Synthesis V. P. Andrade et al. Paper

Regioselective Synthesis of 5-(Trifluoromethyl)[1,2,4]triazolo[1,5-*a*]pyrimidines from β-Enamino Diketones

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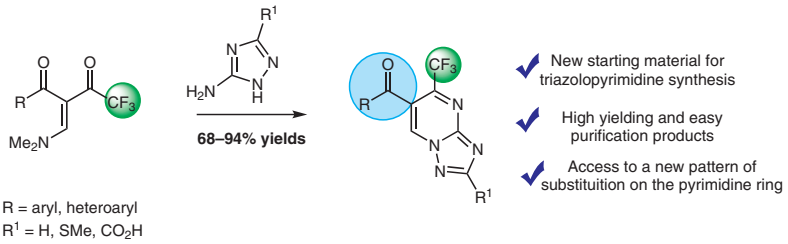

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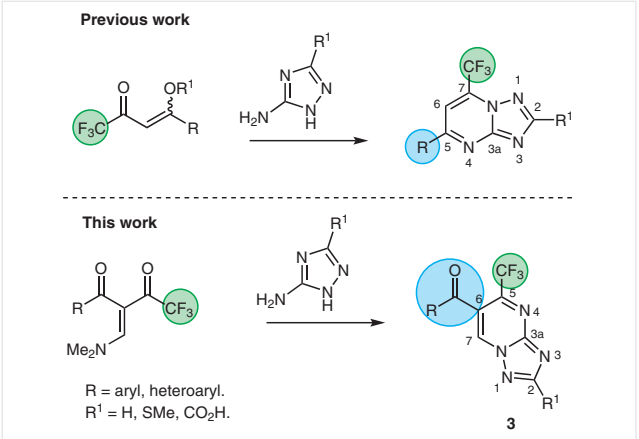
Abstract The use of β-enamino diketones as an easy entry to the regioselective synthesis of [1,2,4]triazolo[1,5-*a*]pyrimidines is reported. These ketones reacted with 3-amino-1*H*-1,2,4-triazoles to furnish exclusively 6-substituted 5-(trifluoromethyl)[1,2,4]triazolo[1,5-*a*]pyrimidines in yields of up to 95%. The regioselectivity of the reactions performed was maintained regardless of the substituent in the starting ketone or aminoazole.

Key words β-enamino diketones, 1,3-diones, triazolopyrimidines, aminotriazoles, fluorinated heterocycles

Due to their extensive biological, pharmacological, and agricultural applications, the triazolopyrimidine scaffold and its derivatives are an important class of compounds.[1–4] Despite the extensive results that have been reported regarding the synthesis of compounds containing these pyrimidine–azole-fused heterocycles, there are few reports regarding those bearing a trifluoromethyl group. Since it is widely known that the insertion of fluorinated groups (e.g., CF_3) can affect the chemical, physical, and biochemical properties of a targeted molecule, the development of new and efficient synthetic routes for these compounds is still a challenge to be explored.[5–9]

A common strategy for the synthesis of the triazolopyrimidine scaffold involves the cyclocondensation reaction of 1,3-dielectrophilic compounds, such as α,β-unsaturated ketones[10–13] and 1,3-dicarbonyl compounds,[14,15] with 3-amino-1*H*-1,2,4-triazoles. Although these starting materials are suitable for the synthesis of the targeted products, they usually furnish regioisomeric mixtures, with lengthy purification steps and low-yielding products.[16–18] In our search for ways to overcome these drawbacks, our research group recently reported the preparation of 7-(trifluoromethyl)[1,2,4]triazolo[1,5-*a*]pyrimidines, from β-alkoxyvinyl trifluoromethyl ketones (enones) and the aforementioned aminoazoles, in very good yields (see Scheme 1).[19] In this previous study, it was shown that the reaction of 4-substituted enones and 3-aminotriazoles furnished exclusively 5-substituted 7-(trifluoromethyl)triazolopyrimidines. In this present study, the same reaction using β-enamino diketones furnished only 6-substituted 5-(trifluoromethyl)triazolopyrimidines (Scheme 1).



Scheme 1 Comparison of the previously reported and present studies

In turn, β-enamino diketones (in which $R^1 = CO_2Et$, see Scheme 2) have proven to be suitable starting materials to prepare pyrazoles,[20] isoxazoles,[21] pyrimidines,[22] and other aza-heterocycles.[23] The synthetic versatility of these specific ketones can be attributed to their three electrophilic reactive sites, which have very different reactivity in cyclocondensation reactions, which leads to highly regiocon-

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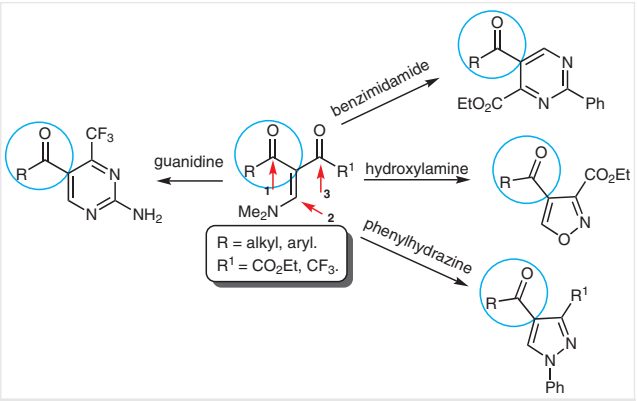
trolled products. In the case of reactions with dinucleophiles, electrophilic centers 2 and 3 undergo the cyclocondensation preferably over 1 (Scheme 2).



