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An Efficient One-pot Three-component Process for Synthesis of Perfluoroalkylated Quinolizines

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A facile multi-component process for the synthesis of perfluoroalkylated quinolizine derivatives was achieved using various arylidenemalononitriles, pyridine, and methyl perfluoroalk-2-ynoates as starting materials. Moderate yields were obtained under mild condition. The structures of perfluoroalkylated quinolizine derivatives were characterized by means of ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, IR, LRMS and HRMS. Furthermore, the reaction mechanism was proposed.

Keywords quinolizines, perfluoroalkylated, multi-component, one-pot reaction

Introduction

Quinolizine skeleton has received constant attention as it is widely distributed in natural products, especially in alkaloid, such as lupinine, berberine, emetine, sparteine, *etc*.[1] Quinolizine derivatives exhibit excellent biological activities,[2] including anti-HIV, antitumor, antibacterial, anti-allergic, anti-ulcer, and anti-hypertensive activities. Multi-component reactions (MCRs) for the synthesis of quinolizine derivatives have been widely reported recently,[3] because MCRs have the following inherent characteristics, *i.e*., chemo- and regioselectivity, atom economy, step efficiency, diversity, and operational simplicity, *etc*. On the other hand, incorporation of fluorine atom or fluoroalkyl group into organic compounds has aroused great interest in the field of modern organic chemistry. However, there were few reports on the synthesis of fluorine-containing quinolizines.[4]

In the context of our general interest in the construction of perfluoroalkylated heterocycles *via* multi-component reactions (MCRs) using methyl perfluoroalk-2-ynoates as fluorinated building blocks,[5] we describe here a facile synthesis of perfluoroalkylated quinolizines *via* a one-pot three-component reaction of pyridine, arylidenemalononitriles and methyl perfluoroalk-2-ynoates.

Experimental

General

Commercially available reagents were used without further purification. Arylidenemalononitriles **1**[6] and methyl perfluoroalk-2-ynoates **3**[7] were prepared according to the known literatures. Solvents were distilled before use. Melting points were recorded on a WRS-1 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: $CFCl_3$ 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) were obtained on Agilent 5973N MSD or apex-III and HRMS (high resolution mass spectra) were obtained on Waters Micromass GCT Premier, Thermo Fisher Scientific LTQFT Ultra or Bruker Daltonics, Inc. APEXIII 7.0 TESLA FTMS. X-ray analysis was performed on a Bruker Smart Apex2 CCD spectrometer. All yields reported in this publication refer to the total yield of the two di-

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astereomers and their ratios were determined on the basis of ^{19}F NMR spectroscopy of the mixtures.

General procedure for preparation of compound 1

Malononitrile (10.0 mmol) was added to a stirred solution of benzaldehyde (10.0 mmol) and piperidine (1.0 mmol) in ethanol (10 mL). The reaction mixture was stirred at room temperature for 5 h. A precipitate was formed and collected by suction filtration, washed with *n*-hexane/ethanol (*V*/*V*＝10∶1), and then dried under high vacuum.

2-Benzylidenemalononitrile (1a)[6a] White solid, yield 89%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.53－7.56 (m, 2H), 7.62－7.65 (m, 1H), 7.79 (s, 1H), 7.90－7.92 (m, 2H).

2-(4-Methylbenzylidene)malononitrile (1b)[6b] White solid, yield 80%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.46 (s, 3H), 7.34 (d, *J*＝7.5 Hz, 2H), 7.72 (s, 1H), 7.81 (d, *J*＝7.5 Hz, 2H).

2-(3-Methylbenzylidene)malononitrile (1c)[6c] White solid, yield 76%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.43 (s, 3H), 7.43－7.44 (m, 2H), 7.69－7.74 (m, 3H).

2-(2-Methylbenzylidene)malononitrile (1d)[6c] White solid, yield 68%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.45 (s, 3H), 7.32－7.37 (m, 2H), 7.48－7.51 (m, 1H), 8.08－8.10 (m, 2H).

2-(4-Chlorobenzylidene)malononitrile (1e)[6b] White solid, yield 75%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.51－7.53 (m, 2H), 7.73 (s, 1H), 7.85－7.87 (m, 2H).

2-(3-Chlorobenzylidene)malononitrile (1f)[6b] White solid, yield 70%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.48－7.52 (m, 1H), 7.59－7.61 (m, 1H), 7.73 (s, 1H), 7.82－7.83 (m, 2H).

2-(2-Chlorobenzylidene)malononitrile (1g)[6b] White solid, yield 58%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.44－7.47 (m, 1H), 7.54－7.56 (m, 2H), 8.18－8.19 (m, 1H), 8.27 (s, 1H).

2-(2,3-Dichlorobenzylidene)malononitrile (1h)[6d] White solid, yield 55%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.39－7.43 (m, 1H), 7.70－7.72 (m, 1H), 8.00－8.02 (m, 1H), 8.26 (s, 1H).

2-(2,4-Dichlorobenzylidene)malononitrile (1i)[6b] White solid, yield 54%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.43－7.45 (m, 1H), 7.57－7.58 (m, 1H), 8.14－8.16 (m, 1H), 8.19 (s, 1H).

2-(2,4-Dimethylbenzylidene)malononitrile (1j)[6e] Pale yellow solid, yield 60%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.30 (s, 3H), 2.41 (s, 3H), 7.03－7.07 (m, 2H), 7.47－7.48 (s, 1H), 8.06 (s, 1H).

2-(4-Nitrobenzylidene)malononitrile (1k)[6a] Brown solid, yield 78%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.88 (s, 1H), 8.07－8.08 (m, 2H), 8.38－8.40 (m, 2H).

2-(3-Nitrobenzylidene)malononitrile (1l)[6a] Brown solid, yield 77%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.18－7.81 (m, 1H), 7.90 (s, 1H), 8.32－8.33 (m, 1H), 8.46－8.48 (m, 1H), 8.66－8.67 (m, 1H).

2-(4-Cyanobenzylidene)malononitrile (1m)[6a] Red solid, yield 57%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.82－7.85 (m, 3H), 7.99－8.00 (m, 2H).

2-(3-Cyanobenzylidene)malononitrile (1n)[6a] Red solid, yield 56%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.70－7.73 (m, 1H), 7.79 (s, 1H), 7.89－7.91 (m, 1H), 8.07－8.08 (m, 1H), 8.20－8.21 (m, 1H).

2-(4-(Trifluoromethyl)benzylidene)malononitrile (1o)[6f] White solid, yield 89%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.76－7.77 (m, 2H), 7.07－7.09 (m, 2H), 8.28 (s, 1H).

2-(4-Fluorobenzylidene)malononitrile (1p)[6g] White solid, yield 85%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.22－7.26 (m, 2H), 7.74 (s, 1H), 7.95－7.98 (m, 2H).

Methyl 4-(2,2-dicyanovinyl)benzoate (1q)[6h] Pale yellow solid, yield 70%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.89 (s, 3H), 7.45 (d, *J*＝8.0 Hz, 2H), 7.67 (d, *J*＝8.0 Hz, 2H), 7.79 (s, 1H).

2-(4-Methoxybenzylidene)malononitrile (1r)[6a] Pale yellow solid, yield 64%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.91 (s, 3H), 7.01 (d, *J*＝9.0 Hz, 2H), 7.65 (s, 1H), 7.91 (d, *J*＝9.0 Hz, 2H).

General procedure for preparation of compounds 4 and 5

To a solution of arylidenemalononitriles **1** (1.0 mmol) and pyridine **2** (1.5 mmol) in acetonitrile (3 mL), methyl perfluoroalk-2-ynoates **3** (2.0 mmol) was added. The mixture was stirred at 0 ℃ for 0.5 h. Then the solvent was removed under vacuum, the residue was purified by column chromatography on silica gel by eluting with petroleum ether/ethyl acetate (20∶1 to 10∶1) to afford the desired products **4a**－**4u**, **5a**－**5u**.

***cis*-Methyl 1,1-dicyano-2-phenyl-4-(trifluoromethyl)-1,9*a*-dihydro-2*H*-quinolizine-3-carboxylate (4a) and *trans*-methyl 1,1-dicyano-2-phenyl-4-(trifluoromethyl)-1,9*a*-dihydro-2*H*-quinolizine-3-carboxylate (5a)** Light yellow solid, yield 81%. m.p. 145.8－146.7 ℃.

