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Convenient synthesis of perfluoroalkyl substituted 2-oxopyridine-fused 1,3-diazaheterocycles via a one-pot three-component reaction

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ABSTRACT

An efficient one-pot synthesis of perfluoroalkylated ring-fused 2-pyridones by three-component reaction of diamine, ketene dithioacetal, and methyl 2-perfluoroalkynoate in EtOH is reported. This protocol has the advantages of easiness, higher yields, and shorter reaction time. A plausible mechanism for this type of cyclization is proposed.

1. Introduction

Many ring-fused 2-pyridones show biological activities.[1] Among these compounds, 2-oxopyridine-fused 1,3-diazaheterocycle moieties are of general interest as a basis for analgesics and antiinflammatory agents in medicinal chemistry.[2] Although a variety of methods for the synthesis of such ring-fused 2-pyridinones are available,[2–6] a survey of literatures shows that the preparation of fluorinated 2-oxopyridine-fused 1,3-diazaheterocycles is challenging because of the paucity of synthetic access.

Multicomponent reactions (MCRs) are powerful tools in creating fused heterocycles because of the inherent molecular diversity, efficiency, and atom-economy.[7]

The ketene dithioacetals of the type **2** are well known as two-carbon synthons and for their push–pull electronic nature.[8] The Michael acceptor characteristics of the ethylene portion of **2** and the possibility of substitution of the two alkylsulfanyl groups with nucleophiles have been well exploited for the synthesis of a variety of heterocycles.[9]

On considering the importance of the introduction of trifluoromethyl or the perfluoroalkyl groups in many biologically active pharmaceutical and agrochemical compounds,[10] and in continuation of our interest in exploiting methyl 2-perfluoroalkynoate as fluorinated building block for the synthesis of perfluoroalkylated heterocycles,[11] herein, we describe an efficient synthesis of perfluoroalkylated 2-oxopyridine-fused 1,3-diazaheterocycles via a new and one-pot three-component reaction between ketene dithioacetal,[12] various diamines and methyl 2-perfluoroalkynoates.[13]

2. Results and discussion

Initially, the three-component reaction of 1,3-propyldiamine **1a** and 1,1-bis(methylthio)-2-nitroethylene **2a** in the presence of methyl 4,4,4-trifluorobut-2-ynoate **3a** as a simple model reaction was investigated to establish the feasibility of the strategy and to optimize the reaction conditions. The reaction was performed in a one-pot two-step process. A mixture of **1a** (1.0 mmol) and 1,1-bis(methylthio)-2-nitroethylene **2a** (1.5 mmol) was stirred in refluxing solvent (5 mL) for 0.5 h, then methyl 4,4,4-trifluorobut-2-ynoate **3a** (1.1 mmol) was added and continued to be stirred for the rest of the designated time. Since the choice of an appropriate reaction medium is of crucial importance for successful synthesis, different solvents, such as methanol, ethanol, acetonitrile,

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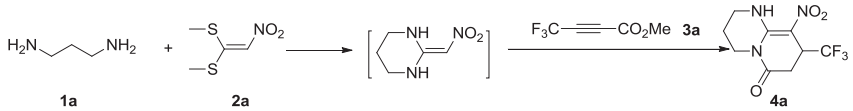
tetrahydrofuran (THF), toluene, and dichloromethane (DCM) were explored. The results are summarized in Table 1. As can be seen from the table, the best results were obtained by refluxing the reaction mixture in EtOH to yield product **4a** in excellent yield (Table 1, entry 7).

Table 1
Optimization of reaction conditions

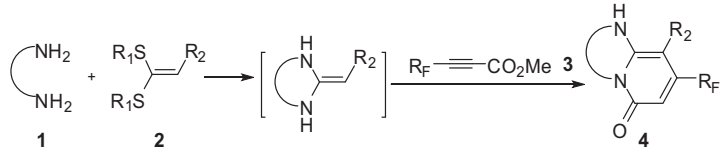


Entry	Solvent	Temperature	Time (h)	Yield[a] (%)
1	DCM	rt	12	34
2	DCM	Reflux	12	39
3	Acetonitrile	Reflux	12	14[b]
4	Toluene	Reflux	12	Trace
5	THF	Reflux	12	40
6	MeOH	Reflux	4	60
7	**EtOH**	**Reflux**	**4**	**95**

Bold entry signifies best result for the reaction condition optimization.
[a] Isolated yield.
[b] The unreacted starting material was recovered.

