Tetrahedron 67 (2011) 2468–2473

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

A novel method for the synthesis of 3-fluoro-4-aryl-2-pyridone via unprecedented denitration

Xiao-Wei Wang [a,b], Hai-Feng Cui [a,b], Hai-Feng Wang [b], Ying-Quan Yang [b], Gang Zhao [b,*], Shi-Zheng Zhu [a,*]

[a] Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China
[b] Key Laboratory of Modern Synthetic Organic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China

ARTICLE INFO

Article history:
Received 24 November 2010
Received in revised form 13 January 2011
Accepted 18 January 2011
Available online 22 January 2011

Keywords:
Cyclization
Denitration
Fluorine-containing 2-pyridone
α,β-Unsaturated ketone

ABSTRACT

A simple and novel method to the synthesis of 3-fluoro-4-aryl-2-pyridone from a Michael-adduct of fluoronitroacetate and α,β-unsaturated ketone is reported. With $(NH_4)_2CO_3$ as the N-source and TsOH as the promoted acid, a series of fluorinated-pyridones was obtained with moderate to good yields.

1. Introduction

Considerable attention has been given to the assembly of 2-pyridone core structure for many years because these structural motifs, which possess potent pharmacological and agrochemical activities are found in a very large number of biologically active natural products and related congeners,[1] such as the Camptothecins,[2] drug candidates active against leukemia,[2b] Huperzine A,[3] a potent acetylcholine esterase inhibitor,[3b] Lyconadin A, which was demonstrated to possess modest anticancer activity,[4] and Merck's L-697,661,[5] an HIV-1 reverse transcriptase inhibitor (Fig. 1).

Numerous methods for construction of cyclic compounds from easily available starting materials have been developed.[6] Generally, there are two mainly synthetic approaches to elaborate 2-pyridone rings, one of which is conversion from other heterocyclics, such as the oxidation of an *N*-substituted pyridinium salt,[7] and the other is condensation from acyclic compounds using Knovenagel-type reactions,[8] such as cross-condensation of cyanoacetoamide with β-dicarbonyl compounds or 2-pyrones with amides. Recently, Smith[9] has reported an efficient protocol to annulate the 5,6-fused 2-pyridonering system, exploiting a tandem condensation of propiolamide and cyclic β-keto methyl esters in water, followed by acid-

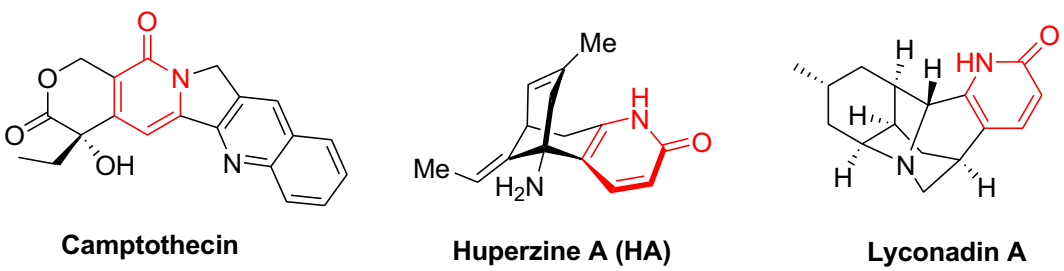


Fig. 1. Some natural products with pyridone unit.

* Corresponding authors. Tel.: +86 21 54925183; fax: +86 21 64166128; e-mail address: zhusz@mail.sioc.ac.cn (S.-Z. Zhu).

0040-4020/$ – see front matter
doi:10.1016/j.tet.2011.01.047

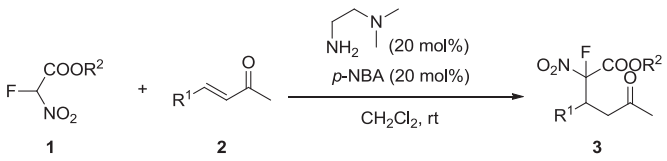
or base-promoted intramolecular ring closure and decarboxylation. This method could be employed in the syntheses of huperzine A and analogues. However, the methods to synthesize fluorine-containing 2-pyridone core structure have been rarely reported. Schlosser[10] reported a simple procotol to synthesis 3-fluoro-2-quinolones from anilines and methyl 2-fluoro-3-methoxyprop-2-enoate via a Knorr–Effenberger-type reaction under strongly acidic conditions.

2. Results and discussion

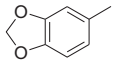
Herein we developed a simple and novel method to synthesis of 3-fluoro-4-aryl-2-pyridone in moderate to good yields. Ketoesters (**3**) can be prepared via Michael addition of fluoronitroacetates (**1**) with α,β-unsaturated methyl ketones (**2**) with good yields. Then, with an ammonium salt and Brønsted acid, ketoesters (**3**) can be easily converted to 3-fluoro-4-aryl-2-pyridones at 100 °C.

