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Regioselectively Controlled Synthesis of N-Substituted (Trifluoromethyl)pyrimidin-2(1*H*)-ones

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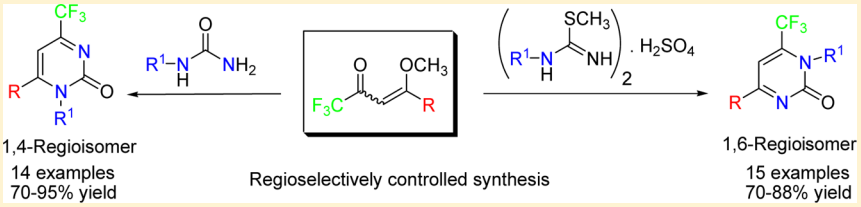
Supporting Information



ABSTRACT: A simple and regioselectively controlled method for the preparation of both 1,4- and 1,6-regioisomers of 1-substituted 4(6)-trifluoromethyl-pyrimidin-2(1*H*)-ones is described. Both regioisomers were synthesized from the cyclocondensation reaction of 4-substituted 1,1,1-trifluoro-4-methoxybut-3-en-2-ones: with nonsymmetric ureas for the 1-substituted 4-(trifluoromethyl)pyrimidin-2(1*H*)-ones (1,4-isomer) and with nonsymmetric 1-substituted 2-methylisothiourea sulfates for the synthesis of 1-substituted 6-(trifluoromethyl)pyrimidin-2(1*H*)-ones (1,6-isomer). Each method furnished only the respective isomer in very good yields. The structure of the products was assigned based on the ^{1}H and ^{13}C NMR as well as 2D HMBC spectral analysis.

INTRODUCTION

Pyrimidin-2-ones are among the most important heterocycles, and they are being used by several research groups as building blocks for target molecules.[1] These are present in various physiologically active molecules, such as the nitrogenated bases of DNAs (DNA) and ribonucleic acids (RNA), as well as in several pharmaceuticals such as antiretroviral drugs,[2] antihistamines (H1),[3] and antibiotics.[4] Important physical and bioactive properties can be achieved by further functionalizing the nitrogen atoms of the pyrimidine ring. In this context, N-substituted nucleic acid bases are known for being effective antiviral[5] and antitumoral agents[6] as well as exhibiting anti-inflammatory[7] and herbicidal activities.[8] The insertion of a trifluoromethyl group into organic molecules can greatly influence the biological activities, due to the unique properties of this group in terms of binding selectivity, lipophilicity, bioavailability, and metabolic stability.[9,10]

Although many trifluoromethylating agents have been developed, especially over the past two decades.[11] The most satisfactory methods for introducing a CF_3 group into heterocycles are still via trifluoromethylated building blocks, such as 4-alkoxy-1,1,1-trifluoroalk-3-en-2-ones.[12] These building blocks, which are easily obtained from the trifluoroacetylation of enol ethers or acetals,[13] have proven to be useful precursors for the synthesis of a series of heterocyclic compounds.[14,15]

Very few studies have dealt with the regioselective derivatization of the nitrogens of the (trifluoromethyl)-pyrimidin-2(1*H*)-one core (see Figure 1). The designation of

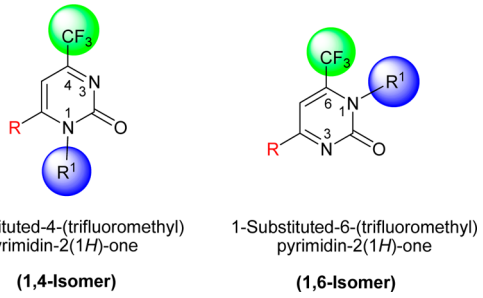


Figure 1. Chemical structure of 1,4- and 1,6-regioisomers of N-substituted 4(6)-(trifluoromethyl)pyrimidin-2(1*H*)-one.

the 1,4- and 1,6-isomers is based on the positions of the N-substituent group (always at the 1-position) relative to the CF_3 group of the pyrimidine ring (Figure 1).

In a search through the literature, only four methods for preparing N-substituted 4(6)-(trifluoromethyl)pyrimidin-2(1*H*)-ones were found. These methods are summarized here.

Gerus et al. performed alkylation on 4-(trifluoromethyl)-pyrimidin-2(1*H*)-ones using diazomethane in ethyl ether at 0 °C, and they obtained a mixture of 2-methoxy-4-(trifluoromethyl)pyrimidine and 1-methyl-4-(trifluoromethyl)pyrimidin-2(1*H*)-one in the ratio of 9:1, in favor of the O-alkylated product.[16] The authors also reported that the 3-methyl-4-

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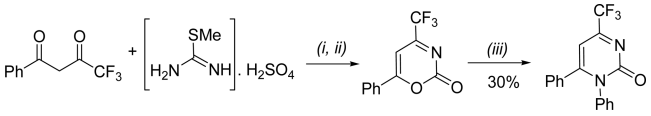
(trifluoromethyl)pyrimidin-2(1*H*)-one was not observed, and they explained the formation of the 1,4-isomer, based on the lower accessibility of the nitrogen atom at the 3-position due to the steric hindrance of the two *ortho* substituents. Methylation of the 4-(trifluoromethyl)pyrimidine-2(1*H*)-thione under similar conditions furnished only the respective 2-methylthiopyrimidine.[16]

In 2004, Agarwal et al. prepared 1,6-diphenyl-4-(trifluoromethyl)pyrimidin-2(1*H*)-one in two reaction steps (Scheme 1).[17] In the first step, a cyclocondensation reaction between

Scheme 1. Synthesis of 1,6-Diphenyl-4-(trifluoromethyl)pyrimidin-2(1*H*)-one[a]



[a]Reaction conditions: (i) KOH, H_2O, room temperature, 18 h; (ii) HCl 10%, reflux, 0.5 h; (iii) Aniline, EtOH, reflux, 4 h.

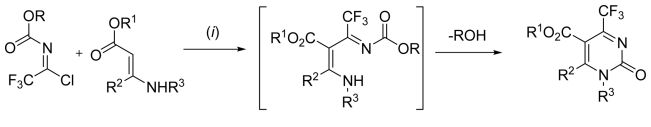
4,4,4-trifluoro-1-phenylbutane-1,3-dione and 2-methylisothiourea sulfate gave an oxazin-2-one intermediate, which was subsequently reacted with aniline to furnish 1,6-diphenyl-4-(trifluoromethyl)pyrimidin-2(1*H*)-one in 30% yield.[17]

Another method, reported by our research group, involved a comparative study of the chemoselectivity and yields for the synthesis of *N*-alkyl-4-trihalomethyl-1*H*-pyrimidin-2-ones, which was achieved by cyclocondensation of 4-alkoxy-1,1,1-trihaloalk-3-en-2-ones with methyl- and allyl-ureas, as well as the N-alkylation of 4-(trifluoromethyl)-1*H*-pyrimidin-2-ones with methyl iodide and allyl bromide.[18] This study showed that the direct alkylation of the 6-substituted pyrimidine ring with alkyl halides usually furnishes a mixture of N1- and O-alkylated products, while the cyclocondensation reaction furnishes only the *N*-alkylated pyrimidinones.[18]

More recently, Sukach et al. reported a method for obtaining a series of 1-substituted-2-oxo-4-(trifluoromethyl)pyrimidine-2(1*H*)-ones via reaction between *N*-(1-chloro-2,2,2-trifluoroethylidene)carbamates and *β*-enaminoesters, in toluene, and in the presence of a tertiary amine, at room temperature for 8 h. Low to moderate reaction yields (31−58%) were obtained. This method, however, furnished only the 1,4-isomer (Scheme 2).[19]

One can see that none of the four methods described for the N-alkylation of the 4-(trifluoromethyl)pyrimidin-2-one core (Figure 1) report alkylation on the nitrogen atom *ortho* to the CF_3 group, probably because the nitrogen is less accessible due to unfavorable steric and electronic effects.