To test the generality of the conversion, ketene dithioacetal **2** was subjected to reaction with a variety of diamines **1** and methyl 2-perfluoroalkynoates **3**. Using the combinations of **2a** with **3a** and a variety of diamines **1a**–**j**, as shown in Table 2, almost all of the tested combinations successfully produced the desired 2-oxopyridine-fused 1,3-diazaheterocycles with good to excellent yields. However, to synthesize 2-oxopyridine-fused eight-membered 1,3-diazaheterocycle **4e**, only a trace amount of conversion with respect to **1e** was observed even when the reaction was conducted for 48 h. The results also suggested that the cis or trans configuration of the corresponding diamine had some influence on this cascade process. For example, ring-closure to compound **4f** was accomplished with *cis*-cyclohexanediamine **1f** while the use of its trans-isomer **1g** gave no product. Aliphatic diamines were proven to be more reactive than aryl diamines. Moreover, these studies clearly reveal that aryl diamines having electron-withdrawing groups on benzene ring are not compatible

Table 2
Synthesis of perfluoroalkylated 2-oxopyridine-fused 1,3-diazaheterocycles[a]



1a 1,3-propyldiamine **1b** 1,2-ethyldiamine **1c** 2,2-dimethy-1,3-propyldiamine
1d 1,4-butyldiamine **1e** 1,5-pentanediamine **1f** *cis*-1,2-cyclohexanediamine
1g *trans*-1,2-cyclohexanediamine **1h** 1,2-benzenediamine
1i 4,5-dichloro-1,2-benzenediamine **1j** 4,5-dimethyl-1,2-benzenediamine
2a R_1 = Me, R_2 = NO_2 **2b** R_1 = Et, R_2 = COPh
3a R_F = CF_3 **3b** R_F = C_2F_5 **3c** R_F = *n*- C_3F_7

Entry	Diamine **1**	Ketene dithioacetal **2**	2-Perfluoroalkynoate **3**	Time (h)	Product **4**	Yield[b] (%)
1	**1a**	**2a**	**3a**	4	**4a**	91
2	**1b**	**2a**	**3a**	4	**4b**	95
3	**1c**	**2a**	**3a**	4	**4c**	90
4	**1d**	**2a**	**3a**	4	**4d**	87
5	**1e**	**2a**	**3a**	48	**4e**	Trace
6	**1f**	**2a**	**3a**	4	**4f**	92
7	**1g**	**2a**	**3a**	48	**4g**	0
8	**1h**	**2a**	**3a**	4	**4h**	76
9	**1i**	**2a**	**3a**	48	**4i**	0
10	**1j**	**2a**	**3a**	48	**4j**	53
11	**1a**	**2b**	**3a**	8	**4k**	78
12	**1b**	**2b**	**3a**	8	**4l**	85
13	**1c**	**2b**	**3a**	8	**4m**	81
14	**1a**	**2a**	**3b**	4	**4n**	80
15	**1b**	**2a**	**3b**	4	**4o**	85
16	**1c**	**2a**	**3b**	4	**4p**	80
17	**1a**	**2a**	**3c**	4	**4q**	67
18	**1b**	**2a**	**3c**	4	**4r**	75
19	**1c**	**2a**	**3c**	4	**4s**	70
20	**1f**	**2a**	**3c**	4	**4t**	63

[a] Reaction conditions: a mixture of **1** (1.0 mmol) and ketene dithioacetal **2** (1.5 equiv) was stirred in refluxing solvent (5 mL) for 0.5 h, then methyl 2-perfluoroalkynoate **3** (1.1 equiv) was added and continued to be stirred for the rest of the designated time.
[b] Isolated yield.

with this process (Table 2, entry 9). This might be due to the fact that the NH_2 groups in **1i** were less nucleophilically active than those in **1h** or **1j**. Sterically demanding diamines, such as **1c** were also successfully converted into the corresponding products (Table 2, entries 3, 13, and 19). In order to expand the scope of the cyclocondensation reaction, **2a** was replaced by ketene dithioacetal **2b**. The reaction proceeded smoothly and afforded the similar results as **2a** after extending reaction time from 4 h to 8 h (Table 2, entries 11–13). Generally, the formation of ring-fused 2-pyridone was less favored with methyl 2-perfluoroalkynoates **3** containing longer carbon chain of perfluoroalkyl group (Table 2, compared entry 1 to entries 14 and 17). However, no corresponding product was obtained under the same reaction conditions when methyl 4,4,4-trifluorobut-2-ynoate was replaced by methyl but-2-ynoate. The structures of compounds **4a**–**t** were deduced from their ^{1}H, ^{19}F and ^{13}C NMR, IR, and mass spectra. Further confirmation of the structure of **4** came from the analysis of single-crystal X-ray data of **4a** (Fig. 1).[14]

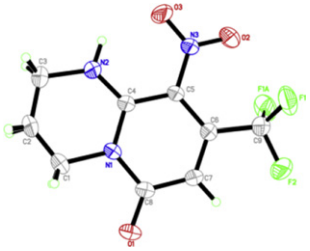


Fig. 1. X-ray structure of compound **4a**.