Firstly, the Michael addition[11] of ethyl 2-fluoro-2-nitroacetate (**1a**) and (*E*)-4-phenylbut-3-en-2-one (**2a**) with some bases, such as DBU, DABCO, Na_2CO_3 etc. was examined in CH_2Cl_2 at room temperature. However, no product was observed fallaciously except that using Et_3N as catalyst at 40 °C, which afforded the ketoester **3a** with about 40% yield. An advantageous method using *N*′,*N*′-dimethylethane-1,2-diamine (**4**) as catalyst and 4-nitrobenzoic acid as cocatalyst could improve the yield to 85%, With this condition at hand, a lot of ketoesters **3** with various substituents were prepared with 75–85% yield (Table 1).

Table 1
Michael addition of fluoronitroacetates with α,β-unsaturated methyl ketones [a]



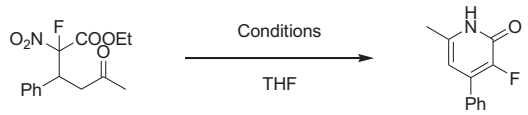
1 2 3

Entry	R^1	R^2	Product	Yield (%)
1	C_6H_5	Et	**3a**	85
2	4-BrC_6H_4	Et	**3b**	81
3	4-$MeOC_6H_4$	Et	**3c**	80
4	2-ClC_6H_4	Et	**3d**	82
5	3-ClC_6H_4	Et	**3e**	77
6	4-ClC_6H_4	Et	**3f**	80
7	4-FC_6H_4	Et	**3g**	78
8		Et	**3h**	79
9	4-$NO_2C_6H_4$	Et	**3i**	82
10	2-naphthyl	Et	**3j**	77
11	2-furan	Et	**3k**	80
12	*n*-C_4H_9	Et	**3l**	75
13	C_6H_5	*i*-Pr	**3m**	78

[a] Isolated yield of the product after column chromatography on silica gel.

Having established a good method for the synthesis of γ-fluoroketone **3**, a further conversion of this product to other useful compounds was investigated. As a test reaction, the cyclization of ethyl-2-fluoro-2-nitro-5-oxo-3-phenylhexanote (**3a**) was initially studied with several different ammonium salt and additives in THF at varied temperatures (Table 2). When we used 10 equiv NH_4OAc as ammonium salt and 0.2 equiv TsOH as additives at different temperatures, it was found that when the reaction temperature was up to the bp, the desired product (**5a**) was provided in higher yield (56%, Table 2, entries 1–3). While changing the amount of NH_4OAc to 5 or 15 equiv, the desired product was obtained in 52% and 55% yield, respectively (Table 2, entries 4 and 5). No reaction was observed when using NH_4Cl as ammonium salt, but the yield could increased to 66% with $(NH_4)_2CO_3$ (Table 2, entries 6 and 7).

Table 2
Optimization of the cyclization conditions [a]



3a 5a

Entry	N-source (equiv)	Additive (equiv)	T (°C)	Yield (%) [b]
1	NH_4OAc (10)	TsOH (0.2)	Reflux	56
2	NH_4OAc (10)	TsOH (0.2)	60	55
3	NH_4OAc (10)	TsOH (0.2)	40	45
4	NH_4OAc (5)	TsOH (0.2)	Reflux	52
5	NH_4OAc (15)	TsOH (0.2)	Reflux	55
6	NH_4Cl (10)	TsOH (0.2)	Reflux	NR
7	$(NH_4)_2CO_3$ (10)	TsOH (0.2)	Reflux	66
8	$(NH_4)_2CO_3$ (10)	None	Reflux	NR
9	$(NH_4)_2CO_3$ (10)	Et_3N (0.2)	Reflux	NR
10	$(NH_4)_2CO_3$ (10)	TsOH (1.0)	Reflux	74
11	$(NH_4)_2CO_3$ (10)	TsOH (2.0)	Reflux	80
12	$(NH_4)_2CO_3$ (10)	CF_3COOH (2.0)	Reflux	59
13	$(NH_4)_2CO_3$ (10)	CF_3SO_3H (2.0)	Reflux	52
14	$(NH_4)_2CO_3$ (10)	*p*-NBA (2.0)	Reflux	NR

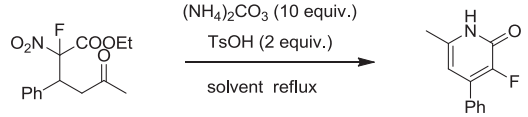
[a] Unless otherwise noted, the reaction was carried out with **3** (0.1 mmol) in THF (1.0 mL) and 50 mg of MS 4 Å was used as additive.
[b] Yield of the isolated product after column chromatography on silica gel.

