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Direct regioselective C_{sp2}–H trifluoromethylation of pyrimidinones and pyridinones

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ABSTRACT

A direct regioselective C_{sp2}–H trifluoromethylation of pyrimidinones and pyridinones using CF_3SO_2Na/$Mn(OAc)_3$ to afford 5-trifluoromethyl pyrimidinones and 3-trifluoromethyl pyridinones in moderate to good yields was described. The reaction showed that the steric hindrance due to bulky groups adjacent to the position of attack by the trifluoromethyl radical had important influence on the yield.

1. Introduction

The incorporation of trifluoromethyl group into medicinal and agrochemical molecules have gained attention since it can dramatically improve their bioactivity, solubility, lipophilicity, membrane permeability and stability.[1–6] Several reports on trifluoromethylation have been published in recent years including trifluoromethylation of heteroarenes via the coupling reaction of heteroaryl halides, amines or boronic acid derivatives with various trifluoromethylating reagents.[1–7] The direct C–H trifluoromethylation of heteroaromatics has focused mainly on electron-rich compounds, such as five-membered heteroarenes, with some being associated with low yields and a mixture of regioisomers.[1c,7] Therefore, the direct regioselective trifluoromethylation of electron-deficient heteroarenes is still a challenge. In continuation of our previous studies on trifluoromethylation,[8] herein, we report a general, straightforward method for the trifluoromethylation of pyrimidinones and pyridinones with CF_3SO_2Na mediated by $Mn(OAc)_3$.

2. Results and discussion

Initially, CF_3SO_2Na/$Mn(OAc)_3$ system was applied to the trifluoromethylation of different types of substrates. The results showed that the reaction of CF_3SO_2Na with styrene, electron-deficient alkenes, conjugated alkynes, thiophene, methoxybenzene, indole, quinoline, chromenone and flavone resulted in a mixture of regioisomers due to these substrates possessing multiple electron density similar sites, leading to the trifluoromethylation non-selective. On the other hand, no reactions were observed in the case of pyridine and quinone. To our delight, when the same conditions were applied to pyrimidinone and pyridinone, both of them afforded the corresponding selective trifluoromethylated compounds in moderate yields (Scheme 1).

In order to get a better yield, other trifluoromethylating systems were tested for the trifluoromethylation of 2,6-diphenyl pyrimidinone (**1a**). The results indicated that neither CF_3SO_2Na/TBHP (*tert*-butyl hydroperoxide), CF_3SO_2Na/TBHP/CuCl nor $TMSCF_3$/PIDA (phenyl iodanediyl diacetate) could react with **1a**, while the reaction of either CF_3SO_2Na/$AgNO_3$, CF_3SO_2Na/I_2O_5 or Togni's reagent with **1a** gave a mixture of regioisomers due to trifluoromethylation occurred both phenyl and pyrimidiyl ring (Table 1, entries 1–6). Consequently, CF_3SO_2Na/$Mn(OAc)_3$ remained the most suitable for the trifluoromethylation of **1a**. After the reaction temperature and

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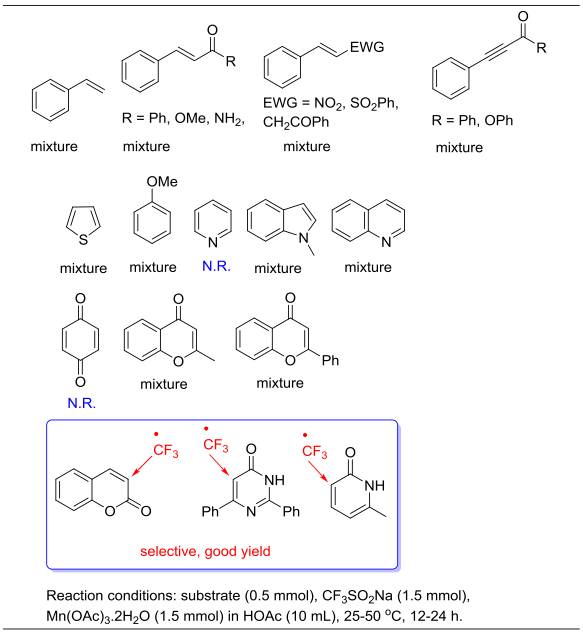
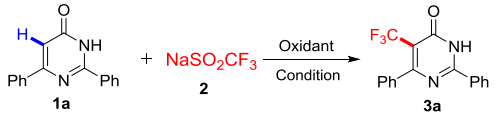


Scheme 1. Exploration of trifluoromethylation of different types of substrates.

ratio of **1a**/CF_3SO_2Na/$Mn(OAc)_3$ were screened, the optimal reaction conditions were determined to be 2,6-diphenyl pyrimidinone **1a** (0.1 mmol), CF_3SO_2Na (0.3 mmol) and $Mn(OAc)_3$ (0.3 mmol) in HOAc (4 mL) at 25 °C for 12 h to give 2,6-diphenyl-3-trifluoromethyl pyrimidinone (**3a**) in 60% yield (Table 1, entry 8).

With the optimized reaction conditions at hand, the scope of pyrimidin-4(3*H*)-ones (**1**) was then investigated (Table 2). In general, the reaction tolerated both aryl and alkyl substitutions at 2- and 6-positions to give regioselective 5-trifluoromethylation products in moderate to good yields. The reactions involving 2,6-diarypyrimidin-4(3*H*)-ones were conducted, and the desired products were obtained in moderate yields (Table 2, **3a**–**3e**).