On the basis of all results mentioned above and the related report,[6f] a plausible mechanism was proposed (Scheme 1). Diamine **1** undergoes nucleophilic attack at C(1) of the tautomer **2′** of ketene dithioacetal **2** to give the adduct **A**. Elimination of one molecule of R_1SH from **A** forms **B**, which cyclizes by a second nucleophilic attack to afford intermediate **C**. Another elimination of R_1SH from **C** affords cyclic ene-1,1-diamine **D**, which can be isolated and identified.[6g] The aza-ene reaction of **D** with 2-perfluoroalkynoate **3** gives **E**, which undergoes an intramolecular imine–enamine tautomerization, followed by an intramolecular nucleophilic attack of the secondary amino group at the CO group of the ester function to close the six membered ring to form compound **4**.

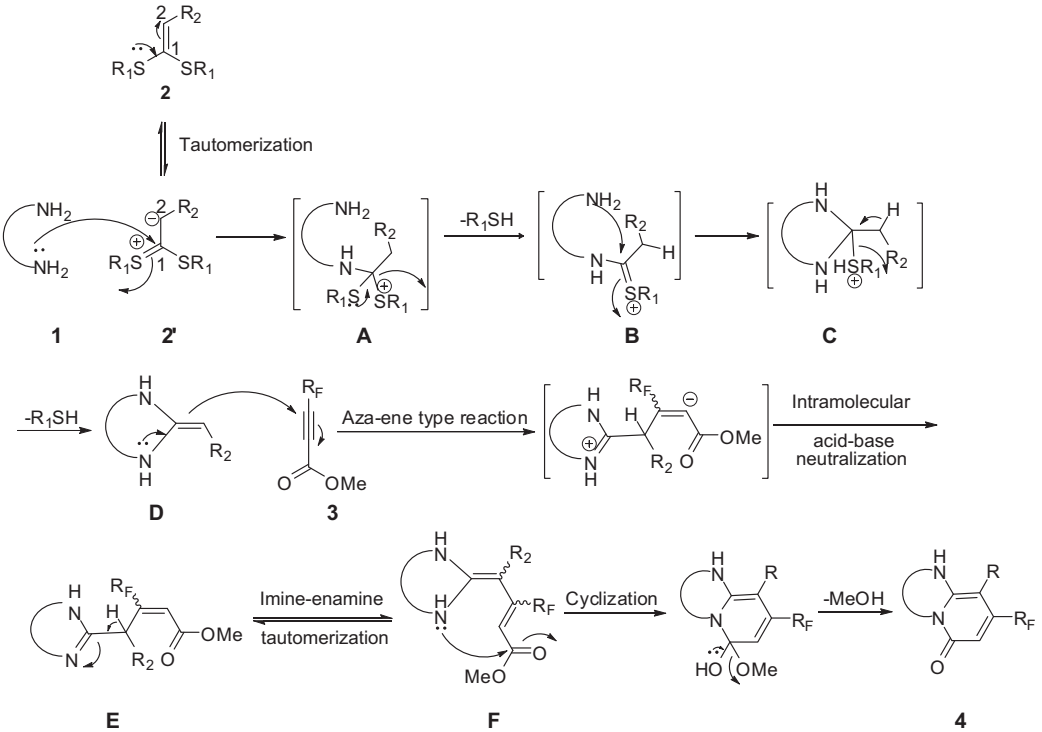
3. Conclusions

We have developed a concise approach to the synthesis of perfluoroalkyl substituted 2-oxopyridine-fused 1,3-diazaheterocycles by one-pot reaction between diamines, ketene dithioacetals, and 2-perfluoroalkynoates. Characteristics of this method are good to excellent yields of the products, mild reaction conditions, and use of easily available starting materials. A plausible mechanism of the ring-closure cascade reaction including nucleophilic substitution, aza-ene reaction, intramolecular imine–enamine tautomerization, followed by cyclization, is proposed.

4. Experimental

4.1. General information

Unless otherwise noted, all reagents were purchased from commercial sources and used without further purification. Solvents were distilled before use. Melting points were recorded on a SGW X_4 instrument and uncorrected. ^{1}H, ^{19}F, and ^{13}C NMR spectra were recorded on a Bruker DRX-500 MHz spectrometer. All chemical shifts are reported in parts per million downfield (positive) of the standard: C_6F_6 for ^{19}F, TMS for ^{1}H and ^{13}C NMR spectra. IR spectra were obtained on an AVATAR370 FT-IR spectrometer. LRMS (lower resolution mass spectra) and HRMS (high resolution mass spectra) were obtained on an Agilent LC/MSD SL and Bruker Daltonics APEXIII 7.0 TESALA FTMS instrument, respectively. X-ray analysis was performed on a Bruker Smart Apex2 CCD spectrometer. All



Scheme 1. Proposed mechanism for the formation of **4**.

yields reported in this publication referred to isolated ones of compounds and their purity was determined by ^{1}H NMR.