Scheme 2. Synthesis of 1-Substituted 2-Oxo-4-(trifluoromethyl)pyrimidin-2(1*H*)-ones[a]



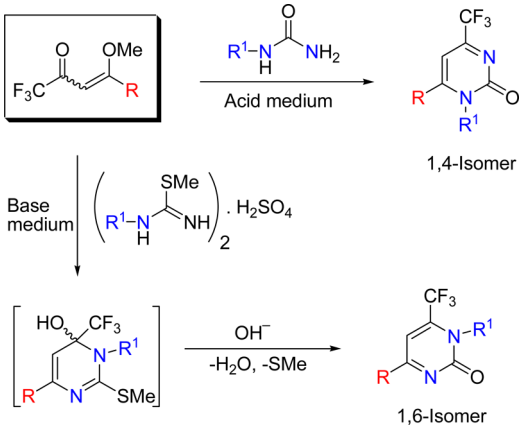
[a]Reaction conditions: (*i*) Toluene, tertiary amine, rt, 8 h.

In this study, we wish to report a concise selective method for obtaining both 1,4- and 1,6-regioisomers of the 4(6)-(trifluoromethyl)pyrimidin-2-one core. This study was designed to accommodate a large range of N-substituents, as well as a series of substituents, on the pyrimidine ring to demonstrate the strength of the method.

RESULTS AND DISCUSSION

The general strategy for the regioselectively controlled synthesis of both 1,4- and 1,6-regioisomers of 4(6)-(trifluoromethyl)pyrimidin-2-ones is shown in Scheme 3.

Scheme 3. General Strategy for the Regioselectively Controlled Synthesis of Both 1,4- and 1,6-Regiosomers of 4(6)-(Trifluoromethyl)pyrimidin-2-ones



The 4-(trifluoromethyl)pyrimidin-2-ones **6a−h** were synthesized in accordance with the method developed previously by our research group. This method relies on the cyclocondensation reaction of enones **1a−h** with 2 equiv of methylurea **2**, in methanol, in the presence of hydrochloric acid, under reflux for 20 h.[18] However, when the same reaction conditions were applied to the cyclocondensation of enones **1a,d** with ureas having R^1 groups bulkier than the methyl (ureas **3−5**), the reaction yields were low, and some *β*-diketone, resulted from the acid hydrolysis of enone **1**, was recovered. Thus, the reaction conditions had to be optimized, and it was found that the best conditions were achieved when larger amounts of concentrated hydrochloric acid were used (entries 9−14, Table 1).

For all substituents used in this study, in both the enones **1a−h** and ureas **2−5**, the cyclocondensation reaction furnished only the 1-substituted 4-(trifluoromethyl)pyrimidin-2-ones **6−9** in very good yields. The optimized reaction conditions and yields for the synthesis of 1,6-disubstituted 4-(trifluoromethyl)-pyrimidin-2-ones are reported in Table 1.

For the synthesis of the 1,6-regioisomers, initially the reaction was tested with the enone **1a** and the 1,2-dimethylisothiourea sulfate **10** in the presence of a 1 M solution of sodium hydroxide, at room temperature. This reaction furnished a mixture of the unreacted enone **1a** and the intermediate **I** (entry 1, Table 2). In a previous study, a structure similar to the intermediate **I** was obtained as a single product, in 98% yield, by performing the reaction using sodium carbonate instead of sodium hydroxide solution, at 0 °C for 2.2 h.[20]

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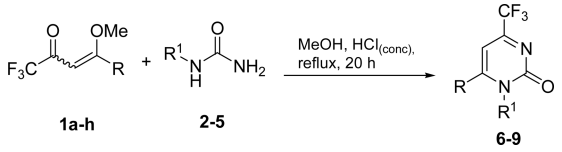
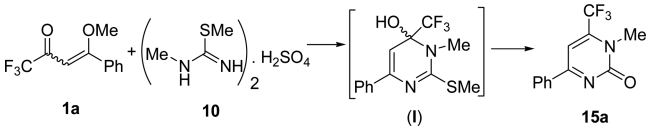
Table 1. Optimized Reaction Conditions and Yields for the Synthesis of 1,6-Disubstituted 4-(Trifluoromethyl)pyrimidin-2-ones 6−9



entry	enone	HCl (mL)[a]	R	R^1 (urea)	product	yield (%)[b]
1	**1a**	1	$-C_6H_5$	−Me (**2**)	**6a**	95
2	**1b**	1	$-4\text{-}MeC_6H_4$	−Me (**2**)	**6b**	80
3	**1c**	1	$-4\text{-}OMeC_6H_4$	−Me (**2**)	**6c**	85
4	**1d**	1	$-4\text{-}FC_6H_4$	−Me (**2**)	**6d**	90
5	**1e**	1	$-4\text{-}ClC_6H_4$	−Me (**2**)	**6e**	84
6	**1f**	1	$-4\text{-}BrC_6H_4$	−Me (**2**)	**6f**	82
7	**1g**	1	$-4\text{-}IC_6H_4$	−Me (**2**)	**6g**	80
8	**1h**	1	−Fur-2-yl	−Me (**2**)	**6h**	90
9	**1a**	5	$-C_6H_5$	−Et (**3**)	**7a**	80
10	**1d**	5	$-4\text{-}FC_6H_4$	−Et (**3**)	**7d**	78
11	**1a**	5	$-C_6H_5$	−Allyl (**4**)	**8a**	81
12	**1d**	5	$-4\text{-}FC_6H_4$	−Allyl (**4**)	**8d**	75
13	**1a**	10	$-C_6H_5$	$-C_6H_5$ (**5**)	**9a**	80
14	**1d**	10	$-4\text{-}FC_6H_4$	$-C_6H_5$ (**5**)	**9d**	70

[a]Reaction conditions: enones **1a−h** (2.5 mmol), ureas **2−5** (5.0 mmol), methanol (10 mL), HCl (37%), reflux, 20 h. [b]Yields of isolated products.

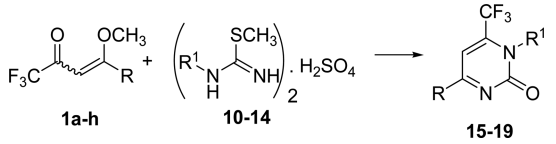
Table 2. Optimization of the Reaction Conditions for Obtaining the Product 15a[a]



entry	temp (°C)[b]	time (h)	product	yield (%)
1	25	2.5	**1a** + **I**	1:9[c]
2	100	2.5	**I** + **15a**	1:2[c]
3	110	2.5	**I** + **15a**	1:3[c]
4	120	2.5	**I** + **15a**	1:4[c]
5	140	2.5	**15a**	89
6	140	1.0	**15a**	50
7	140	2.0	**15a**	88

[a]Reaction conditions: enone **1a** (1.0 mmol), 1,2-dimethylisothiourea sulfate **10** (2.0 mmol); NaOH 1 M (2 mmol, 2 mL). [b]Temperature of the oil bath. [c]Proportion of compounds determined by ^{1}H NMR integrals.

Table 3. Optimized Reaction Conditions and Yields for the Synthesis of 1,4-Disubstituted 6-(Trifluoromethyl)pyrimidin-2-ones 15−19



entry	enone	R	R^1 (urea)	product[a]	yield (%)[b]
1	**1a**	$-C_6H_5$	−Me (**10**)	**15a**	88
2	**1b**	$-4\text{-}MeC_6H_4$	−Me (**10**)	**15b**	80
3	**1c**	$-4\text{-}OMeC_6H_4$	−Me (**10**)	**15c**	85
4	**1d**	$-4\text{-}FC_6H_4$	−Me (**10**)	**15d**	80
5	**1e**	$-4\text{-}ClC_6H_4$	−Me (**10**)	**15e**	81
6	**1f**	$-4\text{-}BrC_6H_4$	−Me (**10**)	**15f**	80
7	**1g**	$-4\text{-}IC_6H_4$	−Me (**10**)	**15g**	70
8	**1h**	−Fur-2-yl	−Me (**10**)	**15h**	79
9	**1a**	$-C_6H_5$	−Et (**11**)	**16a**	82
10	**1d**	$-4\text{-}FC_6H_4$	−Et (**11**)	**16d**	80
11	**1a**	$-C_6H_5$	−Allyl (**12**)	**17a**	70
12	**1d**	$-4\text{-}FC_6H_4$	−Allyl (**12**)	**17d**	72
13	**1a**	$-C_6H_5$	$-C_6H_5$ (**13**)	**18a**	71
14	**1d**	$-4\text{-}FC_6H_4$	$-C_6H_5$ (**13**)	**18d**	70
15	**1a**	$-C_6H_5$	−*s*-Bu (**14**)	**19a**	70

[a]Reaction conditions: enones **1a−h** (1.0 mmol), 2-methylisothiourea sulfates **10−14** (2.0 mmol), sodium hydroxide 1 M solution (2 mmol), 140 °C (temperature of the oil bath), 2 h. [b]Yields of isolated products.

