 8.33 (H-5). The protons of the acetylamino group showed ^1H chemical shifts at δ 10.89 – 11.13 (NH) and the methyl group at δ 2.21– 2.31 ppm.

The typical ^{13}C chemical shifts for the trifluoromethylated heterocycles **3a-p** present of pyrimidine ring carbons at δ 154.8 – 158.3 ppm (C-2), 154.3 – 155.9

(C-4, $^2J_{C\text{-}F}$ = 35), 105.7 – 120.3 (C-5), 158.5 - 169.2 (C-6) and 119.8 – 127.5 (CF_3, $^1J_{C\text{-}F}$ = 275). The carbonyl carbon of the acetylamino group showed ^{13}C chemical shifts at δ 169.0 – 170.3 ppm and the methyl group at δ 20.9 – 24.8 ppm.

We consider the one-pot reaction presented to be a useful and convenient alternative to obtain N^2-protected 4-trifluoromethylpyrimidines. In summary, the use of this methodology allowed for the isolation of a new series of trifluoromethylated 2-acetylaminopyrimidines which have been prepared in an analytically pure form and in good yields. Moreover, examples of 2-aminopyrimidine derivatives have been easily isolated by three similar methods, in good yields, for future chemical and biological studies.

EXPERIMENTAL

Unless otherwise indicated all common reagents and solvents were used as obtained from commercial suppliers without further purification. All melting points were determined on a Reichert Thermovar and on an Electrothermal Mel-Temp 3.0 apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were acquired on a Bruker DPX 400 spectrometer (^1H at 400.13 MHz and ^{13}C at 100.62 MHz) 5 mm sample tubes, 298 K, digital resolution ±0.01 ppm, in DMSO-d_6 and using TMS as internal reference. Mass spectra were registered in a HP 6890 GC connected to a HP 5973 MSD and interfaced by a Pentium PC. The GC was equipped with a split-splitless injector, autosampler, cross-linked HP-5 capillary column (30m, 0.32mm of internal diameter), and helium was used as the carrier gas. The CHN elemental analyses were performed on a Perkin Elmer 2400 CHN elemental analyser (São Paulo University - USP / Brazil).

General Procedure for the Preparation of 6-Substituted 4-Trifluoromethyl-2-acetylaminopyrimidines (3a-n). To a stirred solution of 1-acetylguanidine (0.202g, 2 mmol) in acetonitrile (5 mL) kept at room temperature (20 - 25ºC), was added pure ketone **1** (2 mmol). The mixture was stirred for 24 h at 80 - 85 ºC. After cooling (< 10°C), the crystalline solids were filtered off and recrystallized from ethyl acetate.

4-Trifluoromethyl-6-methyl-2-acetylaminopyrimidine (3a). This compound was obtained as white solid, yield 67%, mp. 117 – 119 °C. ^1H NMR (DMSO-d_6): δ = 10.89 (s, 1H, NH), 7.56 (s, 1H, H-5), 2.55 (s, 3H, CH_3), 2.21 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ = 172.3 (C=O), 169.1 (C-6), 157.8 (C-2), 154.3 (q, $^2J_{CF}$ = 35.0, C-4), 120.5 (q, $^1J_{CF}$ = 275, CF_3), 111.3 (C-5), 24.6 (CH_3), 23.9 (CH_3). MS [*m/z* (%)] for $C_8H_8F_3N_3O$ (219.06): 219 (M^+, 29), 177 (100), 150 (17). Anal. Calcd. for $C_8H_8F_3N_3O$ (219.06): C, 43.80; H, 3.68; N, 19.17%. Found: C, 43.41; H, 3.59; N, 19.07%.