Scheme 2 Uses of β-enamino diketones[20–23]

Most of these heterocycles are prepared using β-enamino diketones (in which $R^1 = CO_2Et$), and the use of derivatives containing the $R^1 = CF_3$ moiety has been little explored. In previous studies with such substrates, a mixture of regioisomers and low-yielding products were usually obtained.[24–26] However, in this present study, we explored the synthetic versatility of trifluoromethyl β-enamino diketones in the cyclocondensation reaction with 3-amino-1*H*-1,2,4-triazoles, in order to prepare a series of new 6-substituted 5-(trifluoromethyl)[1,2,4]triazolo[1,5-*a*]pyrimidines, which furnished both high yields and excellent regioselectivity.

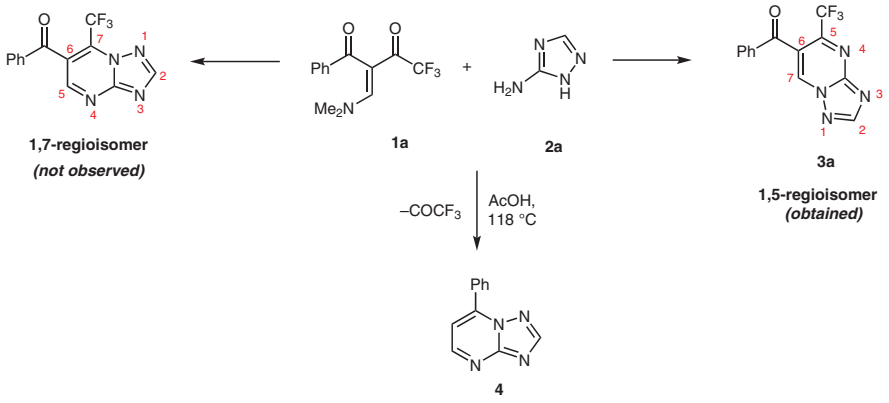
Initially, a series of β-enamino diketones was synthesized by the *C*-acylation reaction of β-enaminones with trifluoroacetic anhydride in the presence of pyridine, in accordance with the method developed previously.[27] The reaction conditions first employed were in accordance with those of Chernyshev and co-workers[28] who prepared trifluoromethyl derivatives containing the triazolopyrimidine scaffold from the reaction of β-keto esters with 1-substituted 3,5-diamino[1,2,4]triazoles, using acetic acid and reflux for 24 hours. However, using these conditions for our model reaction, we observed the elimination of $COCF_3$ from **1a**, before attack of the aminoazole **2a** (Scheme 3). Thus, the β-enamino diketones underwent the reaction with **2a** to furnish **4**, a compound that has already been reported.[19] To obtain the desired products and to maintain the CF_3 group in the molecule (e.g., to provide either the 1,5-regioisomer and/or the 1,7-regioisomer; see Scheme 3), other reaction conditions (see Table 1) had to be developed.

Table 1 Optimization of the Reaction Conditions for the Synthesis of **3a**[a]

Entry	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	AcOH	118	24	–[c]
2	MeCN	25	24	32
3	MeCN	82	8	35
4	MeCN	82	16	70
5	MeCN	82	24	88
6	acetone	56	24	–[d]
7	EtOH	79	24	–[d]

[a] Reaction conditions: **1a** (1 mmol), **2a** (1.5 mmol), solvent (5 mL).
[b] Isolated yield after recrystallization.
[c] Compound **4** was obtained in 65% yield.
[d] Starting material was recovered.

Due to compound **1a** suffering elimination of $COCF_3$ (in the form of trifluoroacetic acid)[29] when the literature conditions were employed,[28] we used solvents other than acetic acid to optimize the reactions conditions. The choice of solvents shown in Table 1 was based on the ability to solubilize **2a**. The reactions were followed by TLC analyses, in which the disappearance of **1a** was examined. The best reaction conditions found were when MeCN was used as the solvent under reflux conditions, since it is already known that heat favors cyclocondensation reactions (Table 1). The optimized time was 24 hours, which is in agreement with



Scheme 3 Possible regioisomers formed from the cyclocondensation reaction of **1a** with **2a**, and product from elimination of the $COCF_3$ group

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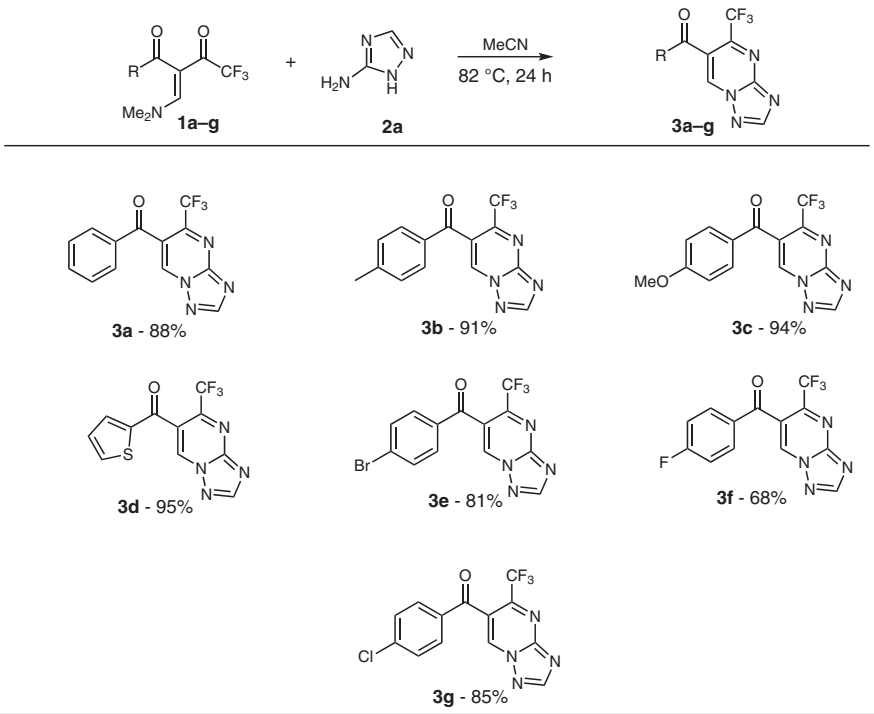