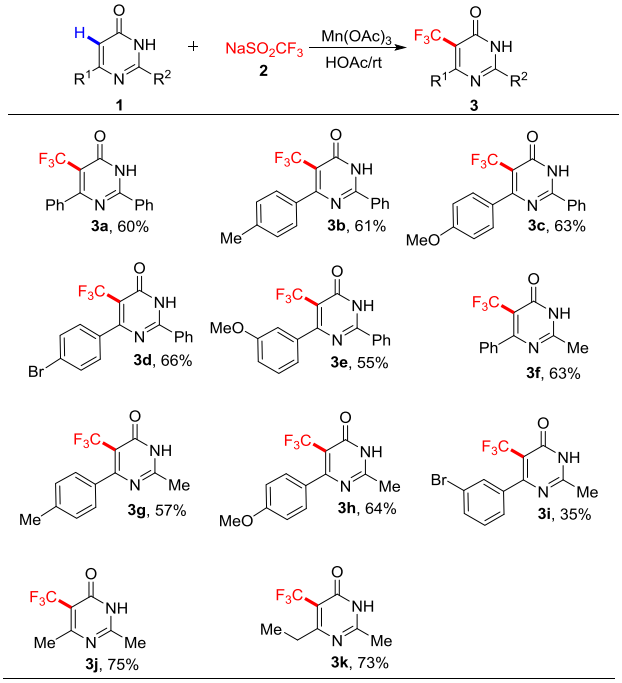
Table 1
Optimization of the reaction conditions[a]



Entry	Reagent	**1a**:Oxidant	Temp (°C)	Yield (%)[b]
1	TBHP	1:3	25	N.R.[c,d]
2	TBHP/CuCl	1:3	25	N.R.[c,e]
3	$TMSCF_3$/PIDA	1:3	50	N.R.[c,f]
4	$AgNO_3$	1:3	50	Mixture [g]
5	I_2O_5	1:3	50	Mixture [d]
6	Togni's reagent	1:3	50	Mixture [h]
7	$Mn(OAc)_3$	1:1	25	26
8	$Mn(OAc)_3$	1:3	25	60
9	$Mn(OAc)_3$	1:4	25	53
10	$Mn(OAc)_3$	1:5	25	46
11	$Mn(OAc)_3$	1:3	50	55
12	$Mn(OAc)_3$	1:3	60	43
13	$Mn(OAc)_3$	1:3	80	30

[a] Unless the otherwise noted, reactions were performed using **1a** (0.20 mmol), **2a** (0.60 mmol) and oxidant in HOAc (4 mL) for 12 h under open-flask atmosphere.
[b] Isolated yield.
[c] N.R. means no reaction.
[d] Solvent: CH_2Cl_2/H_2O (3: 1).
[e] Solvent: CH_2Cl_2/MeOH/H_2O (3: 3: 1).
[f] The mixture of **1a** (0.10 mmol), KF (0.4 mmol), $TMSCF_3$ (0.4 mmol), $PhI(OAc)_2$ (0.30 mmol) in EtOAc (1 mL) at 50 °C for 12 h.
[g] Solvent: NMP.
[h] Solvent: EtOAc.

Table 2
Reactions of pyrimidinones (**1**) with CF_3SO_2Na (**2**)[a]



[a] Unless the otherwise noted, reactions were performed using **1a** (0.50 mmol), **2a** (1.50 mmol) and $Mn(OAc)_3$ (1.50 mmol) in HOAc (10 mL) at 25 °C for 12 h in air;
[b] Isolated yield.

Furthermore, the reactions of 2-methyl-6-arylpyrimidin-4(3*H*)-ones also gave the corresponding products **3f**–**3h** in moderate yields. It is noteworthy that reactions involving 2,6-dialkylpyrimidin-4(3*H*)-ones afforded the products **3j**–**3k** in good yields. It indicated that the small groups adjacent to the position of attack by the trifluoromethyl radical favored to the reaction. The low yield of **3i** was an exception due to the oxidation of the 2-methyl-6-(3-bromophenyl) pyrimidin-4(3*H*)-one (**1i**) thereby forming 3-bromobenzoic acid as a by-product.

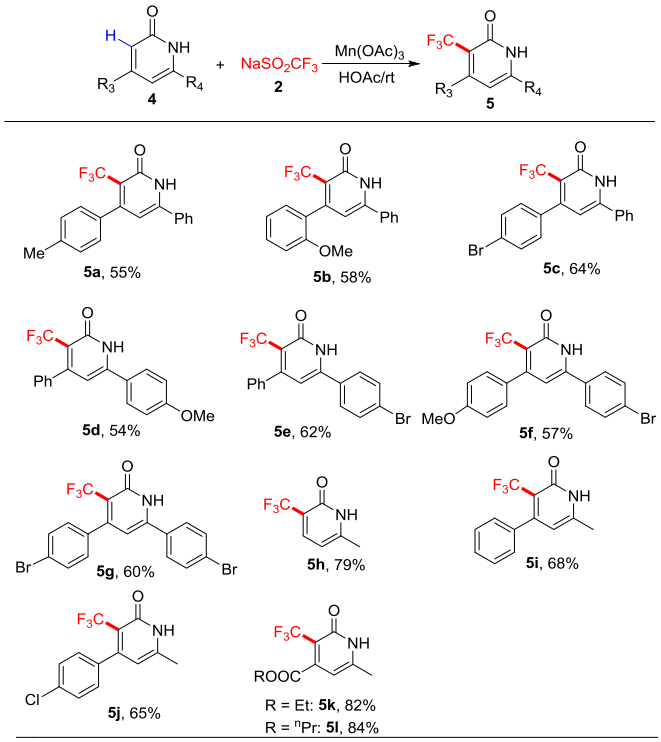
Moving further, the same reaction conditions were applied to pyridin-2(1*H*)-ones **4** thereby obtaining 3-trifluoromethylated pyridin-2(1*H*)-ones **5** in moderate to good yields as shown in Table 3. Remarkably, no 5-trifluoromethylated pyridinones or phenyl-trifluoromethylated products were observed.

Also, it was observed that different aromatic substituents at the 4 and 6-positions of pyridinones had no significant effect on the yield of product. When phenyl group at position 6 of 2,6-diarylpyridinone was substituted by a methyl group, moderate yield of trifluoromethylated product was isolated (Table 3, **5i** and **5j**). It is worthy to note that less sterically hindered pyridinones, such as the unsubstituted **5h**, or ester substituted **5k** and **5l** gave the products in good to excellent yields (Table 3).