4.2. General procedure for the preparation of 2-oxopyridine-fused 1,3-diazaheterocycles 4

Diamine **1** (1.0 mmol) and ketene dithioacetal **2** (1.5 equiv) was mixed and dissolved in EtOH (5 mL). After stirring for 0.5 h under reflux, methyl 2-perfluoroalkynoate **3** (1.1 equiv) was added dropwise into the solution. The reaction mixture was then allowed to stir under reflux for the rest of the designated time (see Table 2). Evaporation of the solvent under reduced pressure resulted in crude product, which was subjected to column chromatography on silica gel for further purification using ethyl acetate/petroleum ether as eluent.

4.2.1. 9-Nitro-8-(trifluoromethyl)-3,4-dihydro-1H-pyrido[1,2-a]pyrimidin-6(2H)-one ***4a***. Light yellow solid; yield: 95%, mp: 251.6–251.8 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.11–2.16 (m, 2H), 3.59–3.62 (m, 2H), 4.06 (t, J=6.0 Hz, 2H), 6.35 (s, 1H), 10.37 (s, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ 18.0, 41.1, 108.2 (q, $^3J_{C-F}$=7.4 Hz), 111.0, 122.4 (q, $^1J_{C-F}$=272.0 Hz), 135.2 (q, $^2J_{C-F}$=32.0 Hz), 150.7, 160.0 ppm; ^{19}F NMR (470 MHz, DMSO-d_6) δ −59.9 (s, CF_3) ppm. IR (KBr): ν 3180, 3121, 2964, 1692, 1582, 1419, 1380, 1344, 1255, 1220, 1152, 1025, 983, 874 cm^{-1}; MS (EI) m/z (%): 262 $[(M-H)]^-$. HRMS (ESI) calcd for $C_9H_8F_3N_3O_3$ $[(M-H)]^-$: 262.0444; found: 262.0445.

4.2.2. 8-Nitro-7-(trifluoromethyl)-2,3-dihydroimidazo[1,2-a]pyridin-5(1H)-one ***4b***. Light yellow solid; yield: 91%, 254.3 °C (decomposed); ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.88 (t, J=9.5 Hz, 2H), 4.11 (t, J=9.5 Hz, 2H), 6.20 (s, 1H), 9.68 (s, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ 43.9, 44.4, 110.0, 110.1 (q, $^3J_{C-F}$=7.3 Hz), 122.2 (q, $^1J_{C-F}$=272.0 Hz), 135.1 (q, $^2J_{C-F}$=32.1 Hz), 153.6, 158.6 ppm; ^{19}F NMR (470 MHz, DMSO-d_6) δ −59.7 (s, CF_3) ppm. IR (KBr): ν 3329, 3117, 2932, 1682, 1596, 1570, 1435, 1337, 1274, 1184, 1155, 1037, 984, 880 cm^{-1}; MS (EI) m/z (%): 248 $[(M-H)]^-$. HRMS (ESI) calcd for $C_8H_6F_3N_3O_3$ $[(M-H)]^-$: 248.0287; found: 248.0288.

4.2.3. 3,3-Dimethyl-9-nitro-8-(trifluoromethyl)-3,4-dihydro-1H-pyrido[1,2-a]pyrimidin-6(2H)-one ***4c***. Light yellow solid; yield: 90%, mp: 175.3–176.2 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.02 (s, 6H), 3.26 (s, 2H), 3.65 (s, 2H), 6.28 (s, 1H), 10.30 (s, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ 23.7, 25.8, 50.4, 51.1, 108.3, 110.9, 122.3 (q, $^1J_{C-F}$=272.0 Hz), 135.3 (q, $^2J_{C-F}$=32.0 Hz), 149.7, 159.8 ppm; ^{19}F NMR (470 MHz, DMSO-d_6) δ −59.8 (s, CF_3) ppm. IR (KBr): ν 3439, 3200, 3161, 2968, 2880, 1679, 1596, 1417, 1355, 1273, 1257, 1202, 1161, 1143, 1017, 971, 865 cm^{-1}; MS (EI) m/z (%): 290 $[(M-H)]^-$. HRMS (ESI) calcd for $C_{11}H_{12}F_3N_3O_3$ $[(M-H)]^-$: 290.0758; found: 290.0758.