Scheme 4 Scope of [1,2,4]triazolo[1,5-*a*]pyrimidines when varying the starting β-enamino diketone

the literature for similar reactions.[28,30] The product was purified by recrystallization from hexane/chloroform (1:1).

Having established the best conditions for the synthesis of **3a**, we prepared a series of [1,2,4]triazolo[1,5-*a*]pyrimidines by reacting different β-enamino diketones **1a–g** with aminoazole **2a**. The products were obtained in moderate (68%) to high (95%) yields; the isolated yields and structures are shown in Scheme 4.

The regiochemistry of the products in Scheme 4 was confirmed by single crystal X-ray analysis of compound **3e** (Figure 1),[31] where the trifluoromethyl group is observed at the 5-position of the pyrimidine ring.

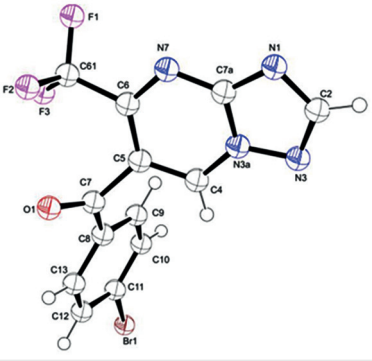
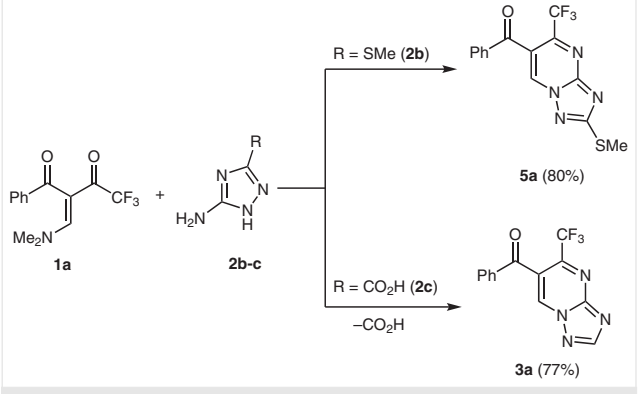


Figure 1 ORTEP diagram of compound **3e**.[31] Ellipsoids are drawn at the 50% probability level.

With the optimized conditions for obtaining compound **3a** in hand (Table 1, entry 5), different aminotriazoles were used to enhance the reaction scope (Scheme 5). When aminotriazole **2b** was used, the corresponding triazolopyrimidine **5a** was furnished in 80% yield. However, when the aminotriazolecarboxylic acid **2c** was used, we observed elimination of the carboxyl group, which may have occurred due to the high temperature used in the reaction. The corresponding product **3a** was obtained in 77% yield. The decarboxylation reaction of aminotriazoles under heating has already been reported.[30]



Scheme 5 Reaction of **1a** with different starting aminotriazoles **2b**,**c**

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Despite the low yield when the reaction of **1a** with **2a** was carried out at room temperature (Table 1, entry 2), we subsequently attempted to perform the reaction with **2c** at room temperature to avoid the decarboxylation process. Consequently, without the heating, the solubility of this specific aminotriazole was too low in all of the tested solvents, and only the starting materials were recovered. Given this result, we enhanced the reaction scope of the [1,2,4]triazolo[1,5-*a*]pyrimidines by reacting different β-enamino diketones **1a–d** with aminotriazole **2b**. The choice of the β-enamino diketones used in this part of the study was based on the best isolated yields obtained for the compounds in Scheme 4. The isolated yields for compounds **5a–d** (Table 2) obtained when using **2b** were very similar to when **2a** was used, which indicates good tolerance regarding structural aspects of the starting materials.

Products **3a–g** and **5a–d** were unambiguously characterized by GC-MS and ^{1}H, ^{13}C, and ^{19}F NMR spectroscopy. Figure 2 shows the ^{1}H, ^{13}C, and ^{19}F NMR chemical shifts obtained for compound **3a**, for which the NMR data can be used to characterize all compounds from series **3** and **5**.