In seeking to obtain the product **15a**, the reaction was tested at elevated temperatures. It was observed that at temperatures between 100 and 120 °C (entries 2−4, Table 2) a mixture of compounds **I** and **15a** was obtained, and with the increase in temperatures, an increase in the proportion of product **15a** was also observed. With the oil bath at a temperature of 140 °C, product **15a** was obtained as a pure compound. Table 2 shows the optimization of the reaction conditions for obtaining the product **15a** selectively.

The optimized conditions for **15a** were applied to the synthesis of all the other products of this series. Many enones with different substituents at the *β*-position (see Table 3) as well as a series of 1-substituted 2-methylisothioureas **10−14** were used to test the regioselectivity of the reactions.

To our surprise, all these reactions furnished only the 1,6-pyrimidine isomer in very good yields. It is interesting to observe that, even with the increase in size of both substituents R and R^1, the regiochemistry was not affected, and only the 1,6-pyrimidine-2-one isomer was obtained (entries 11−15, Table 3). Table 3 shows the optimized reaction conditions and yields for the synthesis of 1,4-disubstituted 6-(trifluoromethyl)-pyrimidin-2-ones **15−19**. To the best of our knowledge, the functionalization of the nitrogen atom neighboring the CF_3 group in (trifluoromethyl)pyrimidine-2-ones has not yet been reported in the literature.

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The structures of the N-substituted 4(6)-(trifluoromethyl)-pyrimidin-2-ones were unambiguously elucidated by mass spectrometry, ^{1}H, ^{13}C, and ^{19}F NMR spectroscopy, and two-dimensional HMBC NMR experiments. The purity of the products was confirmed by CHN elemental analyses.

Based on the two-dimensional HMBC NMR experiments, the assignment of the correct position of the N-substituent group in N-substituted 4(6)-(trifluoromethyl)pyrimidin-2-ones has been reported for related compounds, which can be seen in Figure 2.[18,20,21] In this experiment, for the 1,4-isomer, two

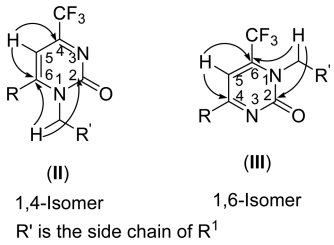

Figure 2. Strategy used for assigning the 1,4- and 1,6-regioisomer of the obtained product by two-dimensional HMBC NMR.

cross-peaks between the N–α-hydrogens and the C2 and C6 were observed (Figure 2, structure **II**). In structure **II**, the C6 was assigned by the cross-peaks with H5 and with the *ortho*-hydrogens of the aryl group, while the C4 was assigned by its characteristic quartet due to the two-bond coupling with the CF_3 group ($^{2}J_{CF} \approx 35$ Hz). For the 1,6-isomer, two cross-peaks between the N-α-hydrogens and the C2 and C6 were observed (Figure 2, structure **III**). In structure **III**, the C4 was assigned by the cross-peaks with H5 and with the *ortho*-hydrogens of the aryl group, while the C6 was assigned by its characteristic quartet due to the two-bond coupling with the CF_3 group. Compounds **9a**, **9d**, **18a**, and **18d** were assigned by comparison with the ^{1}H and ^{13}C NMR chemical shifts of similar structures, as described in Figure 3.

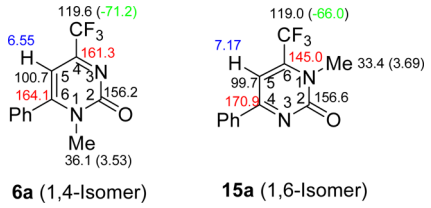

Figure 3. ^{1}H, ^{13}C, and ^{19}F NMR chemical shifts of the regioisomers **6a** and **15a**.

A simpler assignment of the two regioisomers—based on the difference in the chemical shifts of ^{1}H, ^{13}C, or ^{19}F NMR spectra—is now available (Figure 3). For example, the products **6a** and **15a** were used for the model compounds to show the difference in NMR chemical shifts between the two regioisomers. This chemical shift trend was observed for all pairs of regioisomers obtained in this study. One can see that the chemical shift of the H5 of the 1,4-isomer is about 0.60 ppm more shielded than the H5 of the 1,6-isomer. For the ^{13}C NMR spectra, the major differences between the chemical shifts of the two regioisomers are related to the carbon attached to the CF_3 group (which appears as a quartet with $J_{C-F} \approx 35$ Hz) and the carbon attached to the substituent of the pyrimidine ring (Figure 3). In these spectra, the quartet signal of the 1,4-regioisomer (C4 of compound **6a**) is about 16 ppm more deshielded than the corresponding C6 of the 1,6-regioisomer (compound **15a**). The C6 of the 1,4-regioisomer is about 6.0 ppm more shielded than the corresponding C4 of the 1,6-regioisomer. The ^{19}F NMR chemical shifts can also be used for distinguishing the two regioisomers. It was observed that the ^{19}F NMR chemical shift of the CF_3 group of the 1,4-isomer (−71.2 ppm) was about 5 ppm more shielded than the corresponding group of the 1,6-isomer (−66.0 ppm).

A plausible mechanism for the transformation of enones **1a–h** into the pyrimidines **6–9** begins with the acid hydrolysis of enones **1a–h** into the corresponding β-diketones **V** and **Va**, which are in keto–enolic equilibrium (Scheme 4). In a previous study, it was demonstrated that, in solution, structure **Va** was found at a much higher proportion than structure **V**.[22] In the subsequent step, the less hindered nitrogen of the urea performs a nucleophilic addition to the carbon attached to the CF_3 group, because this carbon is more electrophilic due to the electron-withdrawing effect of the CF_3 group, thus leading to the intermediate **VI**, which by prototropism furnishes the intermediate **VIa**. Then, the substituted nitrogen of the urea undergoes a nucleophilic addition to the β-carbon to furnish the cyclic intermediate **VII**, which, in the presence of hydrochloric acid, eliminates a water molecule. Through prototropism, structure **VII** leads to the compound **VIIa**, which subsequently furnishes the pyrimidines **6–9** after elimination of a water molecule.

A plausible reaction mechanism for the synthesis of pyrimidines **15–19** from the cyclocondensation reaction of 4-alkoxy-1,1,1-trifluoroalk-3-en-2-ones with nonsymmetric 1-substituted 2-methylisothiourea sulfates **10–14** is outlined in Scheme 5. Presumably, the reaction starts with the Michael addition of the least hindered amino group of the 2-methylisothiourea at the β-carbon of the enones **1a–h** to furnish the structure **VIII**, which is in equilibrium with its tautomeric structure **VIIIa**. Under basic conditions, the hemiaminal group of the structures **VIII** and **VIIIa** is stable. After the addition of the least substituted nitrogen of the 2-methylisothiourea at the β-carbon of the enone, the carbonyl becomes activated because it is attached to a highly electron-withdrawing trifluoromethyl group and is no longer conjugated to a carbon–carbon double bond. Thus, the addition of the second nitrogen furnishes the tetrahydropyrimidine **IX** which, through a prototropism, generates the intermediate **IXa**. The base-assisted elimination of a methanol molecule yields the structure **X**, which undergoes a nucleophilic addition of a hydroxyl group to give the structure **XI**, which eliminates a thiomethoxy group assisted by the formal negative charge of the N-3. In the last step, a base-assisted elimination of water of structure **XII** furnishes pyrimidines **15–19** in very good yields.