4.2.4. 10-Nitro-9-(trifluoromethyl)-2,3,4,5-tetrahydropyrido[1,2-a][1,3]diazepin-7(1H)-one ***4d***. Light yellow solid; yield: 87%, mp: 156.7–156.9 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.99–2.00 (m, 4H), 3.62–3.65 (m, 2H), 4.27–4.30 (m, 2H), 6.42 (s, 1H), 9.34 (s, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ 23.4, 24.0, 46.0, 46.8, 111.2 (q, $^3J_{C-F}$=6.3 Hz), 114.6, 122.3 (q, $^1J_{C-F}$=274.0 Hz), 135.4 (q, $^2J_{C-F}$=32.0 Hz), 155.2, 161.0 ppm. ^{19}F NMR (470 MHz, $CDCl_3$) δ −60.0 (s, CF_3) ppm. IR (KBr): ν 3437, 3257, 3069, 2966, 2941, 2868, 1687, 1568, 1440, 1380, 1269, 1241, 1193, 1148, 1096, 984, 886 cm^{-1}; MS (EI) m/z (%): 276 $[(M-H)]^-$. HRMS (ESI) calcd for $C_{10}H_{10}F_3N_3O_3$ $[(M-H)]^-$: 276.0598; found: 276.0601.

4.2.5. 4-Nitro-3-(trifluoromethyl)-5a,6,7,8,9,9a-hexahydrobenzo[4,5]imidazo[1,2-a]pyridin-1(5H)-one ***4f***. Light yellow solid; yield: 92%, mp: 209.5–210.6 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.19–1.31 (m, 1H), 1.33–1.49 (m, 2H), 1.49–1.58 (m, 2H), 1.66–1.73 (m, 1H), 2.08–2.11 (m, 1H), 2.19–2.23 (m, 1H), 4.21–4.24 (m, 1H), 4.57–4.67 (m, 1H), 6.22 (s, 1H), 9.65 (s, 1H) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ 19.0, 19.6, 24.2, 24.7, 55.5, 55.7, 110.5, 110.6 (q, $^3J_{C-F}$=7.5 Hz), 122.2 (q, $^1J_{C-F}$=272.0 Hz), 135.0 (q, $^2J_{C-F}$=32.0 Hz), 153.3, 158.4 ppm; ^{19}F NMR (470 MHz, DMSO-d_6) δ −59.7 (s, CF_3) ppm. IR (KBr): ν 3335, 3123, 2945, 2857, 1685, 1597, 1568, 1438, 1331, 1268, 1186, 1154, 1110, 989, 883 cm^{-1}; MS (ESI) m/z (%): 326 $[(M+Na)]^+$. HRMS (ESI) calcd for $C_{12}H_{12}F_3N_3O_3$ $[(M+Na)]^+$: 326.0736; found: 326.0723.

4.2.6. 4-Nitro-3-(trifluoromethyl)benzo[4,5]imidazo[1,2-a]pyridin-1(5H)-one ***4h***. Yellow solid; yield: 76%, mp: 120.2–120.3 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.63 (s, 1H), 7.53–7.56 (m, 1H), 7.65–7.68 (m, 1H), 7.84–7.85 (m, 1H), 8.60–8.61 (m, 1H), 13.86 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 107.8 (q, $^3J_{C-F}$=7.0 Hz), 111.6, 113.7, 116.6, 122.4 (q, $^1J_{C-F}$=272.0 Hz), 124.8, 127.4, 128.0, 132.0, 133.2 (q, $^2J_{C-F}$=32.5 Hz, CF_2), 143.0, 158.0. ^{19}F NMR (470 MHz, DMSO-d_6) δ −59.20 (s, CF_3) ppm. IR (KBr): ν 3292, 3127, 3043, 1685, 1606, 1427, 1327, 1292, 1261, 1164, 1142, 1108, 858 cm^{-1}; MS (EI) m/z (%): 296 $[(M-H)]^-$. HRMS (ESI) calcd for $C_{12}H_6F_3N_3O_3$ $[(M-H)]^-$: 296.0286; found: 296.0288.

4.2.7. 7,8-Dimethyl-4-nitro-3-(trifluoromethyl)benzo[4,5]imidazo[1,2-a]pyridin-1(5H)-one ***4j***. Yellow solid; yield: 53%, 264.7 °C (sublimated); ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.39 (s, 6H), 6.54 (s, 1H), 7.55 (s, 1H), 8.32 (s, 1H), 13.65 (s, 1H) ppm; ^{19}F NMR (470 MHz, DMSO-d_6) δ −59.2 (s, CF_3) ppm. IR (KBr): ν 3459, 3297, 2958, 1683, 1601, 1424, 1305, 1268, 1178, 1139, 1097, 855 cm^{-1}; MS (ESI) m/z (%): 348 $[(M+Na)]^+$. HRMS (ESI) calcd for $C_{14}H_{10}F_3N_3O_3$ $[(M+Na)]^+$: 348.0580; found: 348.0567.