4a: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.50 (s, 3H), 4.55 (s, 1H), 5.06 (d, *J*＝4.5 Hz, 1H), 5.15－5.18 (m, 1H), 5.71－5.74 (m, 1H), 6.30－6.33 (m, 2H), 7.41 (s, 5H); ^{19}F NMR (470 MHz, $CDCl_3$) δ: –59.6 (s, CF_3).

5a: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.57 (s, 3H), 4.38 (s, 1H), 4.65－4.66 (m, 1H), 5.29－5.31 (m, 1H), 5.65－5.67 (m, 1H), 6.30－6.33 (m, 1H), 6.61－6.63 (m, 1H), 7.29－7.30 (m, 2H), 7.41 (s, 3H); ^{19}F NMR (470 MHz, $CDCl_3$) δ: –59.3 (s, CF_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 41.7, 44.2, 48.4, 51.8, 52.8, 53.0, 56.6, 62.6, 101.5, 103.0, 111.4, 111.8, 112.0, 119.9 (q, $^1J_{C\text{-}F}$＝276.5 Hz, CF_3), 120.1, 127.0, 127.4, 129.1, 129.3, 130.0, 130.4, 131.1, 133.1 (q, $^2J_{C\text{-}F}$＝34.5 Hz, CF_3), 164.9; IR (KBr) *v*: 2957, 2372, 2250, 1726, 1637, 1587, 1265, 1178, 985, 705 cm^{-1}; MS (EI) *m*/*z*: 385 $[M]^+$. HRMS (EI) calcd for $C_{20}H_{14}F_3N_3O_2$ $[M]^+$: 385.1038; found 385.1036.

***cis*-Methyl 1,1-dicyano-2-(*p*-tolyl)-4-(trifluoromethyl)-1,9*a*-dihydro-2*H*-quinolizine-3-carboxylate (4b) and *trans*-methyl 1,1-dicyano-2-(*p*-tolyl)-4-(trifluoromethyl)-1,9*a*-dihydro-2*H*-quinolizine-3-**

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carboxylate (5b) Light yellow solid, yield 82%. m.p. 156.5—157.3 ℃.

4b: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.36 (s, 3H), 3.52 (s, 3H), 4.51 (s, 1H), 5.05 (d, J=4.5 Hz, 1H), 5.14—5.17 (m, 1H), 5.70—5.73 (m, 1H), 6.29—6.32 (m, 2H), 7.16—7.19 (m, 2H), 7.28—7.30 (m, 2H); ^{19}F NMR (470 MHz, $CDCl_3$) δ: –59.6 (s, CF_3).

5b: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.36 (s, 3H), 3.58 (s, 3H), 4.34 (s, 1H), 4.63—4.64 (m, 1H), 5.27—5.30 (m, 1H), 5.64—5.67 (m, 1H), 6.29—6.32 (m, 1H), 6.60—6.62 (m, 1H), 7.16—7.19 (m, 2H), 7.21—7.23 (m, 2H); ^{19}F NMR (470 MHz, $CDCl_3$) δ: –59.3 (s, CF_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.3, 41.9, 44.4, 48.1, 51.5, 52.8, 53.0, 56.5, 62.6, 101.4, 102.9, 111.5, 111.8, 112.1, 120.0 (q, $^1J_{C\text{-}F}$=276.4 Hz, CF_3), 120.4, 126.9, 127.3, 127.9, 128.3, 128.9, 129.3, 129.8, 132.9 (q, $^2J_{C\text{-}F}$=34.4 Hz, CF_3), 140.1, 164.9; IR (KBr) ν: 2954, 2256, 2221, 1738, 1647, 1583, 1256, 1190, 1143, 982, 732 cm^{-1}; MS (EI) m/z: 399 $[M]^+$. HRMS (EI) calcd for $C_{21}H_{16}F_3N_3O_2$ $[M]^+$: 399.1195; found 399.1191.

***cis*-Methyl 1,1-dicyano-2-(*m*-tolyl)-4-(trifluoromethyl)-1,9*a*-dihydro-2*H*-quinolizine-3-carboxylate (4c) and *trans*-methyl 1,1-dicyano-2-(*m*-tolyl)-4-(trifluoromethyl)-1,9*a*-dihydro-2*H*-quinolizine-3-carboxylate (5c)** Light yellow solid, yield 84%. m.p. 142.3—143.2 ℃.

4c: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.37 (s, 3H), 3.51 (s, 3H), 4.50 (s, 1H), 5.05 (d, J=4.5 Hz, 1H), 5.15—5.17 (m, 1H), 5.71—5.74 (m, 1H), 6.30—6.33 (m, 2H), 7.19—7.21 (m, 3H), 7.23—7.27 (m, 1H); ^{19}F NMR (470 MHz, $CDCl_3$) δ: –59.6 (s, CF_3).

5c: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.38 (s, 3H), 3.58 (s, 3H), 4.33 (s, 1H), 4.65—4.66 (m, 1H), 5.29—5.31 (m, 1H), 5.66—5.68 (m, 1H), 6.30—6.33 (m, 1H), 6.61—6.63 (m, 1H), 7.05—7.08 (m, 2H), 7.19—7.21 (m, 1H), 7.23—7.27 (m, 1H); ^{19}F NMR (470 MHz, $CDCl_3$) δ: –59.3 (s, CF_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.4, 41.8, 44.2, 48.3, 51.7, 52.8, 53.0, 56.6, 62.6, 101.4, 102.9, 111.5, 111.8, 112.1, 120.0 (q, $^1J_{C\text{-}F}$=276.6 Hz, CF_3), 120.3, 126.9, 127.3, 128.9, 129.3, 129.8, 130.8, 131.0, 132.9 (q, $^2J_{C\text{-}F}$=34.4 Hz, CF_3), 139.0, 165.0, 165.6; IR (KBr) ν: 3132, 1725, 1594, 1384, 1231, 1171, 1112, 696 cm^{-1}; MS (EI) m/z: 399 $[M]^+$. HRMS (EI) calcd for $C_{21}H_{16}F_3N_3O_2$ $[M]^+$: 399.1195; found 399.1187.

***cis*-Methyl 1,1-dicyano-2-(*o*-tolyl)-4-(trifluoromethyl)-1,9*a*-dihydro-2*H*-quinolizine-3-carboxylate (4d) and *trans*-methyl 1,1-dicyano-2-(*o*-tolyl)-4-(trifluoromethyl)-1,9*a*-dihydro-2*H*-quinolizine-3-carboxylate (5d)** Light yellow solid, yield 80%. m.p. 143.5—144.6 ℃.

4d: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.49 (s, 3H), 3.42 (s, 3H), 5.00 (s, 1H), 5.12 (d, J=4.0 Hz, 1H), 5.17—5.20 (m, 1H), 5.73—5.76 (m, 1H), 6.32—6.35 (m, 2H), 7.22—7.25 (m, 2H), 7.27—7.30 (m, 1H), 7.43—7.44 (m, 1H); ^{19}F NMR (470 MHz, $CDCl_3$) δ: –59.6 (s, CF_3).

5d: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.53 (s, 3H), 3.53 (s, 3H), 4.68—4.71 (m, 2H), 5.29—5.30 (m, 1H), 5.73—5.76 (m, 1H), 6.32—6.35 (m, 1H), 6.64—6.65 (m, 1H), 7.09—7.10 (m, 1H), 7.22—7.25 (m, 1H) 7.27—7.30 (m, 2H); ^{19}F NMR (470 MHz, $CDCl_3$) δ: –59.4 (s, CF_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.6, 41.9, 42.5, 44.2, 46.2, 52.7, 56.9, 60.4, 63.2, 101.5, 102.9, 111.5, 111.8, 112.2, 119.0 (q, $^1J_{C\text{-}F}$=276.0 Hz, CF_3), 121.4, 126.4, 126.6, 127.0, 127.5, 128.4, 129.3, 129.4, 129.8, 131.4, 132.2 (q, $^2J_{C\text{-}F}$=34.3 Hz, CF_3), 137.8, 164.9; IR (KBr) ν: 2955, 2372, 2249, 1720, 1645, 1586, 1275, 1189, 1141, 928, 731 cm^{-1}; MS (EI) m/z: 399 $[M]^+$. HRMS (EI) calcd for $C_{21}H_{16}F_3N_3O_2$ $[M]^+$: 399.1195; found 399.1199.