Contrastively, if there was no additive or using Et_3N as the additive, no reaction was observed (Table 2, entries 8 and 9). When reviewing the type and amount of Brønsted acid, we found that 2 equiv of TsOH was the optimal condition (Table 2, entries 10 and 11). Whenever CF_3COOH, CF_3SO_3H or *p*-nitrobenzoic acid was used, no better result was observered (Table 2, entries 12–14).

Next, we examined the influence of solvent on the isolated yield. Slightly lower yields were obtained with the use of chlorine-containing solvents, such as $CHCl_3$ and $ClCH_2CH_2Cl$ (Table 3, entries 4 and 5). When CCl_4 was used as solvent, no product was observed (Table 3, entry 6). If we changed the solvent into ether, such as PhOMe and 1,4-dioxane, the yield were also around 60% (Table 3, entries 2 and 7). Fortunately, when toluene or xylene was used as solvent and the reaction temperature was up to 100 °C, the yield could increased to more than 85% (Table 3, entries 8 and 9). However, DMF being employed as solvent led to lower yield (Table 3, entry 10). Thus, the optimum reaction condition for the transformation was that with 10 equiv of $(NH_4)_2CO_3$ and 2 equiv of TsOH in xylene at 100 °C.

With the optimized condition at hand, a series of 2-fluoro-2-nitro-5-oxo-3-arylhexanote (**3a**–**m**) for the cyclization reaction

Table 3
Screening of solvents for the cyclization conditions [a]



3a 5a

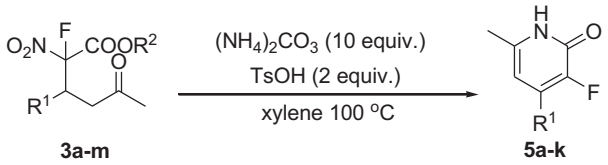
Entry	Solvent	Yield(%)[b]
1	CH_3CN	55
2[c]	PhOMe	62
3	EtOH	69
4	$CHCl_3$	49
5	DCE	56
6	CCl_4	NR
7[c]	Dioxane	55
8[c]	Toluene	86
9[c]	Xylene	89
10[c]	DMF	74

[a] Unless otherwise noted, the reaction was carried out with **3** (0.1 mmol) in solvent (1.0 mL) using 4 Å MS (50 mg) as the additive.
[b] Isolated yield of the product after column chromatography on silica gel.
[c] The reaction was conducted at 100 °C.

were examined (Table 4). Generally, most of the examined substrates with different R^1 group, including electron withdrawing, electron donating or heterocycle substitution, participated in the reaction smoothly and the reaction completed in 1–2 days to provide the desired products with more than 80% yields (Table 4, entries 1–7, 10, and 13). When the R^1 group was 2-naphthyl or 4-nitrophenyl, the yield slightly declined to 69% and 76%, respectively (Table 4, entries 8 and 9). Unfortunately, when the R^1 group was *n*-butyl, no reaction was observed (Table 4, entry 12).

Based on the experimental results, two plausible mechanisms for the cyclization reaction of **3** were showed in Scheme 1. In path A,

Table 4
Scope of the cyclization reaction to synthesize 3-fluoro-4-aryl-2-pyridone[a]