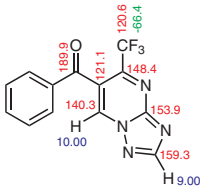
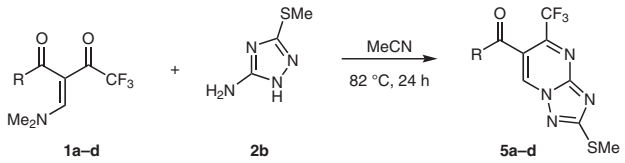


Figure 2 ^{1}H (in blue), ^{13}C (in red), and ^{19}F (in green) NMR chemical shifts obtained for compound **3a**

Table 2 Reaction Scope of [1,2,4]Triazolo[1,5-*a*]pyrimidines **5a–d**[a]



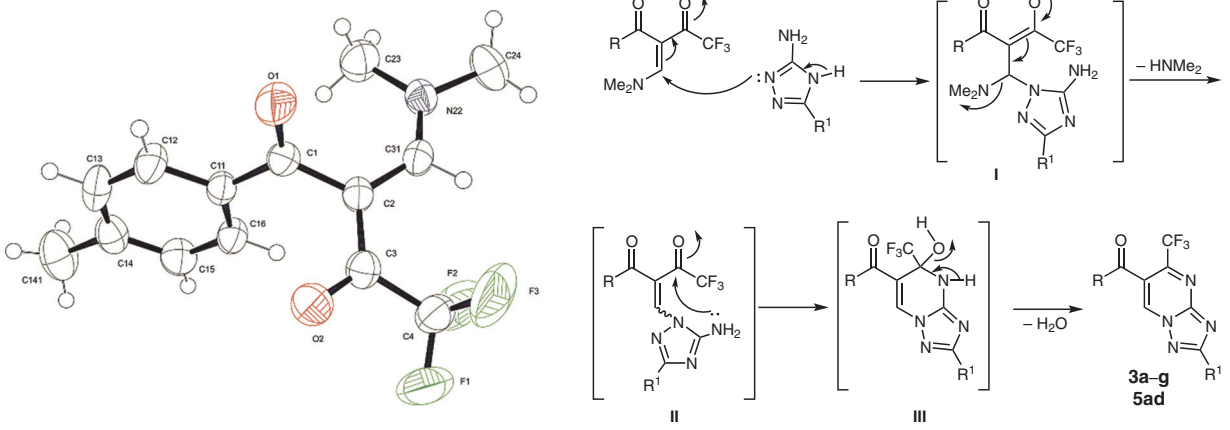
1a–d **2b** **5a–d**

Entry	R	β-Enamino diketone	Product	Yield (%)[b]
1	C_6H_5	**1a**	**5a**	80
2	4-MeC_6H_4	**1b**	**5b**	88
3	4-MeOC_6H_4	**1c**	**5c**	84
4	2-thienyl	**1d**	**5d**	75

[a] Reaction conditions: **1a–d** (1 mmol), **2b** (1.5 mmol), MeCN (5 mL).
[b] Isolated yield after recrystallization.

In agreement with the crystalline structure of the starting β-enamino diketones,[27] a plausible mechanism for the reaction is presented. Single crystals of β-enamino diketone **1b** were obtained by slow evaporation of a chloroform solution. Its ORTEP diagram (Scheme 6)[31] shows that the carbonyl attached to the CF_3 group is in the plane of the carbon–carbon double bond and the dimethylamino group is in an *E*-configuration to this group, making possible the conjugation of these two groups. On the other hand, the carbonyl group attached to the aryl group is outside the molecular plane, not allowing the conjugation of that carbonyl with the rest of the molecule. Thus, the nitrogen of the triazole ring attacks the β-position of the diketone (Scheme 6), followed by the delocalization of charge and elimination of a dimethylamine molecule (intermediate **I**). In the next step, the amino group attacks the carbonyl carbon next to the CF_3 (intermediate **II**), resulting in the closure of the pyrimidine ring (intermediate **III**), which, by delocalization of charges, eliminates a water molecule, thereby providing products **3a–g** and **5a–d**.

In summary, we have presented a successful application of trifluoromethyl β-enamino diketones for the regioselective synthesis of a series of new 6-substituted 5-(trifluoro-



Scheme 6 ORTEP diagram of β-enamino diketone **1b**[31] (ellipsoids are drawn at the 50% probability level) and proposed mechanism for the synthesis of **3a–g** and **5a–d**.

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methyl)[1,2,4]triazolo[1,5-*a*]pyrimidines. Compounds **3a–g** and **5a–d** were obtained in moderate to high yields, through the cyclocondensation reaction of β-enamino diketones with 3-amino-1*H*-1,2,4-triazoles. These new synthesized compounds are excellent models for studies on biological and pharmacological activity.

All reagents were acquired from commercial suppliers and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III spectrometer operating at 400 MHz and at 100 MHz, respectively, on solutions in DMSO-d_6 or $CDCl_3$. Chemical shifts are reported in parts per million (ppm) relative to the internal standard TMS (0 ppm). Peak patterns are indicated using standard abbreviations and coupling constants, *J*, are reported in hertz (Hz). ^{13}C NMR spectra were referenced to the internal solvent signals (central peak 39.5 ppm in DMSO-d_6 or 77.0 ppm in $CDCl_3$). ^{19}F NMR spectra were recorded on a Bruker Avance III 600 spectrometer (operating at 565 MHz), on solutions in DMSO-d_6 and using fluorobenzene as external reference with chemical shifts reported relative to the $CFCl_3$ standard. Mass spectra (GC-MS) were recorded on an Agilent 5975B GC-MSD spectrometer in EI mode. The GC was equipped with a split–splitless injector, autosampler, and crosslinked HP-5 capillary column (30 m, 0.32 mm internal diameter), and helium was used as the carrier gas. CHN microanalyses were performed on an elemental analyzer at the Chemistry Institute of São Paulo University, Brazil.