In order to understand the mechanism of this reaction, some control experiments have been done, and the results in Scheme 2 showed that the reaction of 2,6-diphenyl pyrimidinone (**1a**) with CF_3SO_2Na (**2**) can be inhibited by radical scavenger like TEMPO and 1,1-diphenylethene.

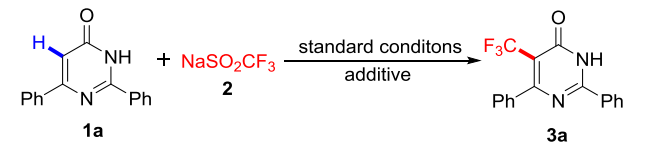
Based on the results above, a possible mechanism is proposed for the reaction of pyrimidinones (**1**) or pyridinones (**4**) with CF_3SO_2Na (**2**) mediated by $Mn(OAc)_3$ (Scheme 3). Trifluoromethyl radical **A** derived from **2** selectively adds to the 5-position of **1** or 3-position of **4** to form intermediate radical **B**, which is oxidized by $Mn(OAc)_3$ to carbocation **C**. Subsequent deprotonation of **C** gave the products **3** and **5**, respectively.

Table 3
Reactions of pyridinones (**4**) with CF_3SO_2Na (**2**)[a]



[a] Unless the otherwise noted, reactions were performed using **4** (0.50 mmol), **2** (1.50 mmol) and $Mn(OAc)_3$ (1.50 mmol) in HOAc (10 mL) at 25 °C for 12 h in air;

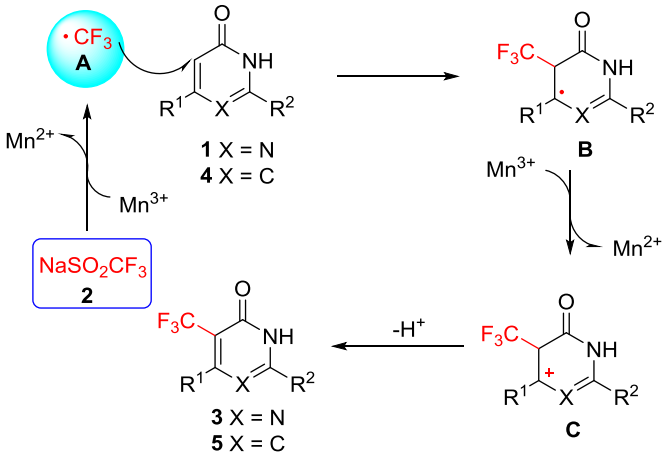
[b] Isolated yield.



additive (equiv)	Yield
TEMPO (0.2 equiv)	45%
TEMPO (1.0 equiv)	20%
TEMPO (3.0 equiv)	not detected
1,1-diphenylethene (3.0 equiv)	18%

Scheme 2. Radical trap experiments.

As depicted in Scheme 3, the regioselectivity of trifluoromethylation of pyrimidinones **1** or pyridinones **4** may be dependent on the combination of compatible substrate, radical initiator and oxidant. In the above reaction, trifluoromethyl radical **A** initiated by $Mn(OAc)_3$ favors to attack the position adjacent to the C=O group to form radical B. This is due to the presence of the carbonyl group which makes the adjacent carbon more reactive. Then, B was rapidly oxidized to carbocation **C** by a second molecule of $Mn(OAc)_3$, thus avoiding other competitive reactions. The final deprotonation of **C** took place readily. Furthermore, comparing the yields of 6-arylpyrimidinones such as **3g** or 4-arylpyridinones (**5i**) with their less sterically hindered analogues (**3j**, **3k** and **5h**, **5k**, **5l**), the latter were obtained in good yields. It is obvious that the substituent R^1 (Scheme 3) offered no stabilization for the radical **B**, so the less bulky substituents at 6-position of pyrimidinones or 4-position of pyridinones facilitated the trifluoromethyl radical attack, leading to the high yield of products.



Scheme 3. Proposed mechanism for the trifluoromethylation.

3. Conclusion

In conclusion, a direct and efficient protocol for trifluoromethylation of pyrimidinones and pyridinones was developed using $CF_3SO_2Na/Mn(OAc)_3$ as reagent. The reaction proceeded under mild conditions in air to afford selectively 5-trifluoromethyl pyrimidinones and 3-trifluoromethyl pyridinones in moderate to good yield. This protocol provides a straightforward, effective and cheap method of synthesizing 5-trifluoromethyl pyrimidinones and 3-trifluoromethyl pyridinones.

4. Experimental section

4.1. General

^1H NMR (400 MHz or 300 MHz), ^{13}C NMR (150 or 100 MHz) and ^{19}F NMR (282 or 376 MHz) spectra were determined with $CDCl_3$ or DMSO-d_6 as solvent and tetramethylsilane (TMS) as internal standard. Chemical shifts were reported in parts per million (ppm) from internal TMS (δ); all coupling constants (J values) were reported in hertz (Hz). High-resolution mass spectra were recorded on a TOF machine (CI and ESI). Column chromatography was performed with 300–400 mesh silica gel using flash column techniques. All of the reagents were used directly as commercially available unless otherwise noted.

4.2. General procedure for the preparation of 5-trifluoromethyl pyrimidinones (3) and 3-trifluoromethyl pyridinones (5)

*4.2.1. Typical procedure for the preparation of 2,6-diphenyl-5-trifluoromethyl pyrimidinone (**3a**).* To a solution of 2,6-diphenyl pyrimidinone (**1a**) (0.16 g, 0.5 mmol) and sodium trifluoromethanesulfinate **2** (0.258 g, 1.5 mmol) in acetic acid (10 mL), was added manganese triacetate hydrate (0.402 g, 1.5 mmol) in batches. The mixture was stirred at 25 °C in air for 12 h. After the completion of the reaction, water (20 mL) was added to the reaction mixture, extracted with ethyl acetate (15 mL×3). The combined organic fractions were dried over anhydrous Na_2SO_4, and concentrated under vacuum to give the crude product, which was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate=2:1) to give 2,6-diphenyl-5-trifluoromethyl pyrimidinone (**3a**).