3a-m **5a-k**

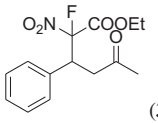
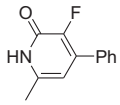
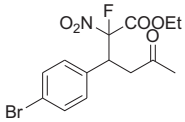
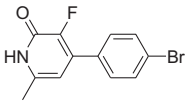
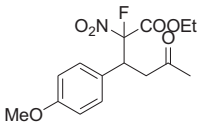
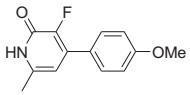
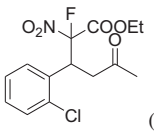
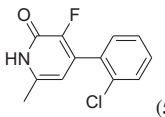
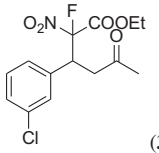
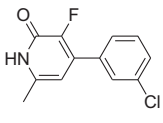
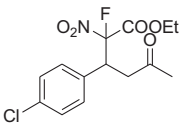
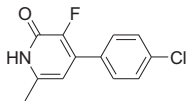
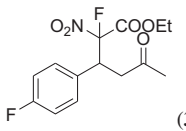
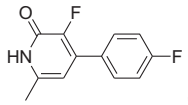
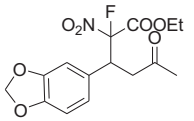
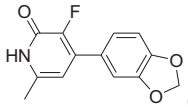
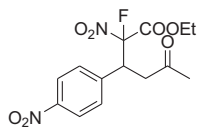
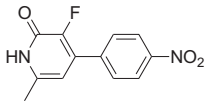
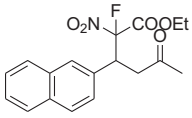
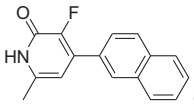
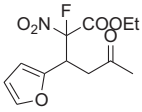
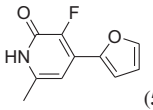
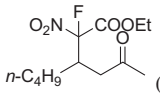
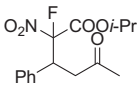
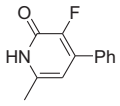
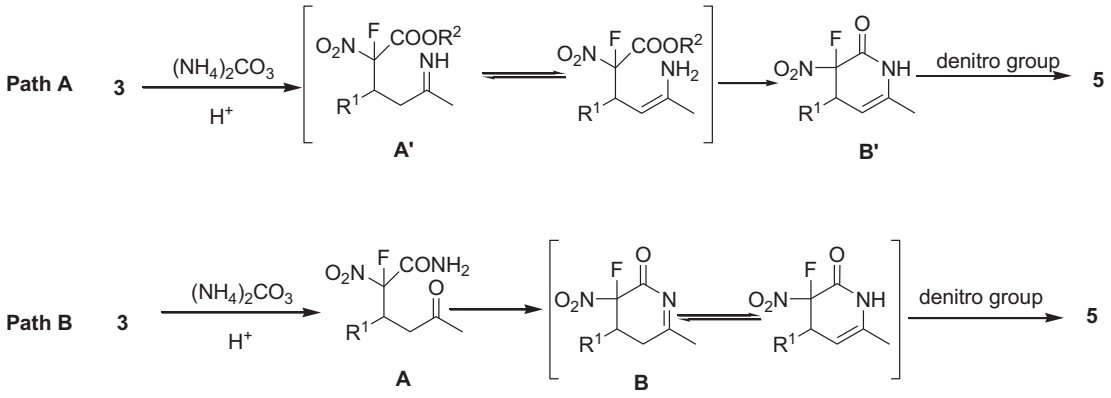
Entry	Substrate	Product	Yield(%) [b]
1	 (**3a**)	 (**5a**)	89
2	 (**3b**)	 (**5b**)	86
3	 (**3c**)	 (**5c**)	82
4	 (**3d**)	 (**5d**)	85
5	 (**3e**)	 (**5e**)	83
6	 (**3f**)	 (**5f**)	82
7	 (**3g**)	 (**5g**)	84
8	 (**3h**)	 (**5h**)	85
9	 (**3i**)	 (**5i**)	76

Table 4 (*continued*)

Entry	Substrate	Product	Yield(%) [b]
10	 (**3j**)	 (**5j**)	69
11	 (**3k**)	 (**5k**)	81
12	 (**3l**)	NR	–
13	 (**3m**)	 (**5a**)	81

[a] Unless otherwise noted, the reaction was carried out with **3** (0.1 mmol) in THF (1.0 mL) using 4 Å MS (50 mg) as the additive.
[b] Isolated yield of the product after column chromatography on silica gel.



Scheme 1. Two plausible mechanisms for the cyclization reaction of **3**.

3 reacted with $(NH_4)_2CO_3$ to give imine A′, which was easily isomerized to enamine. After an intramolecular amidation, the intermediate B′ was obtained and then converted to **5** with a denitro-group step. In path B, an amide was obtained firstly and reacted with ketone to give intermediate B. After an isomerization and denitro-group reaction, the desired product was then obtained.

3. Conclusion

In summary, we have developed a novel and simple method to synthesize a series of monofluorinated pyridones via intramolecular cyclization/denitro-group reactions. By using commercial available ammonium salt ($(NH_4)_2CO_3$) and Brønsted acid (TsOH), the desired products were obtained with up to 89% yields in xylene at 100 °C. Further application of this reaction is in progress in our laboratory.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were recorded at 300 and 100 MHz, respectively, with TMS as the internal standard. ^{19}F NMR spectra were recorded at 282 MHz with $CFCl_3$ as the external standard. IR spectra were recorded in cm^{-1}. Melting points were uncorrected.

All solvents were distilled prior to use unless otherwise noted. All reactions sensitive to moisture or oxygen were conducted under an atmosphere of nitrogen or argon.

4.2. General procedure for the preparation of 3-fluoro-4-aryl-2-pyridone (5)

Under an atmosphere of argon, a solution of compound (**3**) (0.1 mmol), TsOH (0.2 mmol, 34 mg), $(NH_4)_2CO_3$ (1 mmol, 96 mg), and 4 Å MS (40 mg) in xylene (1.0 mL) was heated at 100 °C for appropriate times. When the reaction was completed (monitored by TLC), the reaction system was cooled to room temperature. After removal of the solvent under reduced pressure, the crude product was purified directly by column chromatography on silica gel (hexanes/EtOAc=2/1) to afford the desired products.