4.2.8. 8-Benzoyl-7-(trifluoromethyl)-2,3-dihydroimidazo[1,2-a]pyridin-5(1H)-one ***4k***. Light yellow solid; yield: 78%, mp: 193.3–193.9 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.84 (t, J=9.0 Hz, 2H), 4.24 (t, J=9.0 Hz, 2H), 6.15 (s, 1H), 7.20 (s, 1H), 7.36–7.40 (m, 2H), 7.49–7.52 (m, 1H), 7.56–7.58 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 42.7, 44.1, 93.5, 107.5 (q, $^3J_{C-F}$=5.0 Hz), 122.2 (q, $^1J_{C-F}$=275.0 Hz), 128.1, 128.6, 132.5, 140.0, 141.9 (q, $^2J_{C-F}$=32.0 Hz), 155.9, 159.8, 193.7 ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ −58.2 (s, CF_3) ppm. IR (KBr): ν 3369, 3085, 2980, 2901, 1681, 1611, 1558, 1458, 1328, 1293, 1276, 1167, 1136, 1018, 867 cm^{-1}; MS (ESI) m/z (%): 331 $[(M+Na)]^+$. HRMS (ESI) calcd for $C_{15}H_{11}F_3N_2O_2$ $[(M+Na)]^+$: 331.06620; found: 331.06648.

4.2.9. 9-Benzoyl-8-(trifluoromethyl)-3,4-dihydro-1H-pyrido[1,2-a]pyrimidin-6(2H)-one ***4l***. Light yellow solid; yield: 85%, mp: 224.5–224.8 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.04–2.09 (m, 2H), 3.40–3.43 (m, 2H), 4.07 (t, J=5.8 Hz, 2H), 6.11 (s, 1H), 7.34–7.37 (m, 2H), 7.47–7.49 (m, 1H), 7.55–7.57 (m, 2H), 8.92 (s, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.2, 39.0, 40.0, 93.8, 104.2, 122.3 (q, $^1J_{C-F}$=275.0 Hz), 128.0, 129.1, 132.4, 141.1, 141.3 (q, $^2J_{C-F}$=32.0 Hz), 152.2, 161.0, 195.1 ppm. ^{19}F NMR (470 MHz, $CDCl_3$) δ −57.6 (s, CF_3) ppm. IR (KBr): ν 3317, 3092, 2973, 1677, 1607, 1560, 1471, 1338, 1278, 1156, 1134, 1044, 860 cm^{-1}; MS (ESI) m/z (%): 345 $[(M+Na)]^+$. HRMS (ESI) calcd for $C_{16}H_{13}F_3N_2O_2$ $[(M+Na)]^+$: 345.0825; found: 345.0821.

4.2.10. 9-Benzoyl-3,3-dimethyl-8-(trifluoromethyl)-3,4-dihydro-1H-pyrido[1,2-a]pyrimidin-6(2H)-one ***4m***. Light yellow solid; yield: 81%, mp: 271.0–271.9 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.09 (s, 6H), 3.08–3.09 (m, 2H), 3.76 (s, 2H), 6.15 (s, 1H), 7.36–7.39 (m, 2H), 7.48–7.52 (m, 1H), 7.56–7.58 (m, 2H), 8.93 (s, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.0, 26.5, 50.4, 50.8, 93.5, 104.3, 122.3 (q, $^1J_{C-F}$=275.0 Hz), 128.1, 129.1, 132.4, 141.1, 141.4 (q, $^2J_{C-F}$=32.0 Hz), 151.4, 161.2, 195.1 ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ −57.7 (s, CF_3)

ppm. IR (KBr): ν 3322, 3119, 2960, 1677, 1619, 1547, 1470, 1324, 1279, 1174, 1150, 1042, 857 cm^{-1}; MS (ESI) *m/z* (%): 373 $[(M+Na)]^+$. HRMS (ESI) calcd for $C_{18}H_{17}F_3N_2O_2$ $[(M+Na)]^+$: 373.1134; found: 373.1134.

4.2.11. 8-Nitro-7-(pentafluoroethyl)-2,3-dihydroimidazo[1,2-a]pyridin-5(1H)-one ***4n***. Yellow solid; yield: 80%, mp: 150.6–151.2 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.25 (s, 1H), 6.30 (s, 1H), 4.35 (t, *J*=9.5 Hz, 2H), 4.10 (t, *J*=9.5 Hz, 2H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ 43.9, 44.4, 110.6, 111.1 (t, $^3J_{C-F}$=11.1 Hz), 113.6 (m, CF_2), 119.3 (qt, $^1J_{C-F}$=288.4 Hz, $^2J_{C-F}$=35.8 Hz, CF_3), 135.2 (t, $^3J_{C-F}$=23.7 Hz), 153.5, 158.3 ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ −77.8 (s, CF_3), −102.7 (s, CF_2) ppm. IR (KBr): ν 3381, 3015, 2913, 1680, 1615, 1569, 1426, 1342, 1227, 1146, 1113, 1054, 961 cm^{-1}; MS (EI) *m/z* (%): 298 $[(M-H)]^-$. HRMS (ESI) calcd for $C_9H_6F_5N_3O_3$ $[(M-H)]^-$: 298.0251; found: 298.0257.