5-(Trifluoromethyl)[1,2,4]triazolo[1,5-*a*]pyrimidines 3 and 5; General Procedure

Into a flask were added the β-enamino diketone **1** (1 mmol) along with triazole **2a** (0.126 g, 1.5 mmol) or **2b** (0.196 g, 1.5 mmol) and MeCN (5 mL). The mixture was refluxed for 24 h. After the reaction time was complete, the mixture was allowed to cool to room temperature and the solvent was evaporated under reduced pressure. The residue was washed with water (20 mL), extracted with $CHCl_3$ (3 × 20 mL), and the organic phase separated and dried with anhydrous sodium sulfate. Then, the solvent was evaporated under reduced pressure. The resulting solid was recrystallized from hexane/$CHCl_3$ (1:1, 20 mL). Single crystals of compound **3e** were obtained by slow evaporation of the aforementioned mixture of solvents.

Phenyl(5-(trifluoyromethyl)[1,2,4]triazolo[1,5-*a*]pyrimidin-6-yl)methanone (3a)

White solid; yield: 257 mg (88%); mp 171–173 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.00 (s, 1 H, H-7), 9.00 (s, 1 H, H-2), 8.04 (d, *J* = 7.9 Hz, 2 H, Ar), 7.78 (t, *J* = 7.6 Hz, 1 H, Ar), 7.61 (t, *J* = 7.7 Hz, 2 H, Ar).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 189.9 (C=O), 159.3 (C-2), 153.9 (C-3a), 148.4 (q, $^2J_{C–F}$ = 36.1 Hz, C-5), 140.3 (C-7), 136.5 (Ar), 135.2 (Ar), 131.0 (Ar), 129.4 (Ar), 121.1 (C-6), 120.6 (q, $^1J_{C–F}$ = 271.8 Hz, CF_3).

^{19}F NMR (565 MHz, DMSO-d_6): δ = –66.04 (CF_3).

GC-MS (EI, 70 eV): *m*/*z* (%) = 292 (47, M^+), 215 (15), 105 (100), 77 (40).

Anal. Calcd for $C_{13}H_7F_3N_4O$: C, 53.43; H, 2.82; N, 19.17. Found: C, 53.19; H, 2.41; N, 19.13.

(4-Methylphenyl)(5-(trifluoromethyl)[1,2,4]triazolo[1,5-*a*]pyrimidin-6-yl)methanone (3b)

Yellow solid; yield: 279 mg (91%); mp 188–190 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.05 (s, 1 H, H-7), 8.76 (s, 1 H, H-2), 7.75 (d, *J* = 7.5 Hz, 2 H, Ar), 7.36 (d, *J* = 7.5 Hz, 2 H, Ar), 2.49 (s, 3 H, Me).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 189.4 (C=O), 159.2 (C-2), 153.7 (C-3a), 148.4 (q, $^2J_{C–F}$ = 36.4 Hz, C-5), 146.2 (C-7), 140.0 (Ar), 134.1 (Ar), 131.0 (Ar), 129.9 (Ar), 121.2 (C-6), 120.6 (q, $^1J_{C–F}$ = 276.5 Hz, CF_3), 21.7 (Me).

^{19}F NMR (565 MHz, DMSO-d_6): δ = –63.90 (CF_3).

GC-MS (EI, 70 eV): *m*/*z* (%) = 306 (43, M^+), 215 (6), 119 (100), 91 (37).

Anal. Calcd for $C_{14}H_9F_3N_4O$: C, 54.91; H, 2.96; N, 18.29 Found: C, 54.91; H, 3.08; N, 18.12.

(4-Methoxyphenyl)(5-(trifluoromethyl)[1,2,4]triazolo[1,5-*a*]pyrimidin-6-yl)methanone (3c)

Yellow solid; yield: 303 mg (94%); mp 157–160 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.06 (s, 1 H, H-7), 8.75 (s, 1 H, H-2), 7.83 (d, *J* = 8.9 Hz, 2 H, Ar), 7.02 (d, *J* = 8.9 Hz, 2 H, Ar), 3.93 (s, 3 H, OMe).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 188.0 (C=O), 165.1 (Ar), 159.1 (C-2), 153.7 (C-3a), 148.4 (q, $^2J_{C–F}$ = 36.1 Hz, C-5), 139.9 (C-7), 133.5 (Ar), 129.5 (Ar), 121.4 (C-6), 120.6 (q, $^1J_{C–F}$ = 275.7 Hz, CF_3), 114.8 (Ar), 56.2 (OMe).

GC-MS (EI, 70 eV): *m*/*z* (%) = 322 (55, M^+), 135 (100), 107 (8), 77 (15).

Anal. Calcd for $C_{14}H_9F_3N_4O_2$: C, 52.18; H, 2.82; N, 17.39. Found: C, 52.31; H, 2.98; N, 17.17.

Thien-2-yl(5-(trifluoromethyl)[1,2,4]triazolo[1,5-*a*]pyrimidin-6-yl)methanone (3d)

Brown crystals; yield: 283 mg (95%); mp 205–207 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.13 (s, 1 H, H-7), 9.03 (s, 1 H, H-2), 8.29 (dd, *J* = 1.2, 4.9 Hz, 1 H, Ar), 7.95 (dd, *J* =1.2, 3.9 Hz, 1 H, Ar), 7.32 (dd, *J* = 3.9, 4.9 Hz, 1 H, Ar).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 181.8 (C=O), 159.3 (C-2), 153.7 (C-3a), 148.2 (q, $^2J_{C–F}$ = 36.2 Hz, C-5), 143.4 (Ar), 140.4 (C-7), 139.8 (Ar), 139.0 (Ar), 129.7 (Ar), 120.6 (C-6), 120.5 (q, $^1J_{C–F}$ = 275.8 Hz, CF_3).