***cis*-Methyl 2-(4-chlorophenyl)-1,1-dicyano-4-(trifluoromethyl)-1,9*a*-dihydro-2*H*-quinolizine-3-carboxylate (4e) and *trans*-methyl 2-(4-chlorophenyl)-1,1-dicyano-4-(trifluoromethyl)-1,9*a*-dihydro-2*H*-quinolizine-3-carboxylate (5e)** White solid, yield 85%. m.p. 145.2—146.1 ℃.

4e: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.54 (s, 3H), 4.54 (s, 1H), 5.05 (d, J=4.5 Hz, 1H), 5.17—5.19 (m, 1H), 5.71—5.73 (m, 1H), 6.29—6.34 (m, 2H), 7.35—7.40 (m, 4H); ^{19}F NMR (470 MHz, $CDCl_3$) δ: –59.6 (s, CF_3).

5e: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.60 (s, 3H), 4.35 (s, 1H), 4.58—4.59 (m, 1H), 5.30—5.32 (m, 1H), 5.65—5.67 (m, 1H), 6.29—6.34 (m, 1H), 6.61—6.62 (m, 1H), 7.23—7.24 (m, 1H), 7.35—7.40 (m, 3H); ^{19}F NMR (470 MHz, $CDCl_3$) δ: –59.3 (s, CF_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 41.6, 44.0, 47.6, 51.1, 53.0, 56.6, 58.4, 62.5, 101.6, 103.1, 111.3, 111.8, 111.9, 119.4, 119.9 (q, $^1J_{C\text{-}F}$=276.6 Hz, CF_3), 127.1, 127.4, 129.1, 129.4, 129.7, 130.4, 133.4 (q, $^2J_{C\text{-}F}$=34.4 Hz, CF_3), 136.2, 164.7; IR (KBr) ν: 2959, 2371, 2246, 1744, 1647, 1584, 1218, 1186, 1145, 985, 732 cm^{-1}; MS (EI) m/z: 419 $[M]^+$. HRMS (EI) calcd for $C_{20}H_{13}ClF_3N_3O_2$ $[M]^+$: 419.0648; found 419.0651.

***cis*-Methyl 2-(3-chlorophenyl)-1,1-dicyano-4-(trifluoromethyl)-1,9*a*-dihydro-2*H*-quinolizine-3-carboxylate (4f) and *trans*-methyl 2-(3-chlorophenyl)-1,1-dicyano-4-(trifluoromethyl)-1,9*a*-dihydro-2*H*-quinolizine-3-carboxylate (5f)** White solid, yield 78%. m.p. 143.6—144.4 ℃.

4f: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.55 (s, 3H), 4.53 (s, 1H), 5.05 (d, J=4.5 Hz, 1H), 5.17—5.20 (m, 1H), 5.72—5.74 (m, 1H), 6.30—6.34 (m, 2H), 7.31—7.35 (m, 4H); ^{19}F NMR (470 MHz, $CDCl_3$) δ: –59.6 (s, CF_3).

5f: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.60 (s, 3H), 4.34 (s, 1H), 4.61—4.62 (m, 1H), 5.30—5.32 (m, 1H), 5.67—5.69 (m, 1H), 6.30—6.34 (m, 1H), 6.61—6.63 (m, 1H), 7.20—7.21 (m, 1H), 7.27—7.28 (m, 1H), 7.31—7.35 (m, 2H); ^{19}F NMR (470 MHz, $CDCl_3$) δ: –59.3 (s, CF_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 41.6, 43.8, 47.7, 51.2, 53.0, 56.8, 62.6, 101.7, 103.1, 111.2, 111.7, 111.8 119.3, 119.8 (q, $^1J_{C\text{-}F}$=276.5 Hz, CF_3), 127.1, 127.5, 129.1, 130.4, 133.1, 133.5 (q, $^2J_{C\text{-}F}$=34.5 Hz, CF_3), 135.0, 164.7; IR (KBr) ν: 3132, 1725, 1594, 1384, 1231, 1171, 1112, 696 cm^{-1}; MS (EI) m/z: 419 $[M]^+$. HRMS

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(EI) calcd for $C_{20}H_{13}ClF_3N_3O_2$ $[M]^+$: 419.0648; found 419.0644.

***cis*-Methyl 2-(2-chlorophenyl)-1,1-dicyano-4-(trifluoromethyl)-1,9*a*-dihydro-2*H*-quinolizine-3-carboxylate (4g) and *trans*-methyl 2-(2-chlorophenyl)-1,1-dicyano-4-(trifluoromethyl)-1,9*a*-dihydro-2*H*-quinolizine-3-carboxylate (5g)** White solid, yield 57%. m.p. 142.9－143.6 ℃.

4g: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.46 (s, 3H), 5.13 (s, 1H), 5.19－5.21 (m, 1H), 5.44 (s, 1H), 5.77－5.78 (m, 1H), 6.33－6.36 (m, 2H), 7.32－7.38 (m, 2H), 7.47－7.52 (m, 2H); ^{19}F NMR (470 MHz, $CDCl_3$) δ: –59.5 (s, CF_3).

5g: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.57 (s, 3H), 4.60 (s, 1H), 5.08－5.09 (m, 1H), 5.30－5.31 (m, 1H), 5.72－5.73 (m, 1H), 6.33－6.36 (m, 1H), 6.64－6.65 (m, 1H), 7.32－7.38 (m, 3H), 7.47－7.52 (m, 1H); ^{19}F NMR (470 MHz, $CDCl_3$) δ: –59.4 (s, CF_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 41.8, 44.5, 46.2, 52.8, 57.2, 63.1, 101.8, 102.8, 111.1, 111.6, 119.9 (q, $^1J_{C\text{-}F}$=276.2 Hz, CF_3), 120.2, 127.2, 127.4, 129.1, 129.2, 129.8, 130.4, 131.2, 133.3 (q, $^2J_{C\text{-}F}$=34.2 Hz, CF_3), 135.6, 164.4; IR (KBr) ν: 2953, 2369, 2250, 1725, 1640, 1587, 1274, 1190, 1142, 983, 773 cm^{-1}; MS (ESI) *m*/*z*: 420 $[(M+H)]^+$. HRMS (ESI) calcd for $C_{20}H_{14}ClF_3N_3O_2$ $[(M+H)]^+$: 420.0721; found 420.0712.

***cis*-Methyl 1,1-dicyano-2-(2,3-dichlorophenyl)-4-(trifluoromethyl)-1,9*a*-dihydro-2*H*-quinolizine-3-carboxylate (4h) and *trans*-methyl 1,1-dicyano-2-(2,3-dichlorophenyl)-4-(trifluoromethyl)-1,9*a*-dihydro-2*H*-quinolizine-3-carboxylate (5h)** White solid, yield 50%. m.p. 152.3－152.9 ℃.

4h: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.50 (s, 3H), 5.13 (s, 1H), 5.20－5.22 (m, 1H), 5.51 (s, 1H), 5.73－5.78 (m, 1H), 6.31－6.37 (m, 2H), 7.27－7.30 (m, 1H), 7.43－7.45 (m, 1H), 7.53－7.54 (m, 1H); ^{19}F NMR (470 MHz, $CDCl_3$) δ: –59.5 (s, CF_3).

5h: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.59 (s, 3H), 4.58 (s, 1H), 5.12 (s, 1H), 5.31－5.33 (m, 1H), 5.73－5.78 (m, 1H), 6.31－6.37 (m, 1H), 6.62－6.64 (m, 1H), 7.17－7.18 (m, 1H), 7.27－7.30 (m, 1H), 7.53－7.54 (m, 1H); ^{19}F NMR (470 MHz, $CDCl_3$) δ: –59.5 (s, CF_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 41.6, 45.2, 47.0, 53.0, 57,3, 63.1, 101.9, 103.0, 111.0, 111.6, 119.7, 119.8 (q, $^1J_{C\text{-}F}$=276.5 Hz, CF_3), 127.5, 127.8, 129.1, 131.6, 132.2, 133.6 (q, $^2J_{C\text{-}F}$=33.1 Hz, CF_3), 134.0, 134.3, 164.3; IR (KBr) ν: 2911, 2406, 2368, 1712, 1629, 1274, 1181, 1163, 983, 734 cm^{-1}; MS (ESI) *m*/*z*: 454 $[(M+H)]^+$. HRMS (ESI) calcd for $C_{20}H_{13}Cl_2F_3N_3O_2$ $[(M+H)]^+$: 454.0331; found 454.0323.