4-Trifluoromethyl-6-phenyl-2-acetylaminopyrimidine (3b). This compound was obtained as white solid, yield 80%, mp. 134 – 136 °C. ^1H NMR (DMSO-d_6): δ = 11.05 (s, 1H, NH), 8.33 – 8.37 (m, 2H, ArH), 8.19 (s, 1H, H-5), 7.59 - 7.62 (m, 3H, ArH), 2.30 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ = 169.2 (C=O), 167.2 (C-6), 158.2 (C-2), 155.8 (q, $^2J_{CF}$ = 35, C-4), 134.9, 132.0, 128.8, 127.6, (6C, ArC) 120.5 (q, $^1J_{CF}$ = 275, CF_3), 107.0 (C-5), 24.8 (CH_3). MS [*m/z* (%)] for $C_{13}H_{10}F_3N_3O$ (281.08): 281 (M^+, 62), 239 (100), 69 (5). Anal. Calcd. for $C_{13}H_{10}F_3N_3O$ (281.08): C, 55.52; H, 3.58; N, 14.94%. Found: C, 55.56; H, 3.61; N, 15.09%.

4-Trifluoromethyl-6-(4-methylphenyl)-2-acetylaminopyrimidine (3c): This compound was obtained as white solid; yield 72%; mp. 159 – 161 °C. ^1H NMR (DMSO-d_6): δ = 11.01 (s, 1H, NH), 8.25 (d, 2H, ArH, *J* = 8.2), 8.14 (s, 1H, H-5); 7,39 (d, 2H, ArH, *J* = 8.2), 2.41 (s, 3H, CH_3), 2.28 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ = 169.2 (C=O), 167.0 (C-6), 158.1 (C-2), 155.7 (q, $^2J_{CF}$ = 35, C-4), 142.3, 132.1, 129.4, 127.5, (6C, ArC), 120.5 (q, $^1J_{CF}$ = 275, CF_3), 106.6 (C-5), 24.7 (CH_3), 20.9 (CH_3). MS [*m/z* (%)] for $C_{14}H_{12}F_3N_3O$ (295.09): 295 (M^+, 48), 253 (100), 238 (14).Anal. Calcd. for $C_{14}H_{12}F_3N_3O$ (295.09): C, 56.95; H, 4.10; N, 14.23%. Found: C, 56.72; H, 3.84; N,14.24%.

4-Trifluoromethyl-6-(4-fluorophenyl)-2-acetylaminopyrimidine (3d). This compound was obtained as white solid; yield 55%; mp. 154 – 156 °C. ^1H NMR (DMSO-d_6): δ = 10.99 (s, 1H, NH), 8.39-8.43 (m, 2H, ArH), 8.17 (s, 1H, H-5), 7.39-7.44 (m, 2H, ArH), 2.29 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ = 169.1 (C=O), 166.0 (1C, ArC), 163.2 (C-6), 158.04 (C-2), 155.9 (q, $^2J_{CF}$ = 35, C-4), 131.4, 130.3, 130.2, 116.4, 115.8, (5C, ArC), 127.5 (q, $^1J_{CF}$= 275, CF_3), 106.9 (C-5), 24.7 (CH_3). MS [*m/z* (%)] for $C_{13}H_9F_4N_3O$ (299.07): 299 (M^+,43), 257 (100), 146 (19). Anal. Calcd. for $C_{13}H_9F_4N_3O$ (299.07): C, 52.18; H, 3.03; N, 14.04%. Found: C, 51.95; H, 2.85; N, 13.76%.

4-Trifluoromethyl-6-(4-chlorophenyl)-2-acetylaminopyrimidine (3e). This compound was obtained as white solid; yield 80%; mp. 161 – 163 °C. ^1H NMR (DMSO-d_6): δ = 11.07 (s, 1H, NH), 8.37 (d, 2H, ArH, *J* = 8.3), 8.21 (s, 1H, H-5), 7.65 (d, 2H, ArH, *J* = 7.5), 2.28 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ = 169.1 (C=O), 165.9 (C-6), 158.1 (C-2), 155.9 (q, $^2J_{CF}$=35, C-4), 137.0, 133.7, 129.3, 128.9 (6C, ArC), 119.8 (q, $^1J_{CF}$ = 275, CF_3), 107.0 (C-5), 24.7 (CH_3). MS [*m/z* (%)] for $C_{13}H_9ClF_3N_3O$ (315.04): 315 (M^+,38), 273 (100), 162 (14). Anal. Calcd. for $C_{13}H_9ClF_3N_3O$ (315.04): C, 49.46; H, 2.87; N, 13.31%. Found: C, 49.36; H, 2.88; N,13.11%.