GC-MS (EI, 70 eV): *m*/*z* (%) = 298 (55, M^+), 215 (6), 111 (100), 83 (5).

Anal. Calcd for $C_{11}H_5F_3N_4OS$: C, 44.30; H, 1.69; N, 18.79. Found: C, 44.53; H, 1.72; N, 18.88.

(4-Bromophenyl)-(5-(trifluoromethyl)[1,2,4]triazolo[1,5-*a*]pyrimidin-6-yl)methanone (3e)

Yellow crystals; yield: 300 mg (81%); mp 142–145 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.04 (s, 1 H, H-7), 9.03 (s, 1 H, H-2), 7.98 (d, *J* = 8.4 Hz, 2 H, Ar), 7.83 (d, *J* = 8.5 Hz, 2 H, Ar).

^{13}C NMR (100 MHz, DMSO-d_6): δ =189.2 (C=O), 159.3 (C-2), 153.8 (C-3a), 148.4 (q, $^2J_{C–F}$ = 36.1 Hz, C-5), 140.5 (C-7), 135.6 (Ar), 132.6 (Ar), 132.7 (Ar), 129.8 (Ar), 120.6 (C-6), 120.5 (q, $^1J_{C–F}$ = 276.9 Hz, CF_3).

^{19}F NMR (565 MHz, DMSO-d_6): δ = –63.60 (CF_3).

GC-MS (EI, 70 eV): *m*/*z* (%) = 372 (55, M^+, ^{81}Br), 370 (56, M^+, ^{79}Br), 215 (28), 185 (98), 183 (100), 157 (25), 155 (25).

Anal. Calcd for $C_{13}H_6BrF_3N_4O$: C, 42.07; H, 1.63; N, 15.10. Found: C, 42.29; H, 1.67; N, 15.22.

(4-Fluorophenyl)(5-(trifluoromethyl)[1,2,4]triazolo[1,5-*a*]pyrimidin-6-yl)methanone (3f)

White solid; yield: 211 mg (68%); mp 172–176 °C.

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^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.04 (s, 1 H, H-7), 9.04 (s, 1 H, H-2), 8.14 (dd, J = 9.0, 5.4 Hz, 2 H, Ar), 7.44 (t, J = 9.0 Hz, 2 H, Ar).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 188.7 (C=O), 159.3 (C-2), 153.7 (C-3a), 148.6 (q, $^2J_{C-F}$ = 36.1 Hz, C-5), 140.5 (C-7), 134.2 (Ar), 134.1 (Ar), 120.6 (q, $^1J_{C-F}$ = 277.9 Hz, CF_3), 120.0 (C-6), 116.7 (Ar), 116.5 (Ar).

GC-MS (EI, 70 eV): m/z (%) = 310 (54, M$^+$), 207 (51), 123 (100), 95 (63).

Anal. Calcd for $C_{13}H_6F_4N_4O$: C, 50.33; H, 1.95; N, 18.06. Found: C, 50.13; H, 1.83; N, 18.90.

(4-Chlorophenyl)(5-(trifluoromethyl)[1,2,4]triazolo[1,5-*a*]pyrimidin-6-yl)methanone (3g)

White solid; yield: 278 mg (85%); mp 195–198 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.04 (s, 1 H, H-7), 9.04 (s, 1 H, H-2), 8.07 (d, J = 8.6 Hz, 2 H, Ar), 7.68 (d, J = 8.6 Hz, 2 H, Ar).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 188.9 (C=O), 159.3 (C-2), 153.8 (C-3a), 148.4 (q, $^2J_{C-F}$ = 36.3 Hz, C-5), 140.5 (C-7), 135.2 (Ar), 132.7 (Ar), 129.6 (Ar), 120.6 (q, $^1J_{C-F}$ = 276.3 Hz, CF_3), 120.1 (C-6).

GC-MS (EI, 70 eV): m/z (%) = 328 (15, M$^+$, ^{37}Cl), 326 (44, M$^+$, ^{35}Cl), 215 (16), 141 (32), 139 (100), 113 (10), 111 (32), 75 (14).

Anal. Calcd for $C_{13}H_6ClF_3N_4O$: C, 47.80; H, 1.85; N, 17.15. Found: C, 47.75; H, 1.91; N, 17.12.

(2-(Methylthio)-5-(trifluoromethyl)[1,2,4]triazolo[1,5-*a*]pyrimidin-6-yl)(phenyl)methanone (5a)

White solid; yield: 271 mg (80%); mp 150–153 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.86 (s, 1 H, H-7), 8.02 (d, J = 8.0 Hz, 2 H, Ar), 7.78 (t, J = 8.0 Hz, 1 H, Ar), 7.60 (t, J = 8.0 Hz, 2 H, Ar), 2.73 (s, 3 H, SMe).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 189.9 (C=O), 172.2 (C-2), 154.4 (C-3a), 147.6 (q, $^2J_{C-F}$ = 34 Hz, C-5), 138.5 (C-7), 136.4 (Ar), 135.3 (Ar), 130.8 (Ar), 129.4 (Ar), 120.6 (q, $^1J_{C-F}$ = 282.0 Hz, CF_3), 120.3 (C-6), 13.8 (SMe).