CONCLUSION

In conclusion, this study disclosed a regioselectively controlled procedure for the preparation of both 1,4- and 1,6-regioisomers of 1-substituted 4(6)-trifluoromethyl-pyrimidin-2(1*H*)-ones. The 1,4-regioisomers were obtained from the cyclocondensation reaction of 4-substituted 1,1,1-trifluoro-4-methoxybut-3-en-2-ones with nonsymmetric ureas in methanol and in the presence of hydrochloric acid, while the 1,6-regioisomers were prepared from the cyclocondensation reaction of 4-substituted 1,1,1-trifluoro-4-methoxybut-3-en-2-ones with nonsymmetric 1-substituted 2-methylisothioureia sulfates in the presence of sodium hydroxide solution. Each method furnished only the

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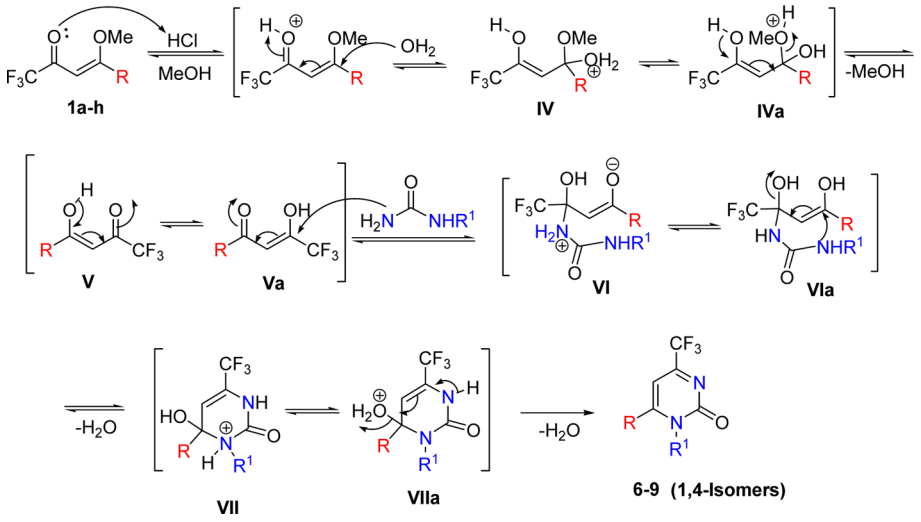
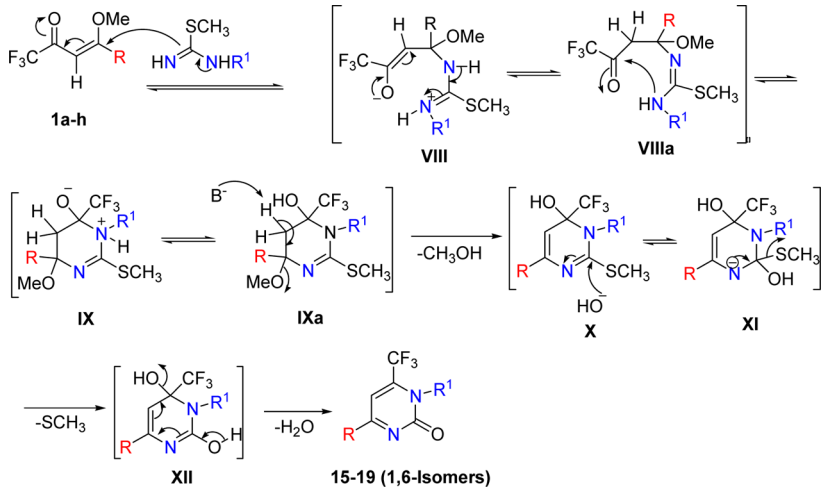
Scheme 4. Proposed Mechanism for the Synthesis of Compounds 6−9



Scheme 5. Proposed Mechanism for the Synthesis of Compounds 15−19



respective regioisomer in very good yields. In addition, this study reported for the first time a method that allows the derivatization of the nitrogen neighbor to the CF_3 group in 1-substituted 6-trifluoromethyl-pyrimidin-2(1*H*)-ones.

EXPERIMENTAL SECTION

General Information. Reagents were purchased and used without further purification. Purification of compounds was performed by flash chromatography using silica gel (230−400 mesh) as the stationary phase. The procedure for obtaining the enones (**1a−h**) was described elsewhere.[13] Thin layer chromatography (TLC) was performed using silica gel plates F-254, 0.25 mm thickness. For visualization, TLC plates were either placed under ultraviolet light or stained with iodine vapor. Most reactions were monitored by TLC for disappearance of the starting material. ^{1}H NMR spectra were recorded at 400 or at 200 MHz using TMS as the internal standard. Chemical shifts δ are quoted in parts per million (ppm), and coupling constants J are given in hertz (Hz). ^{13}C NMR spectra were recorded at 100 MHz in $CDCl_3$ solutions. ^{19}F NMR spectra were recorded at 376 MHz, in $CDCl_3$ using fluorobenzene as the internal reference with the chemical shifts reported according to the $CFCl_3$ standard. The low-resolution mass spectra were recorded on a GC-MS using EI mode (70 eV). All melting points were determined on a melting point apparatus and are uncorrected. The CHN microanalyses were performed for all synthesized products, and they are within ±0.4 for all nuclei.

General Procedure for the Synthesis of 4-Trifluoromethyl-pyrimidin-2(1*H*)-one (6−9).[18] A mixture of enones **1a−h** (2.5 mmol), ureas **2−5** (5.0 mmol), hydrochloric acid (see Table 1) in methanol (10 mL) was heated at reflux and under magnetic stirring for 20 h. The solvent was partially evaporated under reduced pressure, and cold water was added. Compounds **6a−h**, **7−9a,d** precipitated from solution and were collected by filtration. The products **6a−h** were obtained without further purification, and the products **7−9a,d** were purified by column chromatography on silica gel using 5% of ethyl acetate in chloroform as the eluent.

6-Phenyl-4-(trifluoromethyl)-1-methylpyrimidin-2(1H)-one ***(6a)***. White solid (0.603 g, 95% yield). Mp: 120−121 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.53 (s, 3H), 6.55 (s, 1H), 7.40−7.45 (m, 2H, Ar), 7.59 (dd, 2H, J = 8.0 Hz, J = 2.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 36.1, 100.7, 119.3 (q, $^1J_{CF}$ = 276.0 Hz), 127.5, 129.2, 131.2, 132.8, 156.2, 161.3 (q, $^2J_{CF}$ = 36.0 Hz), 164.1. ^{19}F NMR (376 MHz, $CDCl_3$): δ −71.22. MS (GC-MS, EI), m/z (%): 254 (48) [M^+], 253 (100), 239 (100), 226 (18), 177 (52), 118 (23). Anal. Calcd for $C_{12}H_9F_3N_2O$: C, 56.70; H, 3.57; N,11.02%. Found: C, 56.72; H, 3.97; N, 11.29%.

1-Methyl-6-(4-methylphenyl)-4-(trifluoromethyl)pyrimidin-2(1H)-one ***(6b)***. White solid (0.536 g, 80% yield). Mp 110−111 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.47 (s, 3H), 3.53 (s, 3H), 6.53 (s, 1H), 7.34 (d, 2H, J = 8.4 Hz), 7.39 (d, 2H, J_{H9-H8} = 8.4). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.3, 36.1, 100.7, 119.0 (q, $^1J_{CF}$ = 275.0 Hz), 123.5, 129.3, 129.8, 141.9, 156.4, 161.2 (q, $^2J_{CF}$ = 35.0 Hz), 164.4. MS (GC-MS, EI), m/z (%): 268 (70) [M^+], 267 (100), 253 (14), 240 (28), 199

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(12), 176 (88), 91 (53). Anal. Calcd for $C_{13}H_{11}F_3N_2O$: C, 58.21; H, 4.13; N, 10.44%. Found: C, 58.25; H, 4.26; N, 10.58%.