4-Trifluoromethyl-6-(4-bromophenyl)-2-acetylaminopyrimidine (3f). This compound was obtained as white solid; yield 85%; mp. 168 – 170 °C. ^1H NMR (DMSO-d_6): δ = 11.08 (s, 1H, NH), 8.30 (d, 2H, ArH, *J* = 8.8), 8.2 (s, 1H, H-5), 7.80 (d, 2H, ArH, *J* = 8.8), 2.27 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ = 169.0 (C=O), 166.0 (C-6), 158.1 (C-2), 155.9 (q, $^2J_{CF}$ = 35, C-4), 134.0, 131.9, 129.5, 126.0, (6C, ArC), 120.4 (q, $^1J_{CF}$ = 275.5, CF_3), 107.0 (C-5), 24.7 (CH_3). MS [*m/z* (%)] for $C_{13}H_9BrF_3N_3O$ (359.49): 359 (M^+, 48), 317 (100). Anal. Calcd. for $C_{13}H_9BrF_3N_3O$ (359.49): C, 43.36; H, 2.52; N, 15.83. Found: C, 43.06; H, 2.40; N, 15.49%.

4-Trifluoromethyl-6-(4-methoxyphenyl)-2-acetylaminopyrimidine (3g). This compound was obtained as white solid; yield 85%; mp. 133 – 135 °C. ^1H NMR (DMSO-d_6): δ = 10.94 (s, 1H, NH), 8.33 (d, 2H, ArH, *J* = 8.8), 8.10 (s, 1H, H-5), 7.12 (d, 2H, ArH, *J* = 9.0), 3.87 (s, 3H, OCH_3), 2.28 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ = 169.4 (C=O), 166.7 (1C, ArC), 162.6 (C-6), 158.1 (C-2), 155.6 (q, $^2J_{CF}$ = 35, C-4), 129.5, 128.9, 114.3, (5C, ArC), 120.7 (q, $^1J_{CF}$ = 275, CF_3), 106.2 (C-5), 55.4 (OCH_3), 24.9 (CH_3). MS [*m/z* (%)] for $C_{14}H_{12}F_3N_3O_2$ (311.09): 311 (M^+, 57), 269 (100), 254 (14). Anal. Calcd. for $C_{14}H_{12}F_3N_3O_2$ (311.09): C, 54.02; H, 3.89; N, 13.50%. Found: C, 54.10; H, 3.61; N, 13.25%.

4-Trifluoromethyl-6-(4-nitrophenyl)-2-acetylaminopyrimidine (3h). This compound was obtained as white solid; yield 53%; mp. 184 – 186 °C. ^1H NMR (DMSO-d_6): δ = 11.16 (s, 1H, NH), 8.57 (d, 2H, ArH, *J* = 8.8), 8.57 (d, 2H, ArH, *J* = 8.8), 8.42

(s, 1H, H-5), 2.28 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ = 169.0 (C=O), 164.8 (C-6), 158.1 (C-2), 156.4 (q, $^2J_{CF}$ = 35, C-4), 149.2, 140.5, 128.8, 123.7, (6C, ArC), 120.3 (q, $^1J_{CF}$ = 275, CF_3), 108.0 (C-5), 24.7 (CH_3). MS [*m/z* (%)] for $C_{13}H_9F_3N_4O_3$ (326.06): 326 (M^+,24), 284 (100), 238 (19). Anal. Calcd. for $C_{13}H_9F_3N_4O_3$ (326.06): C, 47.86; H, 2.78; N, 17.17%. Found: C, 47.76; H, 2.46; N, 17.02%.