GC-MS (EI, 70 eV): m/z (%) = 338 (100, M$^+$), 293 (13), 215 (11), 105 (47), 77 (43).

Anal. Calcd for $C_{14}H_9F_3N_4OS$: C, 49.70; H, 2.68; N, 16.56. Found: C, 49.81; H, 2.85; N, 16.32.

4-(Methylphenyl)(2-(methylthio)-5-(trifluoromethyl)[1,2,4]triazolo[1,5-*a*]pyrimidin-6-yl)methanone (5b)

White solid; yield: 310 mg (88%); mp 195–198 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.82 (s, 1 H, H-7), 7.90 (d, J = 8.2 Hz, 2 H, Ar), 7.40 (d, J = 8.3 Hz, 2 H, Ar), 2.73 (s, 3 H, SMe), 2.44 (s, 3 H, Me).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 189.4 (C=O), 171.9 (C-2), 154.4 (C-3a), 147.4 (q, $^2J_{C-F}$ = 36.1 Hz, C-5), 146.2 (Ar), 138.5 (C-7), 134.0 (Ar), 131.1 (Ar), 130.0 (Ar), 120.6 (q, $^1J_{C-F}$ = 275.8 Hz, CF_3), 120.4 (C-6), 21.8 (Me), 13.8 (SMe).

GC-MS (EI, 70 eV): m/z (%) = 352 (100, M$^+$), 307 (8), 207 (31), 119 (62), 91 (45).

Anal. Calcd for $C_{15}H_{11}F_3N_4OS$: C, 51.13; H, 3.15; N, 15.90. Found: C, 51.04; H, 3.31; N, 15.60.

(4-Methoxyphenyl)(2-(methylthio)-5-(trifluoromethyl)[1,2,4]triazolo[1,5-*a*]pyrimidin-6-yl)methanone (5c)

White solid; yield: 310 mg (84%); mp 181–183 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.81 (s, 1 H, H-7), 7.98 (d, J = 7.1 Hz, 2 H, Ar), 7.10 (d, J = 7.2 Hz, 2 H, Ar), 3.90 (s, 3 H, OMe), 2.73 (s, 3 H, SMe).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 188.2 (C=O), 171.9 (C-2), 165.0 (Ar), 154.4 (C-3a), 147.4 (q, $^2J_{C-F}$ = 36 Hz, C-5), 138.3 (C-7), 133.5 (Ar), 129.4 (Ar), 120.7 (q, $^1J_{C-F}$ = 276.6 Hz, CF_3), 120.6 (C-6), 114.8 (Ar), 56.3 (OMe), 13.8 (SMe).

^{19}F NMR (565 MHz, DMSO-d_6): δ = –63.90 (CF_3).

GC-MS (EI, 70 eV): m/z (%) = 368 (92, M$^+$), 215 (6), 135 (100), 107 (11), 92 (16), 77 (21).

Anal. Calcd for $C_{15}H_{11}F_3N_4O_2S$: C, 48.91; H, 3.01; N, 15.21. Found: C, 48.33; H, 3.03; N, 14.91.

(2-(Methylthio)-5-(trifluoromethyl)[1,2,4]triazolo[1,5-*a*]pyrimidin-6-yl)(thien-2-yl)methanone (5d)

White solid; yield: 258 mg (75%); mp 120–123 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.96 (s, 1 H, H-7), 8.27 (d, J = 3.8 Hz, 1 H, Ar), 7.91 (d, J = 2.6 Hz, 1 H, Ar), 7.32–7.29 (m, 1 H, Ar), 2.73 (s, 3 H, SMe).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 181.8 (C=O), 172.1 (C-2), 154.4 (C-3a), 147.3 (q, $^2J_{C-F}$ = 36.3 Hz, C-5), 143.3 (C-7), 139.7 (Ar), 139.1 (Ar), 138.7 (Ar), 129.7 (Ar), 120.6 (q, $^1J_{C-F}$ = 272.4 Hz, CF_3), 119.8 (C-6), 13.8 (SMe).

GC-MS (EI, 70 eV): m/z (%) = 345 (16), 344 (100, M$^+$), 343 (3), 249 (13), 111 (63), 83 (7).

Anal. Calcd for $C_{12}H_7F_3N_4OS_2$: C, 41.86; H, 2.05; N, 16.27. Found: C, 42.01; H, 2.08; N, 16.46.

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Supporting Information

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References

(1) Emelina, E. E.; Petrov, A. A. *Russ. J. Org. Chem.* **2009**, *45*, 417.
(2) Okamura, T.; Kurogi, Y.; Hashimoto, K.; Nishikawa, H.; Nagao, Y. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2443.
(3) Novinson, T.; Springer, R. H.; O'Brien, D. E.; Scholten, M. B.; Miller, J. P.; Robins, R. K. *J. Med. Chem.* **1982**, *25*, 420.
(4) Kleschick, W. A.; Gerwick, B. C.; Carson, C. M.; Monte, W. T.; Snider, S. W. *J. Agric. Food Chem.* **1992**, *40*, 1083.
(5) Nie, J.; Guo, H.-C.; Cahard, D.; Ma, J.-A. *Chem. Rev.* **2011**, *111*, 455.
(6) Rulev, A. Y.; Romanov, A. R. *RSC Adv.* **2016**, *6*, 1984.
(7) Tsai, S. W. *J. Mol. Catal. B: Enzym.* **2016**, *127*, 98.
(8) Zhu, W.; Wang, J.; Wang, S.; Gu, Z.; Aceña, J. L.; Izawa, K.; Liu, H.; Soloshonok, V. A. *J. Fluorine Chem.* **2014**, *167*, 37.