6-(4-Methoxyphenyl)-1-methyl-4-(trifluoromethyl)pyrimidin-2(1H)-one (**6c**). White solid (0.609 g, 85% yield). Mp 112−113 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.56 (s, 3H), 3.9 (s, 3H), 6.54 (s, 1H), 7.07 (d, 2H, J = 8.8 Hz), 7.40 (d, 2H, J = 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 36.2, 55.4, 100.6, 119.0 (q, $^1J_{CF}$ = 274.0 Hz), 114.7, 124.3, 129.4, 161.4 (q, $^2J_{CF}$ = 35.0 Hz), 156.6, 161.9, 164.1. MS (GC-MS, EI), m/z (%): 287 (70) [M$^+$], 283 (100), 269 (8,8), 256 (17), 177 (51), 118 (24). Anal. Calcd for $C_{13}H_{11}F_3N_2O_2$: C, 54.93; H, 3.90; N, 9.86%. Found: C, 54.99; H, 3.96; N, 9.94%.

6-(4-Fluorophenyl)-1-methyl-4-(trifluoromethyl)pyrimidin-2(1H)-one (**6d**). Yellow solid (0.612 g, 90% yield). Mp 96−97 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.52 (s, 3H), 6.53 (s, 1H), 7.29 (t, 2H, J = 8.4 Hz), 7.47 (dd, 2H, J = 8.8 Hz, J = 5.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 36.0, 100.8, 116.7 (d, J_{CF} = 22.3 Hz), 119.3 (q, $^1J_{CF}$ = 275.0 Hz), 128.3 (d, J_{CF} = 3.5 Hz), 130.7 (d, J_{CF} = 8.7 Hz), 156.2, 161.4 (q, $^2J_{CF}$ = 36.0 Hz), 163.1, 164.1 (d, $^1J_{CF}$ = 252.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ −71.28 (CF_3), −106,84 (Ar−F). MS (GC-MS, EI), m/z (%): 272 (48) [M$^+$], 271 (100), 269 (6.6), 256 (23), 177 (51), 136 (40). Anal. Calcd for $C_{12}H_8F_4N_2O$: C, 52.95; H, 2.96; N, 10.29%. Found: C, 52.99; H, 3.02; N, 10.40%.

6-(4-Chlorophenyl)-1-methyl-4-(trifluoromethyl)pyrimidin-2(1H)-one (**6e**). Yellow solid (0.604 g, 84% yield). Mp 88−89 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.51 (s, 3H), 6.53 (s, 1H), 7.41 (d, 2H, J = 8.4 Hz), 7.58 (d, 2H, J = 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 36.0, 100.6, 119.3 (q, $^1J_{C-F}$ = 276.0 Hz), 129.7, 129.6, 130.6, 137.7, 156.1, 161.4 (q, $^2J_{CF}$ = 35.0 Hz), 162.9. MS (GC-MS, EI), m/z (%): 288 (50) [M$^+$], 287 (100), 273 (7), 260 (28), 219 (5), 177 (55), 152 (35). Anal. Calcd for $C_{12}H_8ClF_3N_2O$: C, 49.93; H, 2.79; N, 9.70%. Found: C, 50.20; H, 3.02; N, 9.70%.

6-(4-Bromophenyl)-1-methyl-4-(trifluoromethyl)pyrimidin-2(1H)-one (**6f**). White solid (0.678 g, 82% yield). Mp 100−101 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.51 (s, 3H); 6.53 (s, 1H), 7.36 (d, 2H, J = 8.4 Hz), 7.74 (d, 2H, J = 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 36.1, 100.6, 119.3 (q, $^1J_{C-F}$ = 276 Hz), 126.1, 129.7, 131.2, 132.7, 156.1, 161.6 (q, $^2J_{CF}$ = 35.0 Hz), 162.8. MS (GC-MS, EI), m/z (%): 331 (95) [M$^+$], 333 (100), 317 (7), 303 (22), 195 (31), 177 (75). Anal. Calcd for $C_{12}H_8BrF_3N_2O$: C, 43.27; H, 2.42; N, 8.41%. Found: C, 43.40; H, 2.56; N, 8.50%.

6-(4-Iodophenyl)-1-methyl-4-(trifluoromethyl)pyrimidin-2(1H)-one (**6g**). Yellow solid (0.760 g, 80% yield). Mp 110−111 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.51 (s, 3H), 6.52 (s, 1H), 7.18 (d, 2H, J_{H8-H9} = 8.4 Hz), 7.94 (d, 2H, J = 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 36.1, 98.0, 100.5, 119.3 (q, J_{CF} = 276.0 Hz), 129.0, 131.7, 138.7, 156.1, 161.6 (q, J_{CF} = 35.0 Hz), 163.0. MS (GC-MS, EI), m/z (%): 380 (80) [M$^+$], 379 (100), 365 (3), 352 (22), 244 (23), 177 (45). Anal. Calcd for $C_{12}H_8F_3IN_2O$: C, 37.92; H, 2.12; N, 7.37%. Found: C, 38.10, H 2.36, N 7.55%.

6-(Furan-2-yl)-1-methyl-4-(trifluoromethyl)pyrimidin-2(1H)-one (**6h**). Yellow solid (0.549 g, 90% yield). Mp 178−179 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.87 (s, 3H), 6.75−6,73 (m, 1H), 6.95 (s, 1H), 7.23 (d, 1H, J = 4.0), 7.78 (d,1H, J = 2.0). ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.4, 96.1, 113.3, 119.5 (q, $^1J_{CF}$ = 276.0 Hz), 120.1, 143.6, 158.8 (q, $^2J_{C-F}$ = 35.0 Hz), 148.0, 151.9, 155.1. MS (GC-MS, EI), m/z (%): 244 (100) [M$^+$], 243 (11), 225 (13), 216 (41), 177 (35), 108 (40). Anal. Calcd for $C_{10}H_7F_3N_2O_2$: C, 49.19; H, 2.89; N, 11.47%. Found: C, 49.39; H, 3.07; N, 11.74%.

1-Ethyl-6-phenyl-4-(trifluoromethyl)pyrimidin-2(1H)-one (**7a**). Yellow solid (0.536 g, 80% yield). Mp 96−97 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.25 (t, 3H, J = 7.0 Hz), 3.99 (q, 3H, J = 7.0 Hz), 6.49 (s, 1H), 7.40−7.35 (m, 2H), 7.58−7.55 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.2, 43.2, 100.8, 119.0 (q, $^1J_{CF}$ = 274.0 Hz), 127.1, 129.0, 130.8, 132.2, 155.3, 161.1 (q, $^2J_{C-F}$ = 36.0 Hz), 164.0. MS (GC-MS, EI), m/z (%): 268 (29) [M$^+$], 267 (100), 239 (13), 212 (7), 191 (3), 163 (16). Anal. Calcd for $C_{13}H_{11}F_3N_2O$: C, 58.21; H, 4.13; N, 10.44%. Found: C, 58.41; H, 4.30; N, 10.55%.

1-Ethyl-6-(4-fluorophenyl)-4-(trifluoromethyl)pyrimidin-2(1H)-one (**7d**). Yellow solid (0.557 g, 78% yield). Mp 98−99 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.27 (t, 3H, J = 7.0 Hz), 4.00 (q, 3H, J = 7.0 Hz), 6.42 (s, 1H), 7.28 (t, 2H, J = 8.8 Hz), 7.42 (dd, 2H, J = 8.8 Hz, J = 5.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.4, 43.3, 101.1, 116.6 (d, $^2J_{CF}$ = 22.0 Hz), 119.3 (q, $^1J_{CF}$ = 276.0 Hz), 128.4 ($^4J_{CF}$ = 3.5 Hz), 129.6 (d, $^3J_{CF}$ = 8.6 Hz), 155.3, 161.4 (q, $^2J_{CF}$ = 36.0 Hz), 162.9, 163.9 (d, $^1J_{C-F}$ = 252.0 Hz). MS (GC-MS, EI), m/z (%): 286 (27) [M$^+$], 285 (100), 257 (18), 230 (41), 191 (3), 163 (40), 109 (29). Anal. Calcd for $C_{13}H_{10}F_4N_2O$: C, 54.55; H, 3.52; N, 9.79%. Found: C, 54.75; H, 3.90; N, 10.10%.