4.3. Characterization

*4.3.1. 2,6-Diphenyl-5-(trifluoromethyl)pyrimidin-4(3H)-one (**3a**).* White powder, 60% yield (95 mg), mp 258–260 °C. ^1H NMR

(DMSO-d_6, 400 MHz): δ 13.54 (s, 1H), 8.16 (d, J=7.5 Hz, 2H), 7.65 (t, J=7.3 Hz, 1H), 7.48–7.60 (m, 7H). ^{13}C NMR (DMSO-d_6, 101 MHz): δ 165.3, 160.7, 158.8, 138.7, 133.2, 131.8, 130.2, 129.2, 129.0, 128.60, 128.58, 128.4, 123.9 (q, J=272.8 Hz), 110.8 (q, J=27.8 Hz). ^{19}F NMR (DMSO-d_6, 376 MHz): δ −56.3 (CF_3). HRMS (CI-TOF) m/z: M^+ Anal. Calcd for $C_{17}H_{11}F_3N_2O$ 316.0823, found 316.0827.

*4.3.2. 2-Phenyl-6-(p-tolyl)-5-(trifluoromethyl)pyrimidin-4(3H)-one (**3b**).* White powder, 61% yield (101 mg), mp 269–271 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 13.49 (s, 1H), 8.15 (d, J=6.6 Hz, 2H), 7.39–7.69 (m, 5H), 7.30 (d, J=7.0 Hz, 2H), 2.38 (s, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 165.2, 160.8, 158.4, 140.1, 135.8, 133.1, 131.8, 129.2, 128.94, 128.90, 128.7, 124.0 (q, J=272.9 Hz), 110.5 (q, J=30.8 Hz), 21.4. ^{19}F NMR ($CDCl_3$, 282 MHz): δ −56.6 (CF_3). HRMS (EI-TOF) m/z: M^+ Anal. Calcd for $C_{18}H_{13}F_3N_2O$ 330.0980, found 330.0987.

*4.3.3. 6-(4-Methoxyphenyl)-2-phenyl-5-(trifluoromethyl)pyrimidin-4(3H)-one (**3c**).* White solid, 63% yield (109 mg), mp 272.3–274.5 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 13.45 (s, 1H), 8.20 (d, J=7.5 Hz, 2H), 7.75–7.52 (m, 5H), 7.09 (d, J=8.3 Hz, 2H), 3.87 (s, 3H). ^{13}C NMR (DMSO-d_6, 101 MHz): 164.4, 160.8, 158.2, 134.6, 132.6, 130.3, 129.4, 128.8, 128.7, 128.5, 128.4, 123.5 (q, J=272.5 Hz), 55.3. ^{19}F NMR ($CDCl_3$, 376 MHz): −56.5 (CF_3). HRMS (CI-TOF) m/z: $(M+H)^+$ Anal. Calcd for $C_{18}H_{13}F_3N_2O_2$ 347.1007, found 347.1003.

*4.3.4. 6-(4-Bromophenyl)-2-phenyl-5-(trifluoromethyl)pyrimidin-4(3H)-one (**3d**).* White powder, 66% yield (130 mg), mp 251–253 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 13.57 (s, 1H), 8.15 (d, J=7.0 Hz, 2H), 7.72 (d, J=7.7 Hz, 2H), 7.68–7.40 (m, 5H). ^{13}C NMR (DMSO-d_6, 101 MHz): δ 164.1, 160.9, 159.0, 137.9, 133.2, 131.8, 131.5, 130.7, 129.2, 129.0, 123.9 (q, J=273.0 Hz), 123.8. ^{19}F NMR ($CDCl_3$, 376 MHz): δ −56.6 (CF_3). HRMS (CI-TOF) m/z: M^+ Anal. Calcd for $C_{17}H_{10}F_3N_2O$ 395.9908, found 395.9912.

*4.3.5. 6-(3-Methoxyphenyl)-2-phenyl-5-(trifluoromethyl)pyrimidin-4(3H)-one (**3e**).* White powder, 55% yield (95 mg), mp 226–228 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 13.55 (s, 1H), 8.16 (d, J=7.4 Hz, 2H), 7.65 (t, J=7.0 Hz, 1H), 7.56 (t, J=7.3 Hz, 2H), 7.41 (t, J=7.6 Hz, 1H), 7.07–7.14 (m, 3H), 3.81 (s, 3H). ^{13}C NMR (DMSO-d_6, 101 MHz): δ 169.9, 165.4, 163.9, 144.7, 137.9, 136.5, 134.4, 133.9, 133.7, 128.6 (q, J=273.1 Hz), 125.0, 124.9, 120.2, 118.9, 60.4. ^{19}F NMR ($CDCl_3$, 376 MHz): δ −56.6 (CF_3). HRMS (CI-TOF) m/z: M^+ Anal. Calcd for $C_{18}H_{13}F_3N_2O_2$ 346.0929, found 346.0925.

*4.3.6. 2-Methyl-6-phenyl-5-(trifluoromethyl)pyrimidin-4(3H)-one (**3f**).* White powder, 63% yield (80 mg), mp 194–196 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 13.21 (s, 1H), 7.49–7.43 (m, 3H), 7.42–7.38 (m, 2H), 2.37 (s, 3H). ^{13}C NMR (DMSO-d_6, 101 MHz): δ 165.3, 162.0, 159.8, 138.6, 129.9, 128.3, 128.26, 128.25, 123.8 (q, J=272.9 Hz), 110.6 (q, J=29.4 Hz), 21.9. ^{19}F NMR ($CDCl_3$, 376 MHz): δ −56.6 (CF_3). HRMS (EI-TOF) m/z: M^+ Anal. Calcd for $C_{12}H_9F_3N_2O$ 254.0667, found 254.0674.