***cis*-Methyl 1,1-dicyano-2-(2,4-dichlorophenyl)-4-(trifluoromethyl)-1,9*a*-dihydro-2*H*-quinolizine-3-carboxylate (4i) and *trans*-methyl 1,1-dicyano-2-(2,4-dichlorophenyl)-4-(trifluoromethyl)-1,9*a*-dihydro-2*H*-quinolizine-3-carboxylate (5i)** White solid, yield 51%. m.p. 156.4－157.2 ℃.

4i: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.52 (s, 3H), 5.12 (s, 1H), 5.20－5.22 (m, 1H), 5.38 (s, 1H), 5.72－5.78 (m, 1H), 6.30－6.36 (m, 2H), 7.31－7.33 (m, 1H), 7.45－7.47 (m, 2H); ^{19}F NMR (470 MHz, $CDCl_3$) δ: –59.6 (s, CF_3).

5i: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.60 (s, 3H), 4.55 (s, 1H), 4.99－5.00 (m, 1H), 5.31－5.32 (m, 1H), 5.72－5.78 (m, 1H), 6.30－6.36 (m, 1H), 6.62－6.64 (m, 1H), 7.19－7.20 (s, 1H), 7.31－7.33 (m, 1H), 7.45－7.47 (m, 1H); ^{19}F NMR (470 MHz, $CDCl_3$) δ: –59.5 (s, CF_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 31.6, 41.6, 44.1, 45.9, 53.0, 57.3, 60.4, 63.0, 101.9, 102.9, 111.0, 111.6, 119.5, 119.8 (q, $^1J_{C\text{-}F}$=276.5 Hz, CF_3), 127.5, 127.7, 127.8, 129.1, 130.3, 130.5, 133.6 (q, $^2J_{C\text{-}F}$=34.9 Hz, CF_3), 136.4, 136.7, 164.3; IR (KBr) ν: 2938, 2342, 2257, 1728, 1632, 1587, 1266, 1186, 1149, 984, 763 cm^{-1}; MS (ESI) *m*/*z*: 454 $[(M+H)]^+$. HRMS (ESI) calcd for $C_{20}H_{13}Cl_2F_3N_3O_2$ $[(M+H)]^+$: 454.0331; found 454.0325.

***cis*-Methyl 1,1-dicyano-2-(2,4-dimethylphenyl)-4-(trifluoromethyl)-1,9*a*-dihydro-2*H*-quinolizine-3-carboxylate (4j) and *trans*-methyl 1,1-dicyano-2-(2,4-dimethylphenyl)-4-(trifluoromethyl)-1,9*a*-dihydro-2*H*-quinolizine-3-carboxylate (5j)** Light yellow solid, yield 64%. m.p. 166.1－167.2 ℃.

4j: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.31 (s, 3H), 2.44 (s, 3H), 3.44 (s, 3H), 4.95 (s, 1H), 5.10－5.11 (d, J=4.4 Hz, 1H), 5.16－5.18 (m, 1H), 5.70－5.74 (m, 1H), 6.31－6.34 (m, 2H), 7.03－7.04 (m, 2H), 7.30－7.32 (m, 1H); ^{19}F NMR (470 MHz, $CDCl_3$) δ: –59.6 (s, CF_3).

5j: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.31 (s, 3H), 2.48 (s, 3H), 3.54 (s, 3H), 4.66 (s, 2H), 5.28－5.30 (m, 1H), 5.70－5.74 (m, 1H), 6.31－6.34 (m, 1H), 6.63－6.64 (m, 1H), 6.95－6.97 (m, 1H), 7.09－7.10 (m, 1H); ^{19}F NMR (470 MHz, $CDCl_3$) δ: –59.4 (s, CF_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.5, 20.2, 21.0, 21.1, 42.0, 42.7, 44.0, 46.1, 52.7, 52.9, 56.8, 60.4, 63.2, 101.4, 102.8, 111.6, 111.9, 112.3, 112.0 (q, $^1J_{C\text{-}F}$=276.4 Hz, CF_3), 121.7, 126.1, 127.1, 127.4, 128.2, 132.3 (q, $^2J_{C\text{-}F}$=35.0 Hz, CF_3), 137.6, 139.7, 164.9; IR (KBr) ν: 3132, 1725, 1594, 1384, 1231, 1171, 1112, 696 cm^{-1}; MS (ESI) *m*/*z*: 414 $[(M+H)]^+$. HRMS (ESI) calcd for $C_{22}H_{18}F_3N_3O_2$ $[(M+H)]^+$: 414.1347; found 414.1418.

***cis*-Methyl 1,1-dicyano-2-(4-nitrophenyl)-4-(trifluoromethyl)-1,9*a*-dihydro-2*H*-quinolizine-3-carboxylate (4k) and *trans*-methyl 1,1-dicyano-2-(4-nitrophenyl)-4-(trifluoromethyl)-1,9*a*-dihydro-2*H*-quinolizine-3-carboxylate (5k)** Light yellow solid, yield 65%. m.p. 152.1－152.9 ℃.

4k: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.55 (s, 3H), 4.70 (s, 1H), 5.09 (d, J=4.1 Hz, 1H), 5.21－5.23 (m, 1H), 5.73－5.76 (m, 1H), 6.32－6.37 (m, 2H), 7.61－7.63 (m, 2H), 8.28－8.30 (m, 2H); ^{19}F NMR (470 MHz, $CDCl_3$) δ: –59.6 (s, CF_3).

5k: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.55 (s, 3H), 4.47 (s, 1H), 4.62－4.63 (m, 1H), 5.32－5.35 (m, 1H), 5.65－5.67 (m, 1H), 6.32－6.37 (m, 2H), 7.61－7.63 (m, 2H), 8.28－8.30 (m, 2H); ^{19}F NMR (470 MHz, $CDCl_3$) δ: –59.3 (s, CF_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 43.5, 51.1, 53.2, 54.5, 60.4, 62.5, 102.0, 111.0, 111.5, 111.7, 118.3, 119.8 (q, $^1J_{C\text{-}F}$=276.8 Hz, CF_3), 124.2, 124.5, 127.6,

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129.0, 129.9, 130.2, 134.2 (q, $^2J_{C\text{-}F}$=34.7 Hz, CF_3), 138.7, 148.9, 164.6; IR (KBr) *v*: 2912, 2356, 2166, 1732, 1638, 1527, 1351, 1264, 1189, 1150, 988 cm^{-1}; MS (ESI) *m/z*: 431 $[(M+H)]^+$. HRMS (ESI) calcd for $C_{20}H_{14}F_3N_4O_4$ $[(M+H)]^+$: 431.0962; found 431.0955.

***cis*-Methyl 1,1-dicyano-2-(3-nitrophenyl)-4-(trifluoromethyl)-1,9*a*-dihydro-2*H*-quinolizine-3-carboxylate (4l) and *trans*-methyl 1,1-dicyano-2-(3-nitrophenyl)-4-(trifluoromethyl)-1,9*a*-dihydro-2*H*-quinolizine-3-carboxylate (5l)** Light yellow solid, yield 41%. m.p. 149.7－150.6 ℃.

4l: ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 3.54 (s, 3H), 4.70 (s, 1H), 5.10 (d, *J*=4.1 Hz, 1H), 5.22－5.23 (m, 1H), 5.73－5.76 (m, 1H), 6.33－6.37 (m, 2H), 7.63－7.67 (m, 1H), 7.78－7.80 (m, 1H), 8.30－8.31 (m, 2H); ^{19}F NMR (470 MHz, $CDCl_3$) *δ*: –59.6 (s, CF_3).