4-Trifluoromethyl-5-methyl-6-(4-chlorophenyl)-2-acetylaminopyrimidine (**3i**). This compound was obtained as white solid; yield 39%; mp. 158 – 160 °C. ^1H NMR (DMSO-d_6): δ = 10.95 (s, 1H, NH), 7.70 (d, 2H, ArH, *J* = 8.8), 7.62 (d, 2H, ArH, *J* = 8.8), 2.33 (s, 3H, CH_3), 2.21 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ = 169.2 (C=O), 169.0 (C-6), 155.0 (C-2), 153.4 (q, $^2J_{CF}$ = 33.1, C-4), 135.6, 134.8, 131.1, 128.4, (6C, ArC), 123.1 (q, $^1J_{CF}$ = 277, CF_3), 118.3 (C-5), 24.6 (CH_3), 13.8 (CH_3). MS [*m/z* (%)] for $C_{14}H_{11}F_3N_3O_2$ (329.11): 329 (M^+,24), 286 (100). Anal. Calcd. for $C_{14}H_{11}F_3N_3O_2$ (329.11): C, 51.00; H, 3.36; N, 12.74%. Found: C, 50.88; H, 2.99; N, 12.69%.

4-Trifluoromethyl-5-methyl-6-(4-methoxyphenyl)-2-acetylaminopyrimidine (**3j**). This compound was obtained as white solid; yield 36%; Mp. 145 – 147 °C. ^1H NMR (DMSO-d_6): δ = 10.84 (s, 1H, NH), 7.66 (d, 2H, ArH, *J* = 8.8), 7.09 (d, 2H, ArH, *J* = 8.8), 3.85 (s, 3H, OCH_3), 2.36 (s, 3H, CH_3), 2.23 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ = 169.5 (C=O), 169.2 (C-6), 160.0 (ArC), 155.0 (C-2), 153.2 (q, $^2J_{CF}$ = 34, C-4), 131.0, 128.9, 113.6, 113.1 (5C, ArC), 121.4 (q, $^1J_{CF}$ = 277, CF_3), 119.8 (C-5), 55.2 (OCH_3), 24.5 (CH_3), 13.9 (CH_3). MS [*m/z* (%)] for $C_{15}H_{14}F_3N_3O_2$ (325.29): 325 (M^+,71), 283 (100). Anal. Calcd. for $C_{15}H_{14}F_3N_3O_2$ (325.29): C, 55.39; H, 4.34; N, 12.92%. Found: C, 55.23; H, 4.33; N, 12.90%.

4-Trifluoromethyl-6-biphenyl-2-acetylaminopyrimidine (**3k**). This compound was obtained as white solid; yield 70%; mp. 186 – 188 °C. ^1H NMR (DMSO-d_6): δ = 11.06 (s, 1H, NH), 8.43-8.47 (d, 2H, ArH, *J* = 8.5), 8.25 (s, 1H, H-5), 7.88-7.92 (d, 2H, ArH, *J* = 8.5), 7.78-7.83 (m, 2H, ArH), 7.74-7.57 (m, 3H, ArH), 2.30 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ = 169.2 (C=O), 166.7 (C-6), 158.1 (C-2). 155.0 (q, $^2J_{CF}$ = 35, C-4), 143.6, 138.8, 133.8, 128.9, 128.2, 128.1, 127.0, 126.7 (12C, ArC), 120.7 (q, $^1J_{CF}$ = 275, CF_3), 107.0 (C-5), 24.8 (CH_3). MS [*m/z* (%)] for $C_{19}H_{14}F_3N_3O$ (357.11): 357 (M^+,62), 315 (100). Anal. Calcd. for $C_{19}H_{14}F_3N_3O$ (357.11): C, 63.86; H, 3.95; N, 11.76%. Found: C, 63.53; H, 3.97; N, 11.70%.

4-Trifluoromethyl-6-naphthyl-2-acetylaminopyrimidine (**3l**). This compound was obtained as white solid; yield 35%; mp. 127 – 128 °C. ^1H NMR (DMSO-d_6): δ = 11.13 (s, 1H, NH), 8.50-8.52 (m, 1H, ArH), 8.12 - 8.14 (d, 1H, ArH, *J* = 8.3), 8.03 - 8.05 (m, 1H, ArH), 7.89 (s, 1H, H-5), 7.86-7.88 (d, 2H, ArH, *J* = 8.0), 7.65-7.67 (d, 1H, ArH, *J* = 7.6), 7.59-7.67 (m, 2H, ArH), 2.31 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ = 170.1 (C=O), 169.2 (C-6), 157.8 (C-2), 155.4 (q, $^2J_{CF}$ = 35, C-4), 134.0, 133.4, 131.0, 129.8, 128.9, 128.4, 127.2, 126.9, 125.8, 125.2 (10C, ArC), 120.3 (q, $^1J_{CF}$ = 275, CF_3), 111.9 (C-5), 24.7 (CH_3). MS [*m/z* (%)] for $C_{17}H_{12}F_3N_3O$ (331.29): 331 (M^+, 62), 288 (100), 220 (52). Anal. Calcd. for $C_{17}H_{12}F_3N_3O$ (331.29): C, 61.63; H, 3.65; N, 12.68%. Found: C, 61.87; H, 3.68; N, 12.87%.