1-Allyl-6-phenyl-4-(trifluoromethyl)pyrimidin-2(1H)-one (**8a**). White solid (0.567 g, 81% yield). Mp 101−102 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.55 (dm, 2H, J = 5.6 Hz), 4.96 (dm, 1H, J = 18.8 Hz), 5.21 (dm, 1H, J = 10.4 Hz), 5.95−5.85 (ddt, 1H, J = 18.8 Hz, J = 10.4 Hz, J = 5.6 Hz), 6.53 (s, 1H), 7.41−7.39 (m, 2H), 7,59−7,51 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 50.1, 100.9, 118.8, 119.3 (q, $^1J_{CF}$ = 275.0 Hz), 127.6, 129.0, 131.0, 131.1, 132.3, 155.4, 161.8 (q, $^2J_{CF}$ = 36.2 Hz), 164.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ −71.26 (CF_3). MS (GC-MS, EI), m/z (%): 280 (29) [M$^+$], 267 (100), 261 (7), 261 (5), 239 (3), 211 (7). Anal. Calcd for $C_{14}H_{11}F_3N_2O$: C, 60.00; H, 4.20; N, 10.00%. Found: C, 60.30; H, 4.20; N, 10.20%.

1-Allyl-6-(4-fluorophenyl)-4-(trifluoromethyl)pyrimidin-2(1H)-one (**8d**). Yellow solid (0.558 g, 75% yield). Mp 102−103 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.55 (dm, 2H, J = 6.0 Hz), 4.98 (dm, 1H, J = 17 Hz), 5.25 (dm, 1H, J = 10 Hz), 6.01−5.87 (m, 1H), 6.51 (s, 1H), 7.09−7.25 (m, 2H, J = 8.8 Hz), 7.46 (dd, 2H, J = 8, J = 4.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 50.1, 101.2, 116.3 (d, $^2J_{CF}$ = 22 Hz), 118.6, 119.3 (q, $^1J_{CF}$ = 276 Hz), 128.1 ($^4J_{CF}$ = 3.5 Hz), 129.9 (d, $^3J_{CF}$ = 8.6 Hz), 130.8, 155.4, 161.6 (q, $^2J_{CF}$ = 36.0 Hz), 163.4, 164.0 (d, $^1J_{C-F}$ = 252 Hz). MS (GC-MS, EI), m/z (%): 298 (33) [M$^+$], 297 (100), 283 (8), 269 (7), 257 (4), 203 (7). Anal. Calcd for $C_{14}H_{10}F_4N_2O$: C, 56.38; H, 3.38; N, 9.39%. Found: C, 56.45; H, 3.58; N, 9.80%.

1,6-Diphenyl-4-(trifluoromethyl)pyrimidin-2(1H)-one (**9a**).[17] White solid (0.632 g, 80% yield). Mp 109−110 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.70 (s, 1H), 7.12−7.16 (m, 5H), 7.26−7.34 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 100.7 (s, 1H), 119.3 (q, $^1J_{CF}$ = 276 Hz), 128.1, 128.3, 128.5, 129.0, 129.2, 130.5, 132.3, 137.0, 155.6, 162.8 (q, $^2J_{CF}$ = 36 Hz), 163.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ −71.30 (CF_3). MS (GC-MS, EI), m/z (%): 316 (77) [M$^+$], 315 (100), 287 (13), 239 (29), 180 (29), 77 (50). Anal. Calcd for $C_{17}H_{11}F_3N_2O$: C, 64.56; H, 3.51; N, 8.86%. Found: C, 64.56; H, 3.58; N, 9.15%.

6-(4-Fluorophenyl)-1-phenyl-4-(trifluoromethyl)pyrimidin-2(1H)-one (**9d**). Yellow solid (0.584 g, 70% yield). Mp 140−141 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.66 (s, 1H), 6.95 (t, 2H, J = 8.4 Hz), 7.11−7.17 (m, 4H), 7.31−7.35 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 100,6 (s, 1H), 116.0 (d, $^2J_{C-F}$ = 22 Hz), 119.4 (q, $^1J_{C-F}$ = 276 Hz), 128.1, 129.2, 129.4, 130.6 (d, $^3J_{C-F}$ = 8.7 Hz), 137.0, 155.5, 162.9 (q, $^2J_{CF}$ = 36 Hz), 162.5, 163.5 (d, $^1J_{CF}$ = 252 Hz). MS (GC-MS, EI), m/z (%): 334 (90) [M$^+$], 333 (100), 315 (8), 305 (16), 265 (51), 239 (26), 198 (39), 77 (72). Anal. Calcd for $C_{17}H_{10}F_4N_2O$: C, 61.08; H, 3.02; N, 8.38%. Found: C, 61.38; H, 3.38; N, 8.38%.

General Procedure for the Synthesis of 6-Trifluoromethyl-pyrimidin-2(1*H*)-ones (15−19). To a solution of 2-methylisothiurea sulfates **10**−**14** (2.0 mmol) in 1 M water solution of sodium hydroxide (2 mL, 2.0 mmol), the enones **1a**−**h** (1.0 mmol) were added at room temperature, and the reactions were heated until the oil bath reached 140 °C; then, the reactions were kept at this temperature, under magnetic stirring, until the consumption of the enones (approximately 2 h). When the reaction cooled to ambient temperature, water (30 mL) was added to the reaction mixture and extracted with ethyl acetate (3 × 20 mL). The organic layer was evaporated under reduced pressure, and the products **15**−**19** were purified by silica gel column chromatography (Machinery-Nagel 60 A, 70−230 mesh) with a mixture of 5% of ethyl acetate in chloroform used as the eluent.

1-Methyl-4-phenyl-6-(trifluoromethyl)pyrimidin-2(1H)-one (**15a**). Yellow solid (0.223 g, 88% yield). Mp 129−130 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.69 (q, 3H, ^4J = 2.0 Hz), 7.17 (s, 1H), 7.59−7.64 (m, 3H), 8.12 (dd, 2H, J = 8.4 Hz, J = 1.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 33.4 (q, $^4J_{CF}$ = 3.5 Hz), 99.7 (q, $^3J_{CF}$ = 5.0 Hz), 119.0 (q, $^1J_{CF}$ = 274 Hz), 128.9, 127.9, 132.8, 134.7, 145.0 (q, J_{C-F} = 34 Hz), 156.6, 170.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ −66.04 (CF_3). MS (GC-MS, EI), m/z (%): 254 (53) [M$^+$], 253 (100), 239 (1), 185 (31), 170

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(2). Anal. Calcd for $C_{12}H_9F_3N_2O$: C, 56.70; H, 3.57; N, 11.02%. Found: C, 56.79; H, 3.78; N, 11.12%.

*1-Methyl-4-p-tolyl-6-(trifluoromethyl)pyrimidin-2(1H)-one (**15b**).* Yellow solid (0.214 g, 80% yield). Mp 171−172 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.41 (s, 3H), 3.66 (q, 3H, J_{H-F} = 2.0 Hz), 7.11 (s, 1H), 7.29 (d, 2H, J = 8 Hz), 8.01 (d, 2H, J = 8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.3, 33.1 (q, $^4J_{CF}$ = 3.2 Hz), 99.4 (q, $^3J_{CF}$ = 5 Hz), 119.0 (q, $^1J_{CF}$ = 274 Hz), 127.9, 129.6, 132.1, 143.7, 144.7 (q, $^2J_{CF}$ = 30.0 Hz), 156.5, 170.6. MS (GC-MS, EI), m/z (%): 268 (51) [M$^+$], 267 (100), 226 (7), 199 (37). Anal. Calcd for $C_{13}H_{11}F_3N_2O$: C, 58.21; H, 4.13; N, 10.44%. Found: C, 58.51; H, 4.35; N. 10.52%.