5l: ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 3.60 (s, 3H), 4.48 (s, 1H), 4.62－4.63 (m, 1H), 5.34－5.35 (m, 1H), 5.67－5.68 (m, 1H), 6.33－6.37 (m, 1H), 6.63－6.64 (m, 1H), 7.63－7.67 (m, 2H), 8.19－8.21 (m, 1H), 8.30－8.31 (m, 1H); ^{19}F NMR (470 MHz, $CDCl_3$) *δ*: –59.4 (s, CF_3).

^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 40.9, 43.6, 51.0, 53.2, 62.5, 101.9, 111.1, 111.5, 111.7, 118.3, 119.8 (q, $^1J_{C\text{-}F}$=276.6 Hz, CF_3), 124.2, 125.1, 127.5, 129.0, 130.3, 133.7, 134.1 (q, $^2J_{C\text{-}F}$=34.9 Hz, CF_3), 134.8, 148.4, 164.6; IR (KBr) *v*: 2959, 2371, 2249, 1728, 1648, 1584, 1533, 1352, 1305, 1193, 1146, 982 $[M]^+$. HRMS (EI) calcd for $C_{20}H_{13}F_3N_4O_4$ $[M]^+$: 430.0889; found 430.0891.

***cis*-Methyl 1,1-dicyano-2-(4-cyanophenyl)-4-(trifluoromethyl)-2,9*a*-dihydro-1*H*-quinolizine-3-carboxylate (4m) and *trans*-methyl 1,1-dicyano-2-(4-cyanophenyl)-4-(trifluoromethyl)-2,9*a*-dihydro-1*H*-quinolizine-3-carboxylate (5m)** Light yellow solid, yield 67%. m.p. 142.6－143.6 ℃.

4m: ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 3.54 (s, 3H), 4.63 (s, 1H), 5.07 (d, *J*=4.0 Hz, 1H), 5.20－5.22 (m, 1H), 5.72－5.75 (m, 1H), 6.30－6.36 (m, 2H), 7.54－7.56 (m, 2H), 7.72－7.74 (m, 2H); ^{19}F NMR (470 MHz, $CDCl_3$) *δ*: –59.6 (s, CF_3).

5m: ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 3.60 (s, 3H), 4.42 (s, 1H), 4.58－4.59 (m, 1H), 5.32－5.34 (m, 1H), 5.64－5.66 (m, 1H), 6.30－6.36 (m, 1H), 6.59－6.62 (m, 1H), 7.47－7.48 (m, 2H), 7.72－7.74 (m, 2H); ^{19}F NMR (470 MHz, $CDCl_3$) *δ*: –59.3 (s, CF_3).

^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 43.6, 51.5, 53.2, 62.6, 101.9, 111.1, 111.7, 114.2, 116.4, 118.4, 119.8 (q, $^1J_{C\text{-}F}$=277.6 Hz, CF_3), 127.6, 129.0, 129.9, 132.8, 133.1, 134.1 (q, $^2J_{C\text{-}F}$=33.8 Hz, CF_3), 136.8, 164.6; IR (KBr) *v*: 2961, 2371, 2232, 1741, 1637, 1585, 1256, 1183, 1141, 984, 733 cm^{-1}; MS (EI) *m/z*: 410 $[M]^+$. HRMS (EI) calcd for $C_{21}H_{13}F_3N_4O_2$ $[M]^+$: 410.0991; found 410.0998.

***cis*-Methyl 1,1-dicyano-2-(3-cyanophenyl)-4-(trifluoromethyl)-1,9*a*-dihydro-2*H*-quinolizine-3-carboxylate (4n) and *trans*-methyl 1,1-dicyano-2-(3-cyanophenyl)-4-(trifluoromethyl)-1,9*a*-dihydro-2*H*-quinolizine-3-carboxylate (5n)** Light yellow solid, yield 48%. m.p. 145.2－145.9 ℃.

4n: ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 3.61 (s, 3H), 4.60 (s, 1H), 5.08 (d, *J*=4.5 Hz, 1H), 5.20－5.23 (m, 1H), 5.72－5.75 (m, 1H), 6.31－6.36 (m, 2H), 7.55－7.61 (m, 1H), 7.64－7.65 (m, 2H), 7.74－7.76 (m, 1H); ^{19}F NMR (470 MHz, $CDCl_3$) *δ*: –59.6 (s, CF_3).

5n: ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 3.61 (s, 3H), 4.40 (s, 1H), 4.61 (s, 1H), 5.33－5.35 (m, 1H), 5.66－5.67 (m, 1H), 6.31－6.36 (m, 1H), 6.62－6.64 (m, 1H), 7.55－7.60 (m, 3H), 7.74－7.76 (m, 1H); ^{19}F NMR (470 MHz, $CDCl_3$) *δ*: –59.3 (s, CF_3).

^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 43.6, 51.0, 53.1, 62.5, 101.9, 111.1, 111.6, 111.8, 113.4, 117.8, 118.4, 119.8 (q, $^1J_{C\text{-}F}$=276.7 Hz, CF_3), 127.5, 129.0, 130.1, 132.5, 133.3, 133.8, 134.0 (q, $^2J_{C\text{-}F}$=34.5 Hz, CF_3), 164.6; IR (KBr) *v*: 2930, 2330, 2236, 1735, 1639, 1586, 1260, 1189, 1143, 878, 706 cm^{-1}; MS (ESI) *m/z*: 411 $[(M+H)]^+$. HRMS (ESI) calcd for $C_{21}H_{14}F_3N_4O_2$ $[(M+H)]^+$: 411.1063; found 411.1056.

***cis*-Methyl 1,1-dicyano-4-(trifluoromethyl)-2-(4-(trifluoromethyl)phenyl)-1,9*a*-dihydro-2*H*-quinolizine-3-carboxylate (4o) and *trans*-methyl 1,1-dicyano-4-(trifluoromethyl)-2-(4-(trifluoromethyl)phenyl)-1,9*a*-dihydro-2*H*-quinolizine-3-carboxylate (5o)** Light yellow solid, yield 55%. m.p. 134.6－135.2℃.

4o: ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 3.53 (s, 3H), 4.64 (s, 1H), 5.08 (d, *J*=4.3 Hz, 1H), 5.19－5.21 (m, 1H), 5.72－5.75 (m, 1H), 6.31－6.35 (m, 2H), 7.55－7.56 (m, 2H), 7.68－7.70 (m, 2H); ^{19}F NMR (470 MHz, $CDCl_3$) *δ*: –62.9 (s, CF_3), –59.6 (s, CF_3).

5o: ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 3.60 (s, 3H), 4.44 (s, 1H), 4.63－4.64 (s, 1H), 5.32－5.34 (m, 1H), 5.65－5.67 (m, 1H), 6.31－6.35 (m, 1H), 6.61－6.63 (m, 1H), 7.46－7.47 (m, 2H), 7.68－7.70 (m, 2H); ^{19}F NMR (470 MHz, $CDCl_3$) *δ*: –62.9 (s, CF_3), –59.3 (s, CF_3).

^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 43.7, 51.4, 53.1, 62.7, 101.8, 111.1, 111.7, 118.9, 119.8 (q, $^1J_{C\text{-}F}$=276.6 Hz, CF_3), 123.6 (q, $^1J_{C\text{-}F}$=276.6 Hz, CF_3), 126.1, 127.5, 129.1, 129.5, 132.3 (q, $^2J_{C\text{-}F}$=34.9 Hz, CF_3), 133.8 (q, $^2J_{C\text{-}F}$=34.9 Hz, CF_3), 135.4, 164.7; IR (KBr) *v*: 2957, 2369, 2232, 1717, 1639, 1588, 1326, 1147, 1126, 1069, 850 cm^{-1}; MS (EI) *m/z*: 453 $[M]^+$. HRMS (EI) calcd for $C_{21}H_{13}F_6N_3O_2$ $[M]^+$: 453.0912; found 453.0917.

***cis*-Methyl 1,1-dicyano-2-(4-fluorophenyl)-4-(trifluoromethyl)-2,9*a*-dihydro-1*H*-quinolizine-3-carboxylate (4p) and *trans*-methyl 1,1-dicyano-2-(4-fluorophenyl)-4-(trifluoromethyl)-2,9*a*-dihydro-1*H*-quinolizine-3-carboxylate (5p)**: Light yellow solid, yield 88%. m.p. 150.0－150.8 ℃.