*4.2.1. 3-Fluoro-6-methyl-4-phenylpyridin-2(1H)-one (**5a**).* Yield: 89%; yellowish brown solid; mp: 198–199 °C, IR (CH_2Cl_2, film): 3402, 2165, 1661, 1497, 1183, 1126, 1046, 749, 692 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=13.23 (br s, 1H), 7.58 (d, J=7.8 Hz, 2H), 7.51–7.48 (m, 3H), 6.14 (d, J=5.4 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3/CD_3OD$): 157.9 (d, J=27.1 Hz), 146.4 (d, J=244.2 Hz), 139.4 (d, J=5.8 Hz), 136.3 (d, J=9.0 Hz), 132.9, 129.2128.5, 128.4(d, J=6.7 Hz), 106.4, 17.9; ^{19}F NMR ($CDCl_3$):

δ=−146.0 (s, 1F); MS (ESI) (*m*/*z*): 226 (M+Na^+); HRMS calcd for $C_{12}H_{10}NFO$: 203.0746, found: 203.0747.

*4.2.2. 4-(4-Bromophenyl)-3-fluoro-6-methylpyridin-2(1H)-one (**5b**).* Yield: 86%; yellowish brown solid; mp: 238–239 °C, IR (CH_2Cl_2, film): 3411, 2853, 1670, 1477, 1182, 1144, 1049, 761, 659 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=13.25 (br s, 1H), 7.53 (d, *J*=7.8 Hz, 2H), 7.38 (d, *J*=7.2 Hz, 2H), 6.02 (d, *J*=4.8 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 158.7 (d, *J*=24.6 Hz), 146.4 (d, *J*=244.7 Hz), 140.0 (d, *J*=6.1 Hz), 135.1 (d, *J*=8.7 Hz), 132.0, 130.2 (d, *J*=3.7 Hz),123.8, 106.4, 18.8; ^{19}F NMR ($CDCl_3$): δ=−145.0 (s, 1F); MS (ESI) (*m*/*z*): 306 (M+Na^+); HRMS calcd for $C_{12}H_9NBrFO$: 280.9852, found: 280.9857.

*4.2.3. 3-Fluoro-4-(4-methoxyphenyl)-6-methylpyridin-2(1H)-one (**5c**).* Yield: 82%; yellowish brown solid; mp: 234–235 °C, IR (CH_2Cl_2, film): 3417, 2918, 1665, 1451, 1182, 1145, 1031, 762, 664 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=13.11 (br s, 1H), 7.56 (d, *J*=6.0 Hz, 2H), 7.02 (d, *J*=6.6 Hz, 2H), 6.15 (d, *J*=4.8 Hz, 1H), 3.90 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 158.7 (d, *J*=25.4 Hz), 146.4 (d, *J*=228.8 Hz), 139.4 (d, *J*=6.7 Hz), 135.6 (d, *J*=8.1 Hz), 130.1, 130.1, 125.3, 114.2, 106.1, 55.4, 18.8; ^{19}F NMR ($CDCl_3$): δ=−146.3 (s, 1F); MS (ESI) (*m*/*z*): 256 (M+Na^+); HRMS calcd for $C_{13}H_{12}NFO_2$: 233.0852, found: 233.0853.

*4.2.4. 4-(2-Chlorophenyl)-3-fluoro-6-methylpyridin-2(1H)-one (**5d**).* Yield: 85%; yellowish brown solid; mp: 213–214 °C, IR (CH_2Cl_2, film): 3420, 2852, 1654, 1468, 1183, 1148, 1048, 756, 660 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=13.24 (br s, 1H), 7.50 (d, *J*=8.7 Hz, 1H), 7.35 (t, *J*=7.2 Hz, 3H), 5.99 (d, *J*=4.2 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 157.4 (d, *J*=24.6 Hz), 145.5 (d, *J*=245.5 Hz), 138.5 (d, *J*=6.8 Hz), 133.8 (d, *J*=11.6 Hz), 131.7, 131.4, 129.4, 129.2, 129.0, 125.8, 106.1, 17.7; ^{19}F NMR ($CDCl_3$): δ=−139.9 (s, 1F); MS (ESI) (*m*/*z*): 260 (M+Na^+); HRMS calcd for $C_{12}H_9NClFO$: 237.0357, found: 237.0353.