*4-(4-Methoxyphenyl)-1-methyl-6-(trifluoromethyl)pyrimidin-2(1H)-one (**15c**).* Yellow solid (0.241 g, 85% yield). Mp 159−160 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.67 (q, 3H, J = 2.0 Hz), 3.89 (s, 3H), 7.12 (s, 1H), 7.00 (d, 2H, J = 8.0 Hz), 8.12 (d, 2H, J = 10 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 33.1 (q, $^4J_{CF}$ = 3.0 Hz), 55.3, 99.1 (q, $^3J_{C-F}$ = 5.0 Hz), 119.0 (q, $^1J_{CF}$ = 274 Hz), 114.2, 129.9, 126.9, 144.3 (q, $^2J_{CF}$ = 30.0 Hz), 156.6, 163.6, 169.7. MS (GC-MS, EI), m/z (%): 284 (51) [M$^+$], 283 (100), 269 (22), 215 (15), 200 (2). Anal. Calcd for $C_{13}H_{11}F_3N_2O_2$: C, 54.93; H, 3.90; N, 9.86%. Found: C, 55.14; H, 4.00; N, 10.07%.

*4-(4-Fluorophenyl)-1-methyl-6-(trifluoromethyl)pyrimidin-2(1H)-one (**15d**).* Green solid (0.217 g, 80% yield). Mp 147−148 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.7 (q, 3H, J_C = 1.2 Hz), 7.13 (s, 1H), 7.20 (dd, 2H, J = 6.0 Hz, J = 15.0 Hz), 8.16 (dd, 2H, J = 9.0, J = 5.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 33.3 (q, $^4J_{CF}$ = 3.0 Hz), 99.2 (q, $^3J_{CF}$ = 5.0 Hz), 119.0 (q, $^1J_{CF}$ = 274 Hz), 116.1 (d, $^2J_{CF}$ = 22.0 Hz), 130.3 (d, $^3J_{C-F}$ = 9.3 Hz), 131.0 Hz, 145.2 (q, $^2J_{CF}$ = 34.0 Hz), 156.4, 165.5 (d, $^1J_{CF}$ = 254 Hz), 169.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ −66.125 (CF_3), −105.46; MS (GC-MS, EI), m/z (%): 272 (35) [M$^+$], 271 (100), 203 (38), 188 (2). Anal. Calcd for $C_{12}H_8F_4N_2O$: C, 52.95; H, 2.96; N, 10.29%. Found: C, 53.15; H, 3.26; N, 10.42%.

*4-(4-Chlorophenyl)-1-methyl-6-(trifluoromethyl)pyrimidin-2(1H)-one (**15e**).* Yellow solid (0.233 g, 81% yield). Mp 178−179 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.70 (q, 3H, J_{HF} = 1.0 Hz), 7.12 (s, 1H), 7.49 (d, 2H, J = 8.8 Hz), 8.08 (d, 2H, J = 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 33.4 (q, $^4J_{CF}$ = 3.2 Hz), 99.2 (q, $^3J_{CF}$ = 5.2 Hz), 119.1 (q, $^1J_{C-F}$ = 274 Hz), 129.4, 133.2, 139.3, 145.3 (q, $^2J_{CF}$ = 34 Hz), 156.3, 169.6. MS (GC-MS, EI), m/z (%): 288 (51) [M$^+$], 287 (100), 253 (16), 219 (62), 203 (5). Anal. Calcd for $C_{12}H_8ClF_3N_2O$: C, 49.93; H, 2.79; N, 9.70%. Found: C, 49.99; H, 2.95; N, 9.98%.

*4-(4-Bromophenyl)-1-methyl-6-(trifluoromethyl)pyrimidin-2(1H)-one (**15f**).* Yellow solid (0.266 g, 80% yield). Mp 184−185 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.67 (q, 3H, J = 2.0 Hz), 7.09 (s, 1H), 7.67 (d, 2H, J = 8.8 Hz), 7.98 (d, 2H, J = 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 33,4 (q, $^4J_{CF}$ = 3.3 Hz), 99.2 (q, $^3J_{C-F}$ = 5.0 Hz), 119.1 (q, $^1J_{CF}$ = 274 Hz), 128.0, 129.4, 132.2, 133.7, 145.5 (q, $^2J_{CF}$ = 34 Hz), 156.3, 169.9. MS (GC-MS, EI), m/z (%): 333 (51) [M$^+$], 332 (100), 291 (5), 264 (30), 249 (27). Anal. Calcd for $C_{12}H_8BrF_3N_2O$: C, 43.27; H, 2.42; N, 8.41%. Found: C, 43.49; H, 2.42; N, 8.27%.

*4-(4-Iodophenyl)-1-methyl-6-(trifluoromethyl)pyrimidin-2(1H)-one (**15g**).* Yellow solid (0.266 g, 70% yield). Mp 120−121 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.68 (q, 3H, J = 1.0 Hz), 7.10 (s, 1H), 7.82 (d, 2H, J = 8.8 Hz), 7.85 (d, 2H, J = 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 33.4 (q, $^4J_{CF}$ = 3.3 Hz), 99.1 (q, $^3J_{CF}$ = 5.0 Hz), 100.6, 119.1 (q, $^1J_{CF}$ = 274 Hz), 129.2, 134.1, 138.2, 145.3 (q, $^2J_{CF}$ = 34 Hz), 156.3, 170. MS (GC-MS, EI), m/z (%): 380 (90) [M$^+$], 379 (100), 311 (9), 296 (2), 253 (18). Anal. Calcd for $C_{12}H_8F_3IN_2O$: C, 37.92; H, 2.12; N, 7.37%. Found: C, 38.20; H, 2.42; N, 7.47%.

*4-(Furan-2-yl)-1-methyl-6-(trifluoromethyl)pyrimidin-2(1H)-one (**15h**).* Brown solid (0.192 g, 79% yield). Mp 132−133 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.69 (q, 3H, J = 2.0 Hz), 6.65 (q, 1H, J = 1.6 Hz), 7.14 (s, 1H), 7.54 (d, 1H, J = 4 Hz), 7.70 (d, 1H, J = 2.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 33.3 (q, $^4J_{C\ F}$ = 3.0 Hz), 98.5 (q, $^3J_{CF}$ = 5.0 Hz), 113.5, 119.5 (q, $^1J_{CF}$ = 276 Hz), 116.7, 147.2, 145.1 (q, $^2J_{CF}$ = 35.0 Hz), 150.2, 156.4, 161.3. MS (GC-MS, EI), m/z (%): 244 (9) [M$^+$], 243 (100), 228 (1), 202 (73), 175 (57), 160 (27), 106 (18). Anal. Calcd for $C_{10}H_7F_3N_2O_2$: C, 49.19; H, 2.89; N, 11.47%. Found: C, 49.39; H, 3.25; N, 11.48%.

*1-Ethyl-4-phenyl-6-(trifluoromethyl)pyrimidin-2(1H)-one (**16a**).* White solid (0.219 g, 82% yield). Mp 123−124 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43 (t, 3H, J = 7.2 Hz), 3.69 (q, 3H, J = 7.0 Hz), 7.15 (s, 1H), 7.51−7.60 (m, 3H), 8.13 (dd, 2H, J = 7.9 Hz, J = 1.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.4, 42.9 (q, $^4J_{CF}$ = 2.8 Hz), 99.7 (q, $^3J_{CF}$ = 5.4 Hz), 119.0 (q, $^1J_{CF}$ = 274 Hz), 127.9, 129.8, 132.7, 134.9, 144.4 (q, $^2J_{CF}$ = 34.0 Hz), 155.9, 170.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ −64.906 (CF_3). MS (GC-MS, EI), m/z (%): 268 (80) [M$^+$], 267 (100), 269 (60), 199 (22), 171 (42), 128 (71). Anal. Calcd for $C_{13}H_{11}F_3N_2O$: C, 58.21; H, 4.13; N, 10.44%. Found: C, 58.21; H, 4.21; N, 10.51%.