*4.3.7. 2-Methyl-6-(p-tolyl)-5-(trifluoromethyl)pyrimidin-4(3H)-one (**3g**).* White powder, 57% yield (76 mg), mp 218–219 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 13.15 (s, 1H), 7.31 (d, J=8.1 Hz, 2H), 7.26 (d, J=8.1 Hz, 2H), 2.36 (s, 6H). ^{13}C NMR (DMSO-d_6, 101 MHz): δ 165.2, 161.8, 160.1, 139.8, 135.7, 128.9, 128.45, 128.43, 124.0 (q, J=272.9 Hz), 110.3 (q, J=30.9 Hz), 21.9, 21.4. ^{19}F NMR ($CDCl_3$, 376 MHz): δ −56.6 (CF_3). HRMS (EI-TOF) m/z: M^+ Anal. Calcd for $C_{13}H_{11}F_3N_2O$ 268.0823, found 268.0828.

*4.3.8. 6-(4-Methoxyphenyl)-2-methyl-5-(trifluoromethyl)pyrimidin-4(3H)-one (**3h**).* White powder, 64% yield (91 mg), mp 173–174 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 13.30 (s, 1H), 7.50 (d, J=8.2 Hz, 2H), 6.96 (d, J=8.3 Hz, 2H), 3.86 (s, 3H), 2.58 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.4, 162.6, 161.5, 160.0, 130.4, 129.9, 123.1 (q, J=273.8 Hz), 113.6, 111.4, 55.4, 22.0. ^{19}F NMR ($CDCl_3$, 376 MHz): δ −56.2 (CF_3). HRMS (CI-TOF) m/z: M^+ Anal. Calcd for $C_{13}H_{11}F_3N_2O_2$ 284.0773, found 284.0766.

*4.3.9. 6-(3-Bromophenyl)-2-methyl-5-(trifluoromethyl)pyrimidin-4(3H)-one (**3i**).* White powder, 35% yield (58 mg), mp 203–205 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 13.28 (s, 1H), 7.55–7.71 (m, 2H), 7.39 (d, J=7.7 Hz, 1H), 7.32 (t, J=7.8 Hz, 1H), 2.60 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 165.2, 160.8, 139.5, 135.2, 133.1, 131.0, 129.6, 126.8, 122.6 (q, J=273.7 Hz), 122.2, 22.0. ^{19}F NMR ($CDCl_3$, 376 MHz): δ −56.6 (CF_3). HRMS (CI-TOF) m/z: M^+ Anal. Calcd for $C_{12}H_8F_3N_2OBr$ 333.9752, found 333.9754.

*4.3.10. 2,6-Dimethyl-5-(trifluoromethyl)pyrimidin-4(3H)-one (**3j**).* White powder, 75% yield (72 mg), mp 130–131 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.95 (s, 1H), 2.36 (q, J=2.9 Hz, 3H), 2.30 (s, 3H). ^{13}C NMR (DMSO-d_6, 101 MHz): δ 165.2, 161.8, 159.5, 124.6 (q, J=272.9 Hz), 110.6 (q, J=29.3 Hz), 23.3, 21.6. ^{19}F NMR (DMSO-d_6, 376 MHz): δ −56.3 (CF_3). HRMS (CI-TOF) m/z: M^+ Anal. Calcd for $C_7H_7F_3N_2O$ 192.0510, found 192.0508.

*4.3.11. 6-Ethyl-2-methyl-5-(trifluoromethyl)pyrimidin-4(3H)-one (**3k**).* White solid, 73% yield (75 mg), mp 163–165 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.95 (s, 1H), 2.67–2.57 (m, 2H), 2.32 (s, 3H), 1.15 (t, J=7.5 Hz, 3H). ^{13}C NMR (DMSO-d_6, 101 MHz): δ 167.4, 162.1, 159.7, 124.6 (q, J=273.1 Hz), 110.0 (q, J=29.1 Hz), 29.4, 21.7, 13.5. ^{19}F NMR (DMSO-d_6, 376 MHz): δ −56.1 (CF_3). HRMS (CI-TOF) m/z: $(M+H)^+$ Anal. Calcd for $C_8H_9F_3N_2O$ 207.0745, found 207.0743.

*4.3.12. 6-Phenyl-4-(p-tolyl)-3-(trifluoromethyl)pyridin-2(1H)-one (**5a**).* White powder, 55% yield (91 mg), mp 223–224 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.55 (s, 1H), 7.84 (d, J=5.4 Hz, 2H), 7.66 (s, 1H), 7.15–7.62 (m, 6H), 6.46 (s, 1H), 2.37 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 165.4, 143.3, 141.8, 141.0, 137.3, 136.0, 134.1, 133.9, 132.8, 132.4, 129.0 (q, J=273.5 Hz), 26.0 ^{19}F NMR ($CDCl_3$, 376 MHz): δ −56.6 (CF_3). HRMS (CI-TOF) m/z: M^+ Anal. Calcd for $C_{19}H_{14}F_3NO$ 329.1027, found 329.1024.

*4.3.13. 4-(2-Methoxyphenyl)-6-phenyl-3-(trifluoromethyl)pyridin-2(1H)-one (**5b**).* White powder, 58% yield (100 mg), mp 194–196 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 12.94 (s, 1H), 7.90 (s, 2H), 7.50 (s, 3H), 7.40 (t, J=7.5 Hz, 1H), 7.20 (d, J=7.3 Hz, 1H), 7.04 (t, J=7.2 Hz, 1H), 9.97 (d, J=8.3 Hz, 1H), 6.45 (s, 1H), 3.81 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 155.6, 152.8, 148.3, 131.9, 131.0, 130.0, 129.3, 129.2, 128.3, 127.9, 127.1, 123.5 (q, J=273.7 Hz), 120.3, 110.7, 108.2, 107.4 (q, J=24.9 Hz), 55.5. ^{19}F NMR (DMSO-d_6, 376 MHz): δ −55.1 (CF_3). HRMS (CI-TOF) m/z: M^+ Anal. Calcd for $C_{19}H_{14}F_3NO_2$ 345.0977, found 345.0973.