4p: ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 3.53 (s, 3H), 4.55 (s, 1H), 5.06 (d, *J*=4.5 Hz, 1H), 5.16－5.19 (m, 1H), 5.71－5.73 (m, 1H), 6.29－6.33 (m, 2H), 7.09－7.12 (m, 2H), 7.40－7.42 (m, 2H); ^{19}F NMR (470 MHz, $CDCl_3$) *δ*: –110.3－–110.2 (m, F), –59.6 (s, CF_3).

5p: ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 3.59 (s, 3H), 4.36 (m, 1H), 4.59－4.60 (m, 1H), 5.29－5.32 (m, 1H), 5.66－5.67 (m, 1H), 6.30－6.33 (m, 1H), 6.61－6.62 (m, 1H), 7.09－7.11 (m, 2H), 7.28－7.29 (m, 2H); ^{19}F NMR

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(470 MHz, $CDCl_3$) δ: −110.3−−110.2 (m, F), −59.3 (s, CF_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 41.8, 44.1, 47.6, 51.0, 52.9, 56.6, 58.3, 62.6, 101.6, 103.0, 111.4, 111.8, 111.9, 116.2, 116.3, 119.6, 119.9 (q, $^1J_{C\text{-}F}$=280.0 Hz, CF_3), 126.9, 127.4, 129.1, 131.0, 133.2 (q, $^2J_{C\text{-}F}$=34.4 Hz, CF_3), 162.6, 164.8; IR (KBr) ν: 2960, 2356, 2251, 1730, 1639, 1587, 1264, 1178, 1104, 734 cm^{-1}; MS (EI) *m/z*: 403 $[M]^+$. HRMS (EI) calcd for $C_{20}H_{13}F_4N_3O_2$ $[M]^+$: 403.0944; found 403.0950.

***cis*-Methyl 1,1-dicyano-2-(4-(methoxycarbonyl) phenyl)-4-(trifluoromethyl)-2,9*a*-dihydro-1*H*-quinolizine-3-carboxylate (4q) and *trans*-methyl 1,1-dicyano-2-(4-(methoxycarbonyl)phenyl)-4-(trifluormethyl)-2,9*a*-dihydro-1*H*-quinolizine-3-carboxylate (5q)** Light yellow solid, yield 68%. m.p. 184.2−185.4 ℃.

4q: ^1H NMR (500 MHz, $CDCl_3$) δ: 3.50 (s, 3H), 3.92 (s, 3H), 4.63 (m, 1H), 5.07 (d, *J*=4.5 Hz, 1H), 5.17−5.20 (m, 1H), 5.72−5.74 (m, 1H), 6.31−6.34 (m, 2H), 7.49−7.50 (m, 2H), 8.07−8.09 (m, 2H); ^{19}F NMR (470 MHz, $CDCl_3$) δ: −59.6 (s, CF_3).

5q: ^1H NMR (500 MHz, $CDCl_3$) δ: 3.56 (s, 3H), 3.92 (s, 3H), 4.42 (s, 1H), 4.63 (s, 1H), 5.31−5.32 (s, 1H), 5.65−5.67 (m, 1H), 6.31−6.34 (m, 1H), 6.61−6.63 (m, 1H), 7.39−7.40 (m, 2H), 8.07−8.09 (m, 2H); ^{19}F NMR (470 MHz, $CDCl_3$) δ: −59.3 (s, CF_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 43.7, 51.5, 52.4, 53.0, 62.6, 101.7, 111.2, 111.8, 119.3, 119.9 (q, $^1J_{C\text{-}F}$=276.1 Hz, CF_3), 127.5, 129.2, 130.3, 131.8, 133.2, 133.6 (q, $^2J_{C\text{-}F}$=34.6 Hz, CF_3), 164.7, 166.2; IR (KBr) ν: 2947, 2366, 2253, 1724, 1645, 1585, 1286, 1252, 1192, 1144, 1113, 979, 732 cm^{-1}; MS (EI) *m/z*: 443 $[M]^+$. HRMS (EI) calcd for $C_{22}H_{16}F_3N_3O_4$ $[M]^+$: 443.1093; found 443.1090.

***cis*-Methyl 2-(4-chlorophenyl)-1,1-dicyano-4-(pentafluoroethyl)-2,9*a*-dihydro-1*H*-quinolizine-3-carboxylate (4r) and *trans*-methyl 2-(4-chlorophenyl)-1,1-dicyano-4-(pentafluoroethyl)-2,9*a*-dihydro-1*H*-quinolizine-3-carboxylate (5r)** Light yellow solid, yield 56%. m.p. 157.4−158.2 ℃.

4r: ^1H NMR (500 MHz, $CDCl_3$) δ: 3.52 (s, 3H), 4.49 (s, 1H), 4.94 (d, *J*=4.0 Hz, 1H), 5.19−5.22 (m, 1H), 5.68−5.74 (m, 1H), 6.32−6.41 (m, 2H), 7.35−7.41 (m, 4H); ^{19}F NMR (470 MHz, $CDCl_3$) δ: −111.3−−103.9 (m, CF_2), −80.2 (s, CF_3).

5r: ^1H NMR (500 MHz, $CDCl_3$) δ: 3.52 (s, 3H), 4.34 (s, 1H), 4.44−4.45 (m, 1H), 5.29−5.30 (m, 1H), 5.68−5.74 (m, 1H), 6.32−6.41 (m, 1H), 6.73−6.74 (m, 1H), 7.19−7.21 (m, 2H), 7.35−7.41 (m, 2H); ^{19}F NMR (470 MHz, $CDCl_3$) δ: −109.3−−103.6 (m, CF_2), −81.4 (s, CF_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 42.1, 44.0, 48.6, 52.2, 53.0, 57.5, 60.4, 62.8, 102.6, 103.4, 111.1 (tq, $^1J_{C\text{-}F}$=259.8 Hz, $^2J_{C\text{-}F}$=39.5 Hz, CF_2), 111.4, 111.7, 111.8, 112.7, 113.5, 118.5 (qt, $^1J_{C\text{-}F}$=286.6 Hz, $^2J_{C\text{-}F}$=35.9 Hz, CF_3), 124.8, 127.5, 129.3, 130.1 (t, $^2J_{C\text{-}F}$=24.3 Hz, CF_2), 130.7, 131.5, 131.9, 136.3, 158.4, 164.7; IR (KBr) ν: 2953, 2373, 2224, 1739, 1628, 1584, 1250, 1219, 1094, 984, 735 cm^{-1}; MS (ESI) *m/z*: 470 $[(M+H)]^+$. HRMS (ESI) calcd for $C_{21}H_{14}ClF_5N_3O_2$ $[(M+H)]^+$: 407.0689; found 407.0688.

***cis*-Methyl 1,1-dicyano-4-(pentafluoroethyl)-2-(*p*-tolyl)-2,9*a*-dihydro-1*H*-quinolizine-3-carboxylate (4s) and *trans*-methyl 1,1-dicyano-4-(pentafluoro ethyl)-2-(*p*-tolyl)-2,9*a*-dihydro-1*H*-quinolizine-3-carboxylate (5s)** Light yellow solid, yield 50%. m.p. 153.7−154.6 ℃.

4s: ^1H NMR (500 MHz, $CDCl_3$) δ: 2.36 (s, 3H), 3.50 (s, 3H), 4.46−4.70 (m, 1H), 4.92−4.93 (m, 1H), 5.17−5.20 (m, 1H), 5.67−5.73 (m, 1H), 6.30−6.37 (m, 1H), 6.40−6.41 (m, 1H), 7.20−7.22 (m, 3H), 7.28−7.30 (m, 2H); ^{19}F NMR (470 MHz, $CDCl_3$) δ: −111.3−−103.9 (m, CF_2), −80.2 (s, CF_3).