*1-Ethyl-4-(4-fluorophenyl)-6-(trifluoromethyl)pyrimidin-2(1H)-one (**16d**).* Yellow solid (0.228 g, 80% yield). Mp 151−152 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42 (t, 3H, J = 7.2 Hz), 4.60 (q, 3H, J = 7.0 Hz), 7.10 (s, 1H), 7.18 (t, 2H, J = 8.4 Hz), 8.15 (dd, 2H, J = 8.8, J = 5.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.4, 42.9 (q, $^4J_{CF}$ = 2.8 Hz), 99.3 (q, $^3J_{CF}$ = 5.4 Hz), 119.0 (q, $^1J_{CF}$ = 274 Hz), 116.1 (d, $^2J_{CF}$ = 21.9 Hz); 130.2 (d, $^3J_{CF}$ = 9.2 Hz), 131.0 (d, $^4J_{CF}$ = 2.9 Hz), 145.1 (q, $^2J_{CF}$ = 34.0 Hz), 156.7, 165.5 (d, $^1J_{CF}$ = 254 Hz), 169.6. MS (GC-MS, EI), m/z (%): 286 (66) [M$^+$], 285 (62), 258 (100), 217 (37), 189 (60). Anal. Calcd for $C_{13}H_{10}F_4N_2O$: C, 54.55; H, 3.52; N, 9.79%. Found: C, 54.9; H, 3.82; N, 10.10%.

*1-Allyl-4-phenyl-6-(trifluoromethyl)pyrimidin-2(1H)-one (**17a**).* Yellow solid (0.196 g, 70% yield). Mp 99−100 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.72 (d, 2H, J = 6.0 Hz), 5.24−5.32 (m, 2H), 5.89−6.09 (m, 1H), 7.17 (s, 1H), 7.54 (m, 3H), 8.13 (dd, 2H, J = 8.0 Hz, J = 2.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 49.2 (q, $^4J_{CF}$ = 3.0 Hz), 99.8 (q, $^3J_{CF}$ = 6.0 Hz), 119.0, 119.3 (q, $^1J_{CF}$ = 275 Hz), 128.0, 129.0, 130.6, 132.9, 135.0, 145.0 (q, $^2J_{CF}$ = 34.0 Hz), 171.2, 155.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ −64.518 (CF_3). MS (GC-MS, EI), m/z (%): 280 (66) [M$^+$], 279 (100), 265 (8), 251 (13), 239 (12), 211 (62). Anal. Calcd for $C_{14}H_{11}F_3N_2O$: C, 60.00; H, 3.96; N, 10.00%. Found: C, 60.37; H, 4.21; N, 10.38%.

*1-Allyl-4-(4-fluorophenyl)-6-(trifluoromethyl)pyrimidin-2(1H)-one (**17d**).* White solid (0.214 g, 72% yield). Mp 102−103 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.71 (d, 2H, J = 5.6 Hz), 5.26−5.30 (m, 2H), 5.90−6.03 (m, 1H), 7.13 (s, 1H), 7.19 (t, 2H, J = 8.4 Hz), 8.15 (dd, 2H, J = 8.8 Hz, J = 5.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 49.2, 99.4 (q, $^3J_{CF}$ = 5.6 Hz), 116.1 (d, $^2J_{C-F}$ = 21.9 Hz), 118.9, 119.3 (q, J_{CF} = 275 Hz), 130.3 (d, $^3J_{CF}$ = 9.2 Hz), 130.4, 130.6 (d, $^4J_{CF}$ = 2.0 Hz), 144.0 (q, $^2J_{CF}$ = 34.0 Hz), 155.7, 166.2 (d, $^1J_{CF}$ = 253 Hz), 171.2. MS (GC-MS, EI), m/z (%): 298 (71) [M$^+$], 297 (100), 283 (11), 269 (15), 257 (8), 229 (84). Anal. Calcd for $C_{14}H_{10}F_4N_2O$: C, 56.38; H, 3.38; N, 9.39%. Found: C, 56.50; H, 3.45; N, 9.80%.

*1,4-Diphenyl-6-(trifluoromethyl)pyrimidin-2(1H)-one (**18a**).* Yellow solid (0.221 g, 70% yield). Mp 180−181 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (s, 1H), 7.30−7.33 (m, 2H), 7.51−7.53 (m, 5H), 7.60−7.61 (m, 1H), 8.18 (dd, 2H, J = 8.8 Hz, J = 1.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 99.6 (q, $^3J_{CF}$ = 5.0 Hz), 118.7 (q, $^1J_{CF}$ = 274.0), 128.2, 128.4, 129.0, 129.3, 129.8, 133.1, 134.8, 135.7, 145.3 (q, $^2J_{CF}$ = 34.0 Hz), 156.3, 172.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.064 (CF_3). MS (GC-MS, EI), m/z (%): 316 (71) [M$^+$], 315 (100), 247 (57). Anal. Calcd for $C_{17}H_{11}F_3N_2O$: C, 64.56; H, 3.51; N, 8.86%. Found: C, 64.62; H, 3.64; N, 8.99%.

*4-(4-Fluorophenyl)-1-phenyl-6-(trifluoromethyl)pyrimidin-2(1H)-one (**18d**).* Brown solid (0.239 g, 71% yield). Mp 184−185 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (s, 1H), 7.23−7.18 (m, 2H), 7.32−7.30 (m, 5H), 7.5 (t, 2H, J = 2.8 Hz), 8.21 (dd, 2H, J = 8.8 Hz, J = 5.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 99.2 (q, $^3J_{CF}$ = 5.0), 116.2 (d, $^2J_{C-F}$ = 21.9 Hz), 118.7 (q, $^1J_{CF}$ = 274.0 Hz), 128.4, 129.0, 129.3, 129.9, 130.6 (d, $^3J_{CF}$ = 9.2 Hz), 131.0 (d, $^4J_{C-F}$ = 2.0 Hz), 135.6, 145.5 (q, $^2J_{CF}$ = 34.0 Hz), 156.1, 166.2 (d, $^1J_{CF}$ = 253 Hz), 170.9. MS (GC-MS, EI), m/z (%): 334 (71) [M$^+$], 333 (80), 247 (100). Anal. Calcd for $C_{17}H_{10}F_4N_2O$: C, 61.09; H, 3.02; N, 8.38%. Found: C, 61.38; H, 3.31; N, 8.58%.

*1-s-Butyl-4-phenyl-6-(trifluoromethyl)pyrimidin-2(1H)-one (**19a**).* Yellow solid (0.207 g, 70% yield). Mp 105−106 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.97 (t, 3H, J = 7.4 Hz), 1.23 (d, 3H, J = 6.6 Hz), 1.95−2.09 (m, 1H), 2.32−2.43 (m, 1H), 4.09−4.20 (m, 1H), 7.11 (s, 1H), 7.45−7.55 (m, 3H), 8.11 (dd, 2H, J = 8.0 Hz, J = 1.6 Hz). ^{13}C

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NMR (100 MHz, $CDCl_3$): δ 10.9, 17.3, 25.4, 60.4 (q, J_{C-F} = 3.2 Hz), 99.7 (q, J_{C-F} = 5.4 Hz), 119.0 (q, J_{C-F} = 274 Hz), 127.8, 128.9, 132.7, 134.8, 145.7 (q, J_{C-F} = 32.0 Hz), 155.7, 170.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.06 (CF_3). MS (GC-MS, EI), m/z (%): 296 (11) [M^+], 266 (100), 239 (5). Anal. Calcd for $C_{15}H_{15}F_3N_2O$: C, 60.81; H, 5.10; N, 9.45%. Found: C, 60.90; H, 5.30; N, 9.56%.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00382.

^1H, ^{13}C, and ^{19}F NMR spectra and GC-MS of compounds (PDF)

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Notes

The authors declare no competing financial interest.

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