*4.3.14. 4-(4-Bromophenyl)-6-phenyl-3-(trifluoromethyl)pyridin-2(1H)-one (**5c**).* White powder, 64% yield (126 mg), mp 255–256 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.62 (s, 1H), 7.85 (d, J=6.6 Hz, 2H), 7.67 (d, J=8.1 Hz, 2H), 7.50–7.52 (m, 3H), 7.34 (d, J=8.1 Hz, 2H), 6.50 (s, 1H). ^{13}C NMR (DMSO-d_6, 101 MHz): δ 160.6, 154.5, 152.2, 138.2, 131.6, 131.3, 129.9, 129.3, 128.0, 124.2 (q, J=273.3 Hz), 122.5. ^{19}F NMR (DMSO-d_6, 376 MHz): δ −55.1 (CF_3). HRMS (CI-TOF) m/z: M^+ Anal. Calcd for $C_{18}H_{11}F_3NO$ 392.9976, found 392.9970.

*4.3.15. 4-Phenyl-6-(4-methoxyphenyl)-3-(trifluoromethyl)pyridin-2(1H)-one (**5d**).* White solid, 54% yield (93 mg), mp 243–245 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 12.58 (s, 1H), 7.86 (d, J=8.9 Hz, 2H), 7.52–7.44 (m, 3H), 7.35–7.40 (m, 2H), 7.03 (d, J=8.9 Hz, 2H), 6.44 (s, 1H), 3.90 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 166.1, 164.9, 160.0,

154.1, 143.5, 133.8, 132.8, 131.8, 130.0, 128.6 (q, J=273.5 Hz), 119.0, 111.0 (q, J=30.2 Hz), 60.2. ^{19}F NMR (DMSO-d_6, 376 MHz): δ −56.2 (CF_3). HRMS (CI-TOF) m/z: $(M+H)^+$ Anal. Calcd for $C_{19}H_{14}F_3NO_2$ 346.1055, found 346.1038.

*4.3.16. 6-(4-Bromophenyl)-4-phenyl-3-(trifluoromethyl)pyridin-2(1H)-one (**5e**).* White powder, 62% yield (122 mg), mp 268–269 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.64 (s, 1H), 7.87 (d, J=5.1 Hz, 3H), 7.75–7.64 (m, 2H), 7.52–7.54 (m, 3H), 7.29–7.44 (m, 2H), 6.52 (s, 1H). ^{13}C NMR (DMSO-d_6, 101 MHz): δ 160.6, 154.5, 138.2, 131.6, 131.3, 129.9, 129.4, 128.0, 124.2 (q, J=273.3 Hz), 122.5. ^{19}F NMR ($CDCl_3$, 282 MHz): δ −56.6 (CF_3). HRMS (CI-TOF) m/z: M^+ Anal. Calcd for $C_{18}H_{11}F_3NO$ 392.9976, found 392.9974.

*4.3.17. 4-(4-Methoxyphenyl)-6-(4-bromophenyl)-3-(trifluoromethyl) pyridin-2(1H)-one (**5f**).* White powder, 57% yield (121 mg), mp 252–255 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.59 (s, 1H), 7.85 (d, J=8.4 Hz, 2H), 7.74 (d, J=8.6 Hz, 2H), 7.36 (d, J=8.7 Hz, 2H), 7.06 (d, J=8.8 Hz, 2H), 6.59 (s, 1H), 3.84 (s, 3H). ^{13}C NMR (DMSO-d_6, 101 MHz): δ 160.3, 159.6, 155.0, 133.4, 131.8, 130.6, 130.2, 129.6, 128.9, 124.8 (q, J=69.7 Hz), 124.4, 122.4, 113.6, 108.4 (q, J=28.0 Hz), 55.2. ^{19}F NMR ($CDCl_3$, 376 MHz): δ −56.6 (CF_3). HRMS (CI-TOF) m/z: M^+ Anal. Calcd for $C_{19}H_{13}BrF_3NO_2$ 423.0082, found 423.0093.

*4.3.18. 4-(4-Bromophenyl)-6-(4-bromophenyl)-3-(trifluoromethyl) pyridin-2(1H)-one (**5g**).* White powder, 60% yield (141 mg), mp 245–247 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 12.81 (s, 1H), 7.75 (d, J=8.7 Hz, 2H), 7.65 (d, J=8.7 Hz, 2H), 7.60 (d, J=8.4 Hz, 2H), 7.21 (d, J=8.4 Hz, 2H), 6.42 (s, 1H). ^{13}C NMR (DMSO-d_6, 101 MHz): δ 160.1, 153.8, 149.3, 137.6, 134.9, 131.8, 131.1, 130.5, 129.6, 129.4, 124.5, 123.6 (q, J=272.7 Hz), 122.0, 108.0 (q, J=29.5 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz): δ −56.7 (CF_3). HRMS (CI-TOF) m/z: M^+ Anal. Calcd for $C_{18}H_{10}Br_2F_3NO$ 470.9081, found 470.9080.

*4.3.19. 6-Methyl-3-(trifluoromethyl)pyridin-2(1H)-one (**5h**).* White powder, 79% yield (70 mg), mp 154–155 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.32 (s, 1H), 7.80 (d, J=7.4 Hz, 1H), 6.14 (d, J=7.2 Hz, 1H), 2.25 (s, 3H). ^{13}C NMR (DMSO-d_6, 101 MHz): δ 159.7, 152.4, 140.8, 124.2 (q, J=279.6 Hz), 115.3 (q, J=31.3 Hz), 103.6, 18.7. ^{19}F NMR (DMSO-d_6, 376 MHz): δ −63.5 (CF_3). HRMS (CI-TOF) m/z: M^+ Anal. Calcd for $C_7H_6F_3NO$ 177.0401, found 177.0400.