4.2.12. 9-Nitro-8-(pentafluoroethyl)-3,4-dihydro-1H-pyrido[1,2-a]pyrimidin-6(2H)-one ***4o***. Yellow solid; yield: 85%, mp: 131.1–131.4 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 2.17 (t, *J*=6.0 Hz, 2H), 3.62–3.65 (m, 2H), 4.09 (t, *J*=6.0 Hz, 2H), 6.29 (s, 1H), 10.15 (s, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ 18.0, 41.1, 108.7 (t, $^3J_{C-F}$=10.3 Hz), 111.4, 113.8 (m, CF_2), 119.2 (qt, $^1J_{C-F}$=287.0 Hz, $^2J_{C-F}$=36.4 Hz, CF_3), 135.5 (t, $^2J_{C-F}$=23.8 Hz), 150.4, 159.4 ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ −77.0 (s, CF_3), −102.6 (s, CF_2) ppm. IR (KBr): ν 3438, 3267, 2925, 1689, 1589, 1408, 1382, 1345, 1206, 1147, 1120, 1057, 999 cm^{-1}; MS (EI) *m/z* (%): 312 $[(M-H)]^-$. HRMS (ESI) calcd for $C_{10}H_8F_5N_3O_3$ $[(M-H)]^-$: 312.0412; found: 312.0413.

4.2.13. 3,3-Dimethyl-9-nitro-8-(pentafluoroethyl)-3,4-dihydro-1H-pyrido[1,2-a]pyrimidin-6(2H)-one ***4p***. Yellow solid; yield: 81%, mp: 209.1–209.4 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 1.15 (s, 6H), 3.27–3.28 (m, 2H), 3.76 (s, 2H), 6.31 (s, 1H), 10.16 (s, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ 23.74, 111.3, 108.8 (t, $^3J_{C-F}$=10.6 Hz), 51.18, 50.34, 25.83, 113.8 (m, CF_2), 119.3 (qt, $^1J_{C-F}$=287.6 Hz, $^2J_{C-F}$=37.8 Hz, CF_3), 135.6 (t, $^2J_{C-F}$=23.8 Hz), 149.6, 159.6 ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ −77.0 (s, CF_3), −102.5 (s, CF_2) ppm. IR (KBr): ν 3262, 3074, 2972, 1687, 1582, 1434, 1356, 1198, 1134, 1041, 956 cm^{-1}; MS (EI) *m/z* (%): 340 $[(M-H)]^-$. HRMS (ESI) calcd for $C_{12}H_{12}F_5N_3O_3$ $[(M-H)]^-$: 340.0723; found: 340.0726.

4.2.14. 8-Nitro-7-(n-heptafluoropropyl)-2,3-dihydroimidazo[1,2-a]pyridin-5(1H)-one ***4q***. Yellow solid; yield: 67%, mp: 161.9–162.3 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 4.07 (t, *J*=9.5 Hz, 2H), 4.32 (t, *J*=9.5 Hz, 2H), 6.26 (s, 1H), 8.25 (s, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ 43.9, 44.4, 109.6 (m, CF_2), 110.6, 111.0 (t, $^3J_{C-F}$=11.7 Hz), 115.7 (m, CF_2), 117.8 (qt, $^1J_{C-F}$=288.4 Hz, $^2J_{C-F}$=35.3 Hz, CF_3), 135.6 (t, $^2J_{C-F}$=23.1 Hz), 153.5, 158.3 ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ −80.8 (t, *J*=10.3 Hz, CF_3), −99.8 (m, CF_2), −119.2 (s, CF_2) ppm. IR (KBr): ν 3431, 3099, 2918, 1681, 1616, 1594, 1440, 1337, 1225, 1191, 1134, 1117, 927 cm^{-1}; MS (EI) *m/z* (%): 348 $[(M-H)]^-$. HRMS (ESI) calcd for $C_{10}H_6F_7N_3O_3$ $[(M-H)]^-$: 348.0218; found: 348.0225.