5s: ^1H NMR (500 MHz, $CDCl_3$) δ: 2.36 (s, 3H), 3.50 (s, 3H), 4.31−4.32 (m, 1H), 4.46−4.47 (m, 1H), 4.49−4.50 (m, 1H), 5.25−5.28 (m, 1H), 5.67−5.73 (m, 1H), 6.30−6.37 (m, 1H), 6.72−6.74 (m, 1H), 7.11−7.13 (m, 2H), 7.20−7.22 (m, 2H); ^{19}F NMR (470 MHz, $CDCl_3$) δ: −109.4−−103.6 (m, CF_2), −81.4 (s, CF_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.9, 43.4, 50.6, 53.1, 60.9, 80.3, 111.3 (tq, $^1J_{C\text{-}F}$=258.6 Hz, $^2J_{C\text{-}F}$=38.6 Hz, CF_2), 113.0, 113.9, 114.8, 118.7 (qt, $^1J_{C\text{-}F}$=286.8 Hz, $^2J_{C\text{-}F}$=36.4 Hz, CF_3), 129.2, 129.7, 130.2, 130.6 (t, $^2J_{C\text{-}F}$=24.7 Hz, CF_2), 131.2, 131.4, 132.6, 146.1, 161.7; IR (KBr) ν: 2919, 2312, 2226, 1794, 1626, 1587, 1248, 1153, 1016, 875 cm^{-1}; MS (ESI) *m/z*: 450 $[(M+H)]^+$. HRMS (ESI) calcd for $C_{22}H_{18}F_5N_3O_2$ $[(M+H)]^+$: 450.1235; found 450.1230.

***cis*-Methyl 2-(4-chlorophenyl)-1,1-dicyano-4-(*n*-heptafluoropropyl)-2,9*a*-dihydro-1*H*-quinolizine-3-carboxylate (4t) and *trans*-methyl 2-(4-chlorophenyl)-1,1-dicyano-4-(*n*-heptafluoropropyl)-2,9*a*-dihydro-1*H*-quinolizine-3-carboxylate (5t)** Light yellow solid, yield 48%. m.p. 127.9−128.8 ℃.

4t: ^1H NMR (500 MHz, $CDCl_3$) δ: 3.53 (s, 3H), 4.51−4.52 (m, 1H), 4.93−4.94 (m, 1H), 5.22−5.25 (m, 1H), 5.74−5.76 (m, 1H), 6.34−6.49 (m, 1H), 6.77−6.79 (m, 1H), 7.38−7.44 (m, 4H); ^{19}F NMR (470 MHz, $CDCl_3$) δ: −122.3 (s, CF_2), −109.1−−101.7 (m, CF_2), −80.6−−80.2 (m, CF_3).

5t: ^1H NMR (500 MHz, $CDCl_3$) δ: 3.53 (s, 3H), 4.37−4.38 (m, 1H), 4.44−4.45 (m, 1H), 5.31−5.33 (m, 1H), 5.74−5.76 (m, 1H), 6.34−6.49 (m, 1H), 6.77−6.79 (m, 1H), 7.22−7.24 (m, 2H), 7.38−7.44 (m, 2H); ^{19}F NMR (470 MHz, $CDCl_3$) δ: −124.0−−121.9 (m, CF_2), −107.5−−100.3 (m, CF_2), −80.2−−80.1 (m, CF_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 44.1, 48.7, 50.7, 52.3, 52.9, 57.5, 60.4, 62.8, 102.7, 103.4, 109.0 (m, CF_2), 111.5, 111.8, 112.4, 112.7, 112.9 (m, CF_2), 113.5, 114.3 117.5 (qt, $^1J_{C\text{-}F}$=286.4 Hz, $^2J_{C\text{-}F}$=33.9 Hz, CF_3), 127.5, 130.1 (t, $^2J_{C\text{-}F}$=24.8 Hz, CF_2), 130.8, 131.9, 141.1, 158.4; IR (KBr) ν: 2914, 2370, 2340, 1741, 1627, 1586, 1223, 1115, 742 cm^{-1}; MS (ESI) *m/z*: 520 $[(M+H)]^+$. HRMS (ESI) calcd for $C_{22}H_{14}ClF_7N_3O_2$ $[(M+H)]^+$:

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520.0591; found 520.0665.

***cis*-Methyl 1,1-dicyano-4-(*n*-heptafluoropropyl)-2-(*p*-tolyl)-2,9*a*-dihydro-1*H*-quinolizine-3-carboxylate (4u) and *trans*-methyl 1,1-dicyano-4-(*n*-heptafluoroprpyl)-2-(*p*-tolyl)-2,9*a*-dihydro-1*H*-quinolizine-3-carboxylate (5u)** Light yellow solid, yield 45%. m.p. 124.3—125.1 ℃.

4u: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.31 (s, 3H), 3.48 (s, 3H), 4.47 (s, 1H), 4.90—4.91 (m, 1H), 5.17—5.19 (m, 1H), 5.68—5.73 (m, 1H), 6.30—6.37 (m, 1H), 6.44—6.46 (m, 1H), 7.20—7.21 (m, 4H); ^{19}F NMR (470 MHz, $CDCl_3$) δ: −122.5 (s, CF_2), −108.7—−100.9 (m, CF_2), −80.3—−80.2 (m, CF_3).

5u: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.31 (s, 3H), 3.48 (s, 3H), 4.33—4.34 (s, 1H), 4.47 (s, 1H), 5.26—5.28 (m, 1H), 5.68—5.73 (m, 1H), 6.30—6.37 (m, 1H), 6.73—6.75 (m, 1H), 7.12—7.13 (m, 2H), 7.27—7.29 (m, 2H); ^{19}F NMR (470 MHz, $CDCl_3$) δ: −123.9—−121.6 (m, CF_2), −107.3—−99.3 (m, CF_2), −80.3—−80.2 (s, CF_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.9, 43.5, 50.8, 53.1, 61.0, 109.3 (m, CF_2), 112.3, 113.0, 113.8, 114.3 (m, CF_2), 114.8, 117.7 (qt, $^1J_{C\text{-}F}$=284.6 Hz, $^2J_{C\text{-}F}$=30.1 Hz, CF_3), 129.2, 129.7, 130.6, 131.2 (t, $^2J_{C\text{-}F}$=26.7 Hz, CF_2), 146.1, 161.7; IR (KBr) ν: 2924, 2372, 2222, 1747, 1628, 1587, 1219, 1152, 1111, 875 cm^{-1}; MS (ESI) *m*/*z*: 500 $[(M+H)]^+$. HRMS (ESI) calcd for $C_{22}H_{17}F_3N_3O_4$ $[(M+H)]^+$: 500.1142; found 500.1215.

Results and Discussion

Initially, a mixture of pyridine **2** (1.5 mmol), 2-benzylidenemalononitrile (**1a**) (1.0 mmol) and methyl 4,4,4-trifluorobut-2-ynoate (**3a**) (2.0 mmol) was stirred in acetonitrile (3.0 mL) at room temperature for 1.0 h. Two diastereomeric compounds **4a** and **5a** were obtained in 50% total yield (Table 1, Entry 3).

The structure of the quinolizine derivative **4a** was confirmed by single-crystal X-ray analysis (Figure 1).[8] According to the interaction signals between H_a and H_b in NOESY spectra (Figure 2), the configuration of diastereomer **4a** was also established.

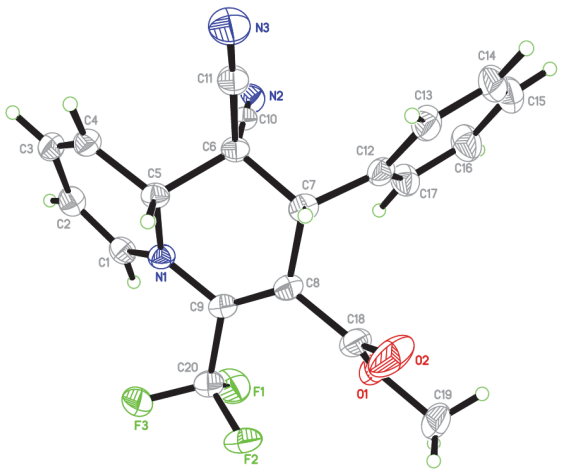


Figure 1 X-ray structure of compound **4a**.