*4.3.20. 4-Phenyl-6-methyl-3-(trifluoromethyl)pyridin-2(1H)-one (**5i**).* White solid, 68% yield (86 mg), mp 197–198 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 13.55 (s, 1H), 7.51–7.41 (m, 3H), 7.35–7.29 (m, 2H), 6.06 (s, 1H), 2.48 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 162.3, 156.3, 148.2, 138.2, 128.1, 127.6, 126.58, 126.56, 123.0 (q, J=274.7 Hz), 113.21 (q, J=28.9 Hz), 109.2, 18.5. ^{19}F NMR ($CDCl_3$, 376 MHz): δ −56.4 (CF_3). HRMS (CI-TOF) m/z: $(M+H)^+$ Anal. Calcd for $C_{13}H_{10}F_3NO$ 254.0793, found 254.0791.

*4.3.21. 4-(4-Chlorophenyl)-6-methyl-3-(trifluoromethyl)pyridin-2(1H)-one (**5j**).* White powder, 65% yield (93 mg), mp 183–185 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.41 (s, 1H), 7.51 (d, J=8.2 Hz, 2H), 7.30 (d, J=8.2 Hz, 2H), 5.96 (s, 1H), 2.25 (s, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 160.0, 154.7, 150.4, 138.0, 133.7, 129.3, 128.7, 124.2 (q, J=273.3 Hz), 112.5 (q, J=30.3 Hz), 107.7, 19.0. ^{19}F NMR ($CDCl_3$, 376 MHz): δ −56.6 (CF_3). HRMS (CI-TOF) m/z: M^+ Anal. Calcd for $C_{13}H_9F_3NOCl$ 287.0325, found 287.0323.

*4.3.22. Ethyl-6-methyl-2-oxo-3-(trifluoromethyl)-1,2-dihydropyridine-4-carboxylate (**5k**).* White powder, 82% yield (102 mg), mp 178–179 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 13.45 (s, 1H), 6.09 (s, 1H), 4.39 (q, J=7.1 Hz, 2H), 2.44 (s, 3H), 1.38 (t, J=7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.9, 161.9, 151.7, 146.8 (q, J=2.6 Hz), 122.4 (q, J=272.7 Hz), 112.5 (q, J=31.4 Hz), 103.9, 62.8, 19.2, 13.8. ^{19}F NMR ($CDCl_3$, 376 MHz): δ −61.1 (CF_3). HRMS (CI-TOF) m/z: M^+ Anal. Calcd for $C_7H_6F_3NO$ 249.0613, found 249.0612.

*4.3.23. Propyl-6-methyl-2-oxo-3-(trifluoromethyl)-1,2-dihydropyridine-4-carboxylate (**5l**).* White powder, 84% yield (110 mg), mp 178–179 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 13.45 (s, 1H), 6.09 (s, 1H), 4.27 (t, J=6.7 Hz, 2H), 2.43 (s, 3H), 1.82–1.69 (m, 2H), 1.00 (t, J=7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 166.1, 161.8, 151.8, 146.8 (q, J=2.5 Hz), 122.5 (q, J=272.6 Hz), 112.4 (q, J=31.3 Hz), 103.9, 68.3, 21.6, 19.1, 10.2. ^{19}F NMR ($CDCl_3$, 376 MHz): δ −61.1 (CF_3). HRMS (CI-TOF) m/z: M^+ Anal. Calcd for $C_7H_6F_3NO$ 249.0613, found 249.0612.

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Supplementary data

Supplementary data (Experimental procedures, characterization data, and copies of the ^{1}H NMR, ^{13}C NMR and 19F NMR spectra for the products are available) associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2016.04.048.