4-Trifluoromethyl-6-(2-thienyl)-2-acetylaminopyrimidine (**3m**). This compound was obtained as white solid; yield 48%; mp. 143 – 145 °C. ^1H NMR (DMSO-d_6): δ = 8.34 (d, 1H, ArH, *J* =3.9), 8.13 (s, 1H, H-5), 7.95 (d, 1H, ArH, *J* = 4.9), 7.30 (t, 1H, ArH, *J* = 4.4), 2.29 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ = 169.5 (C=O), 162.2 (C-6), 158.1 (C-2), 155.5 (q, $^2J_{CF}$ = 35, C-4), 128.9, 130.9, 132.9, 140.7, (4C, Thienyl), 120.5 (q, $^1J_{CF}$ = 275, CF_3), 105.7 (C-5), 24.9 (CH_3). MS [*m/z* (%)] for $C_{11}H_8SF_3N_3O$ (287.03): 287 (M^+,67), 245 (100), 69 (5). Anal. Calcd. for $C_{11}H_8SF_3N_3O$ (287.03): C, 45.99; H, 2.81; N, 14.63%. Found: C, 45.90; H, 2.53; N, 14.60%.

4-Trifluoromethyl-6-(2-furyl)-2-acetylaminopyrimidine (**3n**). This compound was obtained as white solid; yield 52%; mp. 126 – 128 °C. ^1H NMR (DMSO-d_6): δ = 8.07 (s, 1H, ArH), 7.79 (s, 1H, H-5), 7.60 (d, 1H, ArH, *J* = 2.5), 6.82 (t, 1H, ArH, *J* =1.8), 2.28 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ = 170.0 (C=O), 158.5 (C-6), 158.3 (C-6), 155.5 (q, $^2J_{CF}$ = 35, C-4), 150.2, 147.7, 115.7, 113.5 (4C, Furyl), 120.5 (q, $^1J_{CF}$ = 275, CF_3), 105.3 (C-5), 25.0 (CH_3). MS [*m/z* (%)] for $C_{11}H_8F_3N_3O_2$ (271.08): 271 (M^+,71), 229 (100). Anal. Calcd. for $C_{11}H_8F_3N_3O_2$ (271.08): C, 48.72; H, 2.97; N, 15.49%. Found: C, 48.96; H, 3.01; N, 15.66%.

General Procedure for the Preparation of Fused-cycloalkane 4-Trifluoromethyl-2-acetylaminopyrimidines (**3o-p**). To a stirred solution of 1-acetylguanidine (0.707g, 7 mmol) in propan-2-ol (10 mL) kept at room temperature (20 - 25ºC), was added pure ketone **1** (5 mmol) and boron trifluoride diethyl etherate (sol. 45% in MeOH) (10 drops). The mixture was stirred for 20 h at 80 - 85 ºC. After cooling (< 10°C), the crystalline solids were filtered off, washed with propan-2-ol to remove the residual 1-acetylguanidine and recrystallized from ethyl acetate.