*4.2.5. 4-(3-Chlorophenyl)-3-fluoro-6-methylpyridin-2(1H)-one (**5e**).* Yield: 83%; yellowish brown solid; mp: 205–206 °C, IR (CH_2Cl_2, film): 3405, 2923, 1669, 1455, 1184, 1145, 1047, 759, 690 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=12.45 (br s, 1H), 7.88 (s, 1H), 7.80 (s, 3H), 6.41 (d, *J*=5.4 Hz, 1H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 157.7 (d, *J*=25.4 Hz), 146.4 (d, *J*=245.8 Hz), 139.7 (d, *J*=6.7 Hz), 134.8 (d, *J*=8.6 Hz), 134.6 (d, *J*=11.4 Hz), 129.9, 128.5, 128.5 (d, *J*=3.6 Hz), 126.8, 126.7, 105.8, 18.0; ^{19}F NMR (DMSO-d_6): δ=−145.1 (s, 1F); MS (ESI) (*m*/*z*): 260 (M+Na^+); HRMS calcd for $C_{12}H_9NClFO$: 237.0357, found: 237.0350.

*4.2.6. 4-(4-Chlorophenyl)-3-fluoro-6-methylpyridin-2(1H)-one (**5f**).* Yield: 82%; yellowish brown solid; mp: 212–214 °C, IR (CH_2Cl_2, film): 3405, 2173, 1665, 1493, 1183, 1110, 1048, 768, 678 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=12.18 (br s, 1H), 7.62–7.55 (m, 4H), 6.12 (d, *J*=5.7 Hz, 1H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): 156.6 (d, *J*=26.4 Hz), 146.6 (d, *J*=223.7 Hz), 140.6 (d, *J*=3.4 Hz), 134.5, 133.2 (d, *J*=9.0 Hz), 132.3, 130.8 (d, *J*=3.8 Hz), 129.3, 129.2, 103.7, 18.6; ^{19}F NMR (DMSO-d_6): δ=−145.6 (s, 1F); MS (ESI) (*m*/*z*): 260 (M+Na^+); HRMS calcd for $C_{12}H_9NClFO$: 237.0357, found: 237.0352.

*4.2.7. 3-Fluoro-4-(4-fluorophenyl)-6-methylpyridin-2(1H)-one (**5g**).* Yield: 84%; yellowish brown solid; mp: 189–190 °C, IR (CH_2Cl_2, film): 3398, 2924, 1665, 1465, 1199, 1147, 1041, 769, 682 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=12.16 (br s, 1H), 7.66–7.62 (m, 2H), 7.37–7.32 (m, 2H), 6.12 (d, *J*=5.1 Hz, 1H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): 163.3 (d, *J*=245.6 Hz), 156.6 (d, *J*=25.3 Hz), 146.5 (d, *J*=242.1 Hz), 140.5, 133.4 (d, *J*=8.8 Hz), 131.3 (d, *J*=3.7 Hz), 116.1 (d, *J*=21.6 Hz), 104.0, 18.6; ^{19}F NMR (DMSO-d_6): δ=−145.0 (s, 1F), −111.8 (m, 1F); MS (ESI) (*m*/*z*): 244 (M+Na^+); HRMS calcd for $C_{12}H_9NF_2O$: 221.0652, found: 221.0656.

*4.2.8. 4-(Benzo[d][1,3]dioxol-5-yl)-3-fluoro-6-methylpyridin-2(1H)-one (**5h**).* Yield: 85%; yellowish brown solid; mp: 225–226 °C, IR (CH_2Cl_2, film): 3434, 2921, 1659, 1456, 1188, 1160, 1032, 761, 662 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.08 (d, *J*=8.1 Hz, 2H), 6.91 (d, *J*=7.8 Hz, 2H), 6.14 (d, *J*=5.1 Hz, 1H), 6.04 (s, 2H), 2.35 (s, 3H); ^{13}C NMR(100 MHz, $CDCl_3$): 157.9 (d, *J*=25.4 Hz), 148.6, 148.0, 146.5 (d, *J*=242.9 Hz), 139.1 (d, *J*=5.6 Hz), 135.9 (d, *J*=8.9 Hz), 126.4, 122.8 (d, *J*=4.3 Hz), 108.9, 108.4, 106.3, 101.5, 18.2; ^{19}F NMR ($CDCl_3$): δ=−145.9 (s, 1F); MS (ESI) (*m*/*z*): 270 (M+Na^+); HRMS calcd for $C_{13}H_{10}NFO_3$: 247.0645, found: 247.0642.

*4.2.9. 3-Fluoro-6-methyl-4-(4-nitrophenyl)pyridin-2(1H)-one (**5i**).* Yield: 76%; yellowish brown solid; mp: 251–252 °C, IR (CH_2Cl_2, film): 3409, 2190, 1673, 1519, 1184, 1119, 1048, 749, 696 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=12.29 (br s, 1H), 8.34 (d, *J*=6.0 Hz, 2H), 7.85 (d, *J*=8.4 Hz, 2H), 6.18 (d, *J*=5.4 Hz, 1H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): 156.5 (d, *J*=26.4 Hz), 146.4 (d, *J*=243.0 Hz), 141.1, 140.0, 132.4 (d, *J*=8.6 Hz), 130.4 (d, *J*=3.7 Hz), 129.1, 124.2, 103.4, 18.7; ^{19}F NMR (DMSO-d_6): δ=−144.1 (s, 1F); MS (ESI) (*m*/*z*): 271 (M+Na^+); HRMS calcd for $C_{12}H_9N_2FO_3$: 248.0597, found: 248.0595.