References and notes

1. 2015 reviews see (a) Liu, X.; Xu, C.; Wang, M.; Liu, Q. *Chem. Rev.* **2015**, *115*, 683; (b) Charpentier, J.; Fruh, N.; Togni, A. *Chem. Rev.* **2015**, *115*, 650; (c) Alonso, C.; Marigorta, E. M.; Rubiales, G.; Palacios, F. *Chem. Rev.* **2015**, *115*, 1847.
2. 2014 reviews see (a) Egami, H.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 8294; (b) Chu, L. L.; Qing, F. L. *Acc. Chem. Res.* **2014**, *47*, 1513; (c) Koike, T.; Akita, M. *Top. Catal.* **2014**, *57*, 967; (d) Merino, E.; Nevado, C. *Chem. Soc. Rev.* **2014**, *43*, 6598; (e) Santschi, N.; Togni, A. *Chimia* **2014**, *68*, 419; (f) Zhang, C. *Org. Biomol. Chem.* **2014**, *12*, 6580; (g) Bizet, V.; Besset, T.; Ma, J. A.; Cahard, D. *Curr. Top. Med. Chem.* **2014**, *14*, 901; (h) Xu, J.; Liu, X.; Fu, Y. *Tetrahedron Lett.* **2014**, *55*, 585; (i) Zhang, C. P.; Chen, Q. Y.; Guo, Y.; Xiao, G. C.; Gu, Y. C. *Coord. Chem. Rev.* **2014**, *261*, 28.
3. 2013 reviews see (a) Lopez, S. E.; Salazar, J. *J. Fluorine Chem.* **2013**, *156*, 73; (b) Landelle, G.; Panossian, A.; Pazenok, S.; Vors, J. P.; Leroux, F. R. *Beilstein J. Org. Chem.* **2013**, *9*, 2476; (c) Chen, P.; Liu, G. *Synthesis* **2013**, *45*, 2919; (d) Barata-Vallejo, S.; Postigo, A. *Coord. Chem. Rev.* **2013**, *257*, 3051; (e) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 8214; (f) Liu, H.; Gu, Z.; Jiang, X. *Adv. Synth. Catal.* **2013**, *355*, 617.
4. 2012 reviews see (a) Mace, Y.; Magnier, E. *Eur. J. Org. Chem.* **2012**, 2479; (b) Liu, T.; Shen, Q. *Eur. J. Org. Chem.* **2012**, 6679; (c) Lu, C.; Shen, Q.; Liu, D. *Chin. J. Org. Chem.* **2012**, *32*, 1380; (d) Wu, X. F.; Neumann, H.; Beller, M. *Chem.—Asian. J.* **2012**, *7*, 1744; (e) Qing, F. *Chin. J. Org. Chem.* **2012**, *32*, 815; (f) Studer, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 8950; (g) Ye, Y.; Sanford, M. S. *Synlett* **2012**, *23*, 2005; (h) Jin, Z.; Hammond, G. B.; Xu, B. *Aldrichimica Acta* **2012**, *45*, 67; (i) Bruckl, T.; Baxter, R.; Ishihara, Y.; Baran, P. S. *Acc. Chem. Res.* **2012**, *45*, 826; (j) Barata-Valejo, S.; Postigo, D. A. *Eur. J. Org. Chem.* **2012**, 1889; (k) Besset, T.; Schneider, C.; Cahard, D. D. *Angew. Chem., Int. Ed.* **2012**, *51*, 5048; (l) Wang, X.; Zhang, Y.; Wang, J. B. *Sci. Sin. Chim.* **2012**, *42*, 1417.
5. 2011 reviews see (a) Tomashenko, O. A.; Grushin, V. V. *Chem. Rev.* **2011**, *111*, 4475; (b) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470; (c) Roy, S.; Gregg, B. T.; Gribble, G. W.; Le, V. D.; Roy, S. *Tetrahedron* **2011**, *67*, 2161; (d) Amii, H. *J. Synth. Org. Chem. Jpn.* **2011**, *69*, 752; (e) Valero, G.; Companyo, X.; Ríos, R. *Chem.—Eur. J.* **2011**, *17*, 2018; (f) Nie, J.; Guo, H.-C.; Cahard, D.; Ma, J. A. *Chem. Rev.* **2011**, *111*, 455; (g) Grygorenko, O. O.; Artamonov, O. S.; Komarov, I. V.; Mykhailiuk, P. K. *Tetrahedron* **2011**, *67*, 803; (h) Dilman, A. D.; Levin, V. V. *Eur. J. Org. Chem.* **2011**, 831.
6. 2010 reviews see (a) Shibata, N.; Matsnev, A.; Cahard, D. *Beilstein J. Org. Chem.* **2010**, *6*, 65; (b) Sato, K.; Tarui, A.; Omote, M.; Ando, A.; Kumadaki, I. *Synthesis* **2010**, 1865; (c) Boechat, N.; Bastos, M. M. *Curr. Org. Synth.* **2010**, *7*, 403; (d) Zheng, Y.; Ma, J. A. *Adv. Synth. Catal.* **2010**, *352*, 2745; (e) Lundgren, R. J.; Stradiotto, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 9322.
7. (a) Pitre, S. P.; McTiernan, C. D.; Ismaili, H.; Scaiano, J. *ACS Catal.* **2014**, *4*, 2530; (b) Nishida, T.; Ida, H.; Kuninobu, Y.; Kanai, M. *Nat. Commun.* **2014**, *5*, 3387; (c) Straathof, N. J. W.; Gemoets, H. P. L.; Wang, X.; Schouten, J. C.; Hessel, V.; Noel, T. *ChemSusChem* **2014**, *7*, 1612; (d) Seo, S.; Taylor, J. B.; Greaney, M. F. *Chem. Commun.* **2013**, 6385; (e) Cui, L.; Matusaki, Y.; Tada, N.; Miura, T.; Uno, B.; Itoha, A. *Adv. Synth. Catal.* **2013**, *355*, 2203; (f) Cai, S.; Chen, C.; Sun, Z.; Xi, C. *Chem.*

Commun. **2013**, 4552; (g) Chu, L.; Qing, F. L. *J. Am. Chem. Soc.* **2012**, *134*, 1298; (h) Mejía, E.; Togni, A. *ACS Catal.* **2012**, *2*, 521; (i) Iqbal, N.; Choi, S.; Ko, E.; Cho, E. J. *Tetrahedron Lett.* **2012**, *53*, 2005; (j) Fujiwara, Y.; Dixon, J. A.; Hara, F. O.; Funder, E. D.; Dixon, D. D.; Rodriguez, R. A.; Baxter, R. D.; Herle, B.; Sach, N.; Collins, M. R.; Ishihara, Y.; Baran, P. S. *Nature* **2012**, *492*, 95; (k) Nagib, D. A.; MacMillan, D. W. C. *Nature* **2011**, *480*, 224; (l) Ji, Y.; Brueckl, T.; Baxter, R. D.; Fujiwara, Y.; Seiple, I. B.; Su, S.; Blackmond, D. G.; Baran, P. S. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 14411; (m) Mu, X.; Chen, S.; Zhen, X.; Liu, G. *Chem.—Eur. J.* **2011**, *17*, 6039; (n) Kino, T.; Nagase, Y.; Ohtsuka, Y.; Yamamoto, K.; Uraguchi, D.; Tokuhisa, K.; Yamakawa, D. T. *J. Fluorine Chem.* **2010**, *131*, 98; (o) Wiehn, M. S.; Vinogradova, E. V.; Togni, A. *J. Fluorine Chem.* **2010**, *131*, 951; (p) Shimizu, R.; Egami, H.; Nagi, T.; Chae, J.; Hamashima, Y.; Sodeoka, M. *Tetrahedron Lett.* **2010**, *51*, 5947; (q) Yoshida, M.; Yoshida, T.; Kobayashi, M.; Kamigata, N. *J. Chem. Soc., Perkin Trans. 1* **1989**, 909; (r) Lishchynskyi, A.; Berthon, G.; Grushin, V. V. *Chem. Commun.* **2014**, 10237; (s) Miyake, Y.; Ota, S.; Shibata, M.; Nakajima, K.; Nishibayashi, Y. *Org. Biomol. Chem.* **2014**, *12*, 5594; (t) Kawai, H.; Sugita, Y.; Tokunaga, E.; Sato, H.; Shiro, M.; Shibata, N. *Chem. Open* **2014**, *3*, 14.

8. Cao, X. H.; Pan, X. Q.; Zhou, P. J.; Zou, J. P.; Asekun, O. T. *Chem. Commun.* **2014**, 3359.