4-Trifluoromethyl-5,6,7,8-tetrahydro-2-acetylaminoquinazoline (**3o**). This compound was obtained as white solid; yield 42%; mp. 152 – 154 °C. ^1H NMR (DMSO-d_6): δ = 10.74 (s, 1H, NH), 2.82 (m, 4H, $2CH_2$), 2.18 (s, 3H, CH_3), 1.81 (s, 4H, $2CH_2$). ^{13}C NMR (DMSO-d_6): δ = 171.3 (C=O), 169.2 (C-8a), 154.8 (C-2), 151.8 (q, $^2J_{CF}$ = 33, C-4), 121.4 (q, $^1J_{CF}$ = 277, CF_3), 127.6 (C-4a), 31.0 (CH_2), 26.5 (CH_2), 26.3 (CH_2), 25.4 (CH_2), 25.1 (CH_2), 24.9 (CH_3). MS [*m/z* (%)] for $C_{11}H_{12}F_3N_3O$ (259.23): 259 (M^+,24), 216 (100), 189 (43). Anal. Calcd. for $C_{11}H_{12}F_3N_3O$ (259.23): C, 50.97; H, 4.67; N, 16.21%. Found: C, 51.07; H, 4.71; N, 16.30%.

4-Trifluoromethyl-6,7,8,9-tetrahydro-5*H*-cyclohepta[*d*]-2-acetylaminopyrimidine (**3p**). This compound was obtained as white solid; yield 62%; mp. 167 – 169 °C. ^1H NMR (DMSO-d_6): δ = 10.75 (s, 1H, NH), 3.05 (m, 2H, CH_2), 2.84 (m, 2H, CH_2), 2.19 (s, 3H, CH_3), 1.82 (m, 2H, CH_2), 1.64 (m, 2H, CH_2), 1.61 (m, 2H, CH_2). ^{13}C NMR (DMSO-d_6): δ = 177.0 (C=O), 169.2 (C-9a), 154.8 (C-2), 150.2 (q, $^2J_{CF}$=35, C-4), 121.5 (q, $^1J_{CF}$ =275, CF_3), 127.6 (C-4a), 31.0 (CH_2), 26.5 (CH_2), 26.3 (CH_2), 25.4 (CH_2), 25.1 (CH_2), 24.9 (CH_3). MS [*m/z* (%)] for $C_{12}H_{14}F_3N_3O$ (273.25): 273 (M^+, 29), 231 (100), 203 (29). Anal. Calcd. for $C_{12}H_{14}F_3N_3O$ (273.25): C, 52.75; H, 5.16; N, 15.38%. Found: C, 52.69; H, 5.12; N, 15.62%.

General Procedures for the Preparation of 6-Substituted 4-Trifluoromethyl-2-aminopyrimidines (4a, 4b, 4e, 4g).

Method A [4]. To a stirred solution of acetylaminopyrimidines **3** (2 mmol) in methanol (20 mL) kept at room temperature (20 - 25ºC), was added in one portion $Fe(NO_3)_3$•$9H_2O$ (0.2 mmol, 0.08g). The mixture was stirred for 24 h at 40 ºC. After cooling (< 5°C), the crystalline solids were collected by filtration and recrystallized from ethanol (58 – 90 % yields).

Method B [20]. To a stirred solution of acetylaminopyrimidines **3** (2 mmol) in ethanol (15 mL) kept at room temperature (20 - 25ºC), was added, in one portion, concentrated HCl (15 mL). The mixture was refluxed for 20 h. After cooling (< 5°C), the reaction was neutralized with an aqueous solution of

NaOH (50% w/v). The solids were collected by filtration, washed with ice-water (20 mL), dried under reduced pressure in a P_2O_5 dessicator and recrystallized from ethanol (66 – 80 % yields).

Method C [21]. To a stirred solution of acetyl-aminopyrimidines **3** (2 mmol) in a mixture of ethanol:water (7:3) (10 mL) kept at room temperature (20 - 25ºC), was added in one portion NaOH (1 *M*, 10 mL). The mixture was refluxed for 20 h. After cooling (< 5°C), the reaction was neutralized with 37% HCl. The solids were collected by filtration, washed with ice-water (20 mL), dried under reduced pressure in a P_2O_5 dessicator and recrystallized from ethanol (70 – 85 % yields).