*4.2.10. 3-Fluoro-6-methyl-4-(naphthalen-2-yl)pyridin-2(1H)-one (**5j**).* Yield: 69%; yellowish brown solid; mp: 209–210 °C, IR (CH_2Cl_2, film): 3425, 2854, 1657, 1475, 1197, 1118, 1048, 762, 652 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=12.18 (br s, 1H), 8.17 (s, 1H), 8.05–7.97 (m, 3H), 7.69 (d, *J*=8.4 Hz, 1H), 7.59 (t, *J*=4.2 Hz, 2H), 6.25 (d, *J*=5.7 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR(100 MHz, DMSO-d_6): 161.4 (d, *J*=26.4 Hz), 151.5 (d, *J*=230.0 Hz), 145.2 (d, *J*=6.0 Hz), 139.1 (d, *J*=9.1 Hz), 138.0 (d, *J*=4.4 Hz), 135.7, 133.6, 133.4, 133.3, 132.8, 132.3, 131.9, 131.1, 131.1, 109.0, 23.4; ^{19}F NMR ($CDCl_3$): δ=−145.9 (s, 1F); MS (ESI) (*m*/*z*): 529 (2M+Na^+); HRMS calcd for $C_{16}H_{12}NFO$: 253.0903, found: 253.0906.

*4.2.11. 3-Fluoro-4-(furan-2-yl)-6-methylpyridin-2(1H)-one (**5k**).* Yield: 81%; yellowish brown solid; mp: 209–210 °C, IR (CH_2Cl_2, film): 3435, 2925, 1666, 1490, 1203, 1145, 1049, 763, 582 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=8.09 (s, 1H), 7.51 (t, *J*=3.0 Hz, 1H), 7.03 (d, *J*=1.8 Hz, 1H), 6.96 (d, *J*=5.1 Hz, 1H), 2.72 (s, 3H); ^{13}C NMR(100 MHz, $CDCl_3$/CD_3OD): 161.4 (d, *J*=24.7 Hz), 148.5 (d, *J*=244.9 Hz), 143.7 (d, *J*=5.9 Hz), 136.5, 129.4 (d, *J*=8.1 Hz), 119.0, 129.2, 118.9, 116.4, 105.1, 17.9; ^{19}F NMR ($CDCl_3$): δ=−141.7 (s, 1F); MS (ESI) (*m*/*z*): 216 (M+Na^+); HRMS calcd for $C_{10}H_8NFO_2$: 193.0539, found: 193.0535.

4.3. General procedure for the preparation of ketoester (3)

A solution of α,β-unsaturated methyl ketones (**2**) (0.1 mmol), fluoronitroacetates (**1**) (0.15 mmol), *N*′,*N*′-dimethylethane-1,2-diamine (**4**) (20 mol %) and 4-nitrobenzoic acid (20 mol %) in CH_2Cl_2 (1.0 mL) was reacted at room temperture for appropriate times. After removal of the solvent under reduced pressure, the crude product was purified directly by column chromatography on silica gel (hexanes/EtOAc=5/1) to afford the desired products.

Acknowledgements

This research was supported by the National Natural Science Foundation of China (No.21032006, 20172064), the QT Program, Shanghai Natural Science Council.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.01.047. These data