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(9) Ruzziconi, R.; Buonerba, F. *J. Fluorine Chem.* **2013**, *152*, 12.
(10) Kolosov, M. A.; Kulyk, O. G.; Starchenko, O. I.; Orlov, V. D. *Chem. Heterocycl. Compd.* **2013**, *49*, 1166.
(11) Lipson, V. V.; Desenko, S. M.; Ignatenko, I. V.; Shishkin, O. V.; Shishkina, S. V. *Russ. Chem. Bull.* **2006**, *55*, 345.
(12) Lipson, V. V.; Desenko, S. M.; Orlov, V. D.; Shishkin, O. V.; Shirobokova, M. G.; Chernenko, V. N.; Zinov'eva, L. I. *Chem. Heterocycl. Compd.* **2000**, *36*, 1329.
(13) Druzhinin, S. V.; Balenkova, E. S.; Nenajdenko, V. G. *Tetrahedron* **2007**, *63*, 7753.
(14) Kuznetsova, O. A.; Filyakova, V. I.; Pashkevich, K. I.; Ulomskii, E. N.; Plekhanov, P. V.; Rusinov, G. L.; Kodess, M. I.; Rusinov, V. L. *Russ. Chem. Bull.* **2003**, *52*, 1190.
(15) Boechat, N.; Pinheiro, L. C. S.; Silva, T. S.; Aguiar, A. C. C.; Carvalho, A. S.; Bastos, M. M.; Costa, C. C. P.; Pinheiro, S.; Pinto, A. C.; Mendonça, J. S.; Dutra, K. D. B.; Valverde, A. L.; Santos-Filho, O. A.; Ceravolo, I. P.; Krettli, A. U. *Molecules* **2012**, *17*, 8285.
(16) Liu, Y. C.; Qu, R. Y.; Chen, Q.; Yang, J. F.; Cong-Wei, N.; Zhen, X.; Yang, G. F. *J. Agric. Food Chem.* **2016**, *64*, 4845.
(17) Krasovsky, A. L.; Moiseev, A. M.; Nenajdenko, V. G.; Balenkova, E. S. *Synthesis* **2002**, 901.
(18) Zanatta, N.; Amaral, S. S.; dos Santos, J. M.; Fernandes, L. da. S.; Bonacorso, H. G.; Martins, M. A. P. *J. Heterocycl. Chem.* **2011**, *48*, 1085.
(19) Frizzo, C. P.; Scapin, E.; Marzari, M. R. B.; München, T. S.; Zanatta, N.; Bonacorso, H. G.; Buriol, L.; Martins, M. A. P. *Ultrason. Sonochem.* **2014**, *21*, 958.
(20) Da Silva, M. J. V.; Poletto, J.; Jacomini, A. P.; Pianoski, K. E.; Gonçalves, D. S.; Ribeiro, G. M.; Melo, S. M. D. S.; Back, D. F.; Moura, S.; Rosa, F. A. *J. Org. Chem.* **2017**, *82*, 12590.
(21) Silva, R. G. M.; Da Silva, M. J. V.; Jacomini, A. P.; Moura, S.; Back, D. F.; Basso, E. A.; Rosa, F. A. *RSC Adv.* **2018**, *8*, 4773.
(22) Rosa, F. A.; Machado, P.; Fiss, G. F.; Vargas, P. S.; Fernandes, T. S.; Bonacorso, H. G.; Zanatta, N.; Martins, M. A. P. *Synthesis* **2008**, 3639.
(23) Souza, T. F.; Silva, M. J. V.; Silva, R. G. M.; Gonçalves, D. S.; Simon, P. A.; Jacomini, A. P.; Basso, E. A.; Moura, S.; Martins, M. A. P.; Back, D. F.; Rosa, F. A. *Asian J. Org. Chem.* **2017**, *6*, 627.
(24) Berber, H.; Soufyane, M.; Santillana-Hayat, M.; Mirand, C. *Tetrahedron Lett.* **2002**, *43*, 9233.
(25) Touzot, A.; Soufyane, M.; Berber, H.; Toupet, L.; Mirand, C. *J. Fluorine Chem.* **2004**, *125*, 1299.
(26) Mirand, C.; Soufyane, M.; van den Broek, S.; Khamliche, L. *Heterocycles* **1999**, *51*, 2445.
(27) Rosa, F. A.; Machado, P.; Rossatto, M.; Vargas, P. S.; Bonacorso, H. G.; Zanatta, N.; Martins, M. A. P. *Synlett* **2007**, 3165.
(28) Chernyshev, V. M.; Astakhov, A. V.; Starikova, Z. A. *Tetrahedron* **2010**, *66*, 3301.
(29) Wang, L.-H.; Zhao, J. *Eur. J. Org. Chem.* **2018**, 4345.
(30) Souza, L.; Santos, J.; Mittersteiner, M.; Andrade, V.; Lobo, M.; Santos, F.; Bortoluzzi, A.; Bonacorso, H.; Martins, M.; Zanatta, N. *Synthesis* **2018**, *50*, 3686.
(31) CCDC 1488187 (**3e**) and CCDC 1865842 (**1b**) contain the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

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