4.2.15. 9-Nitro-8-(n-heptafluoropropyl)-3,4-dihydro-1H-pyrido[1,2-a]pyrimidin-6(2H)-one ***4r***. Yellow solid; yield: 75%, mp: 125.2–125.7 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 2.18–2.23 (m, 2H), 3.65–3.68 (m, 2H), 4.13 (t, *J*=6.0 Hz, 2H), 6.32 (s, 1H), 10.32 (s, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.4, 39.3, 40.5, 109.6 (t, $^3J_{C-F}$=11.4 Hz), 110.1 (m, CF_2), 111.8, 115.5 (m, CF_2), 118.0 (qt, $^1J_{C-F}$=290.1 Hz, $^2J_{C-F}$=36.0 Hz, CF_3), 137.4 (t, $^2J_{C-F}$=24.4 Hz), 150.4, 159.2 ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ −81.0 (t, *J*=10.5 Hz, CF_3), −99.5 (m, CF_2), −119.2 (s, CF_2) ppm. IR (KBr): ν 3433, 3129, 2924, 1686, 1577, 1428, 1343, 1234, 1197, 1173, 1142, 1086, 952 cm^{-1}; MS (EI) *m/z* (%): 362 $[(M-H)]^-$. HRMS (ESI) calcd for $C_{11}H_8F_7N_3O_3$ $[(M-H)]^-$: 362.0386; found: 362.0381.

4.2.16. 3,3-Dimethyl-9-nitro-8-(n-heptafluoropropyl)-3,4-dihydro-1H-pyrido[1,2-a]pyrimidin-6(2H)-one ***4s***. Yellow solid; yield: 70%, mp: 215.6–215.7 °C; ^1H NMR (500 MHz, DMSO-d_6) δ 1.01 (s, 6H), 3.25 (s, 2H), 3.66 (s, 2H), 6.14 (s, 1H), 10.24 (s, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ 23.8, 25.8, 50.4, 51.2, 108.8 (t, $^3J_{C-F}$=11.2 Hz), 109.4 (m, CF_2), 111.3, 116.0 (m, CF_2), 118.0 (qt, $^1J_{C-F}$=290.8 Hz, $^2J_{C-F}$=38.1 Hz, CF_3), 136.0 (t, $^2J_{C-F}$=23.9 Hz), 149.7, 159.6 ppm; ^{19}F NMR (470 MHz, DMSO-d_6) δ −80.5 (t, *J*=10.1 Hz, CF_3), −98.7 (m, CF_2), −117.6 (s, CF_2) ppm. IR (KBr): ν 3439, 3230, 2925, 1677, 1595, 1419, 1354, 1228, 1196, 1133, 1117, 1104, 926 cm^{-1}; MS (ESI) *m/z* (%): 414 $[(M+Na)]^+$. HRMS (ESI) calcd for $C_{13}H_{12}F_7N_3O_3$ $[(M+Na)]^+$: 414.0668; found: 414.0659.

4.2.17. 4-Nitro-3-(n-heptafluoropropyl)-5a,6,7,8,9,9a-hexahydrobenzo[4,5]imidazo[1,2-a]pyridin-1(5H)-one ***4t***. Yellow solid; yield: 63%, mp: 193.3–193.5 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 1.28–1.88 (m, 6H), 2.13–2.16 (m, 1H), 2.37–2.40 (m, 1H), 4.27–4.30 (m, 1H), 4.67–4.72 (m, 1H), 6.25 (s, 1H), 8.16 (s, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.0, 20.0, 25.4, 55.5, 56.1, 109.6 (m, CF_2), 111.8, 112.8 (t, $^3J_{C-F}$=11.6 Hz), 115.1 (m, CF_2), 118.0 (qt, $^1J_{C-F}$=286.5 Hz, $^2J_{C-F}$=34.6 Hz, CF_3), 136.7 (t, $^2J_{C-F}$=23.8 Hz), 153.0, 158.0 ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ −80.9 (t, *J*=10.2 Hz, CF_3), −99.81 (m, CF_2), −119.1 (s, CF_2) ppm. IR (KBr): ν 3357, 3071, 2951, 1679, 1594, 1439, 1334, 1225, 1200, 1112, 1083, 940 cm^{-1}; MS (ESI) *m/z* (%): 426 $[(M+Na)]^+$. HRMS (ESI) calcd for $C_{14}H_{12}F_7N_3O_3$ $[(M+Na)]^+$: 426.0663; found: 426.0659.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.03.080. These data include MOL files and InChiKeys of the most important compounds described in this article.

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14. CCDC 875267 (**4a**) contains all crystallographic details of this publication and is available free of charge at www.ccdc.cam.ac.uk/consts/retrieving.html or can be ordered from the following address: Cambridge Crystallographic Data Centre, 12 Union Road, GB-Cambridge CB21EZ; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk. Unit cell parameters (**4a**): *a*: 7.7031(18) Å; *b*: 7.1192(17) Å; *c*: 9.495(2) Å; β: 104.330(2); γ: 110.65(2); space group: *P*21/*m*.