include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. (a) Du, W. *Tetrahedron* **2003**, *59*, 8649; (b) Jiang, H.; Luo, X.; Bai, D. *Curr. Med. Chem.* **2003**, *10*, 2231; (c) Misra, R.; Pandey, R. C.; Silverton, J. V. *J. Am. Chem. Soc.* **1982**, *104*, 4478.
2. (a) Wall, M. E.; Wani, M. C.; Cook, C. E.; Palmer, K. H.; McPhail, A. T.; Sim, G. A. *J. Am. Chem. Soc.* **1966**, *88*, 3888; (b) Wall, M. E. *Med. Res. Rev.* **1998**, *18*, 299.
3. (a) Kozikowski, A. P.; Campiani, G.; Sun, L.-Q.; Wang, S.; Saxena, A.; Doctor, B. P. *J. Am. Chem. Soc.* **1996**, *118*, 11357; (b) Campiani, G.; Kozikowski, A. P.; Shaomeng, W.; Liu, M.; Nacci, V.; Saxena, A.; Doctor, B. P. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1413.
4. Kobayashi, J.; Hirasawa, Y.; Yoshida, N.; Morita, H. *J. Org. Chem.* **2001**, *66*, 5901.
5. Parreira, R. L. T.; Abrahao, O.; Galembeck, S. E. *Tetrahedron* **2001**, *57*, 3243.
6. Recent methods: (a) Yermolayev, S. A.; Gorobets, N. Y.; Desenko, S. M. *J. Comb. Chem.* **2009**, *11*, 44; (b) Li, S.; Wang, S. *J. Heterocycl. Chem.* **2008**, *45*, 1875; (c) Imase, H.; Noguchi, K.; Hirano, M.; Tanaka, K. *Org. Lett.* **2008**, *10*, 3563; (d) Liu, J.; Liang, D.; Wang, M.; Liu, Q. *Synthesis* **2008**, 3633; (e) Chen, L.; Zhao, Y.-L.; Liu, Q.; Cheng, C.; Piao, C.-R. *J. Org. Chem.* **2007**, *72*, 9259; (f) Zhang, R.; Zhang, D.; Guo, Y.; Zhou, G.; Jiang, Z.; Dong, D. *J. Org. Chem.* **2008**, *73*, 9504; (g) Xiang, D.; Wang, K.; Liang, Y.; Zhou, G.; Dong, D. *Org. Lett.* **2008**, *10*, 345; (h) Pan, W.; Dong, D.; Wang, K.; Zhang, J.; Wu, R.; Xiang, D.; Liu, Q. *Org. Lett.* **2007**, *9*, 2421; (i) Tsai, T.; Chung, W.; Chang, J.; Hsu, R.; Chang, N. *Tetrahedron* **2007**, *63*, 9825; (j) Boisse, T.; Rigo, B.; Millet, R.; Henichart, J.-P. *Tetrahedron* **2007**, *63*, 10511; (k) Pemberton, N.; Jakobsson, L.; Almqvist, F. *Org. Lett.* **2006**, *8*, 935; (l) Kondo, T.; Nomura, M.; Ura, Y.; Wada, K.; Mitsudo, T. *Tetrahedron Lett.* **2006**, *47*, 7107; (m) Duong, H. A.; Louie, J. *J. Organomet. Chem.* **2005**, *690*, 5098; (n) Duong, H.; Cross, M.; Louie, J. *J. Am. Chem. Soc.* **2004**, *126*, 11438; (o) Paulvannan, K.; Chen, T. *J. Org. Chem.* **2000**, *65*, 6160; (p) Brun, E.; Gil, S.; Mestres, R.; Parra, M. *Synthesis* **2000**, 273; (q) Alberola, A.; Calvo, L.; Ortega, A.; Carmen Sanudo Ruiz, M.; Yustos, P. *J. Org. Chem.* **1999**, *64*, 9493; (r) Chandra Sheker Reddy, A.; Narsaiah, B.; Venkataratnam, R. *Tetrahedron Lett.* **1996**, *37*, 2829; (s) Takaoka, K.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **1996**, *37*, 4973; (t) Zhang, S.; Liebeskind, L. *J. Org. Chem.* **1999**, *64*, 4042; (u) Furukawa, I.; Fujisawa, H.; Kawazome, M.; Nakai, Y.; Ohta, T. *Synthesis* **1998**, 1715; (v) Ghosez, L.; Jnoff, E.; Bayard, P.; Sainte, F.; Beaudegnies, R. *Tetrahedron* **1999**, *55*, 3387; (w) Grosche, P.; Holtzel, A.; Walk, T.; Trautwein, A.; Jung, G. *Synthesis* **1999**, 1961; (x) Katritzky, A.; Belyakov, S.; Sorochinsky, A.; Henderson, S.; Chen, J. *J. Org. Chem.* **1997**, *62*, 6210; (y) Barluenga, J.; Tomas, M.; Suarez, A.; Gotor, V. *Tetrahedron Lett.* **1988**, *29*, 4855; (z) Deodhar, K.; Kekare, M.; Pednekar, S. *Synthesis* **1985**, 328; (aa) Hong, P.; Yamazaki, H. *Synthesis* **1977**, 50.
7. (a) Decker, H. *Chem. Ber.* **1892**, *25*, 443; (b) Mohrle, H.; Weber, H. *Tetrahedron* **1970**, *26*, 2953.
8. Jones, G. *Org. React.* **1967**, *15*, 204.
9. Smith, A.; Atasoylu, O.; Beshore, D. *Synlett* **2009**, 2643.
10. Volle, J.; Mävers, U.; Schlosser, M. *Eur. J. Org. Chem.* **2008**, 2430.
11. Cui, H.; Yang, Y.; Wang, X.; Chai, Z.; Li, P.; Cai, Y.; Zhu, S.; Zhao, G. *Tetrahedron* **2011**, *67*, 312.