4-Trifluoromethyl-6-methyl-2-aminopyrimidine (**4a**). This compound was obtained as white solid, yield 58 % (A), 66 % (B), 70 % (C), mp. 127 – 129 ºC (mp. 129 ºC, lit. [22]). ^{1}H NMR (DMSO-d_6): δ = 7.21 (s, 2H, NH_2), 6.88 (s, 1H, H5), 2.36 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ = 171.9 (C-6), 163.6 (C-2), 154.7 (q, $^2J_{CF}$ =34, C-4), 120.9 (q, $^1J_{CF}$ =275, CF_3), 105.2 (C-5), 24.7 (CH_3). MS [*m/z* (%)] for $C_6H_6N_3F_3$ (177.05) = 177(M^+, 100), 158 (27), 108 (40), 69 (60).

4-Trifluoromethyl-6-phenyl-2-aminopyrimidine (**4b**). This compound was obtained as white solid, yield 90 % (A), 80 % (B), 76 % (C), mp. 130 – 132 °C (mp. 133 – 133.5 ºC, lit. [22]). ^{1}H NMR (DMSO-d_6): δ = 8.16 – 8.21 (m, 2H, ArH), 7.56 – 7.57 (m, 3H, ArH), 7.52 (s, 1H, H5), 7.40 (s, 2H, NH_2). ^{13}C NMR (DMSO-d_6): δ = 166.9 (C-6), 163.9 (C-2), 156.1 (q, $^2J_{CF}$ = 34, C-4), 135.9, 131.3, 129.1, 128.7 (6C, ArC), 120.1 (q, $^1J_{CF}$ =275, CF_3), 100.8 (C-5). MS [*m/z* (%)] for $C_{11}H_8N_3F_3$ (239.07) = 239 (M^+, 100), 218 (14), 128 (27), 77 (17).

4-Trifluoromethyl-6-(4-chlorophenyl)-2-aminopyrimidine (**4e**). This compound was obtained as white solid, yield 86 % (A), 77 % (B), 83 % (C), mp. 181 – 183 °C. ^{1}H NMR (DMSO-d_6): δ = 8.20 – 8.24 (d, 2H, ArH), 7.57 – 7.59 (d, 2H, ArH), 7.63 (s, 1H, H5), 7.43 (s, 2H, NH_2). ^{13}C NMR (DMSO-d_6): δ = 165.7 (C-6), 163.9 (C-2), 156.3 (q, $^2J_{CF}$ = 34, C-4), 136.3, 134.6, 128.9, 128.8 (6C, ArC), 120.1 (q, $^1J_{CF}$ =275.4, CF_3), 100.7 (C-5). MS [m/z (%)] for $C_{11}H_7N_3F_3Cl$ (273.03) = 273 (M^+, 100), 252 (12), 162 (20), 75 (15). Anal. Calcd. for $C_{11}H_7ClF_3N_3$ (273.03): C, 48.28; H, 2.58; N, 15.36%. Found: C, 48.40; H, 2.64; N, 15.51%.

4-Trifluoromethyl-6-(4-methoxyphenyl)-2-aminopyrimidine (**4g**). This compound was obtained as white solid, yield 81 % (A), 76 % (B), 85 % (C), mp. 192 – 193 °C. ^{1}H NMR (DMSO-d_6): δ = 8.16 - 8.20 (d, 2H, ArH), 7.48 (s, 1H, H5), 7.29 (s, 2H, NH_2), 7.06 - 7.10 (d, 2H, ArH), 3.85 (OCH_3). ^{13}C NMR (DMSO-d_6): δ = 166.4 (C-6), 163.8 (C-2), 162.0 (ArC), 155.8 (q, $^2J_{CF}$ = 34, C-4), 128.9, 128.1, 114.1 (5C, ArC), 120.8 (q, $^1J_{CF}$ = 275, CF_3), 100.0 (C-5), 55.3 (OCH_3). MS [*m/z* (%)] for $C_{12}H_{10}N_3F_3O$ (269.23) = 269 (M^+, 100), 254 (7), 206 (12), 92 (6). Anal. Calcd. for $C_{12}H_{10}F_3N_3O$ (269.23): C, 53.54; H, 3.74; N, 15.61%. Found: C, 53.72; H, 3.80; N, 15.79%.

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* Author to whom correspondence should be addressed (E-mail: heliogb@base.ufsm.br).

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