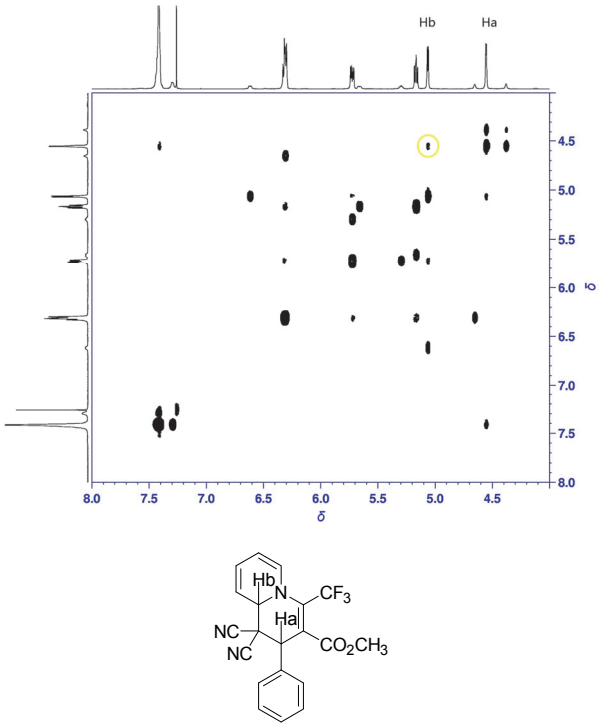
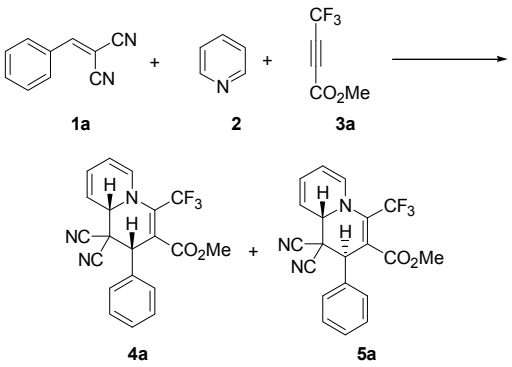


Figure 2 NOESY spectrum of compounds **4a** and **5a**.

Table 1 Optimization of the reaction conditions[a]



Entry	Solvent	T/℃	t/h	1 : 2 : 3	Yield[b]/%
1	CH_2Cl_2	25	1	1.0 : 1.0 : 1.2	33
2	THF	25	1	1.0 : 1.0 : 1.2	42
3	MeCN	25	1	1.0 : 1.0 : 1.2	50
4	Acetone	25	1	1.0 : 1.0 : 1.2	48
5	EtOH	25	1	1.0 : 1.0 : 1.2	—
6	Toluene	25	1	1.0 : 1.0 : 1.2	35
7	MeCN	0	1	1.0 : 1.0 : 1.2	67
8	MeCN	−10	1	1.0 : 1.0 : 1.2	68
9	MeCN	80	1	1.0 : 1.0 : 1.2	45
10	MeCN	0	1	1.0 : 1.5 : 2.0	82
11	MeCN	0	0.5	1.0 : 1.5 : 2.0	83
12	MeCN	0	2	1.0 : 1.5 : 2.0	77

[a] Reaction conditions: pyridine **2** (1.5 mmol), 2-benzylidenemalononitrile **1a** (1.0 mmol) and methyl 4,4,4-trifluorobut-2-ynoate (**3a**) (2.0 mmol), solvent 3.0 mL. [b] Total isolated yield of **4a** and **5a**.

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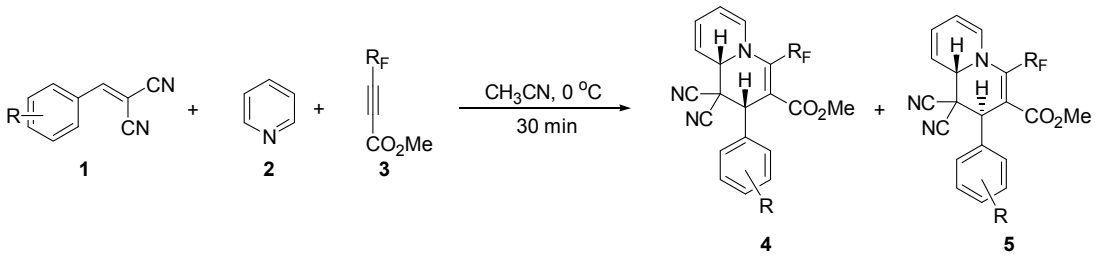
Table 2 Scope for the synthesis of perfluoroalkylated quinolizines[a]



Entry	R	1	Perfluoroalkynoate 3	Products 4 and 5	Ratio (4∶5)	Yield[b]/%
1	H	**1a**	**3a**	**4a**+**5a**	6∶1	81
2	4-Me	**1b**	**3a**	**4b**+**5b**	6∶1	82
3	3-Me	**1c**	**3a**	**4c**+**5c**	5∶1	84
4	2-Me	**1d**	**3a**	**4d**+**5d**	3∶1	80
5	4-Cl	**1e**	**3a**	**4e**+**5e**	7∶1	85
6	3-Cl	**1f**	**3a**	**4f**+**5f**	6∶1	78
7	2-Cl	**1g**	**3a**	**4g**+**5g**	3∶1	57
8	2,3-Dichloro	**1h**	**3a**	**4h**+**5h**	3∶1	50
9	2,4-Dichloro	**1i**	**3a**	**4i**+**5i**	3∶:1	51
10	2,3-Dimethyl	**1j**	**3a**	**4j**+**5j**	3∶1	64
11	4-NO_2	**1k**	**3a**	**4k**+**5k**	10∶1	65
12	3-NO_2	**1l**	**3a**	**4l**+**5l**	8∶1	41
13	4-CN	**1m**	**3a**	**4m**+**5m**	12∶1	67
14	3-CN	**1n**	**3a**	**4n**+**5n**	9∶1	48
15	4-OMe	**1r**	**3a**	—	—	—
16	4-CF_3	**1o**	**3a**	**4o**+**5o**	8∶1	55
17	4-F	**1p**	**3a**	**4p**+**5p**	7∶1	88
18	4-CO_2Me	**1q**	**3a**	**4q**+**5q**	9∶1	68
19	4-Cl	**1e**	**3b**	**4r**+**5r**	2.6∶1	56
20	4-Me	**1b**	**3b**	**4s**+**5s**	2.6∶1	50
21	4-Cl	**1e**	**3c**	**4t**+**5t**	2∶1	48
22	4-Me	**1b**	**3c**	**4u**+**5u**	2∶1	45

[a] Reaction conditions: pyridine **2** (1.5 mmol), arylidenemalononitriles **1** (1.0 mmol) and methyl perfluoroalk-2-ynoates **3** (2.0 mmol) were stirred in acetonitrile (3.0 mL) at 0 ℃ for 0.5 h. [b] Total isolated yield of **4** and **5**.

Encouraged by the above result, we used the three-component reaction of pyridine **2**, 2-benzylidenemalononitrile **(1a)** and methyl 4,4,4-trifluorobut-2-ynoate (**3a**) as model substrates to optimize the reaction conditions. As shown in Table 1, acetonitrile was found to be the most appropriate solvent (Table 1, Entries 1—6). And temperature was found to have an obvious influence on the reaction yield (Table 1, Entries 7—9). The suitable temperature is 0 ℃. Besides, similar results could be obtained when the reaction time was shortened to 0.5 h (Table 1, Entry 11). Therefore, the best result (83% yield) was obtained in acetonitrile at 0 ℃ for 0.5 h.

Having established the optimized conditions, the scope and generality of the present method were explored and the results were summarized in Table 2. Various arylidenemalononitriles with electron-withdrawing or electron-donating groups on the aromatic ring worked well under standard conditions, affording diastereomeric mixtures of the corresponding quinolizines in moderate to good yields. Electron-rich arylidenemalononitriles gave higher yield than electron-deficient ones. Substantial steric hindrance was tolerated on the aromatic ring at the *para*-, *meta*-, and *ortho*-positions with the slightly decreasing of the total yield and the lowering ratio of the major isomer **4** in diastereomeric mixture (Table 2, Entry 2 vs. 3 vs. 4, and Entry 5 vs. 6 vs. 7). With the number of carbon atoms of methyl perfluoroalk-2-ynoates **3** increasing, both the total yield of the product and the ratio of the major diastereomer **4** decreased. If substituted pyridines were used as starting materials, the reaction system became complicated and no desired product was obtained.

Based on the experimental results and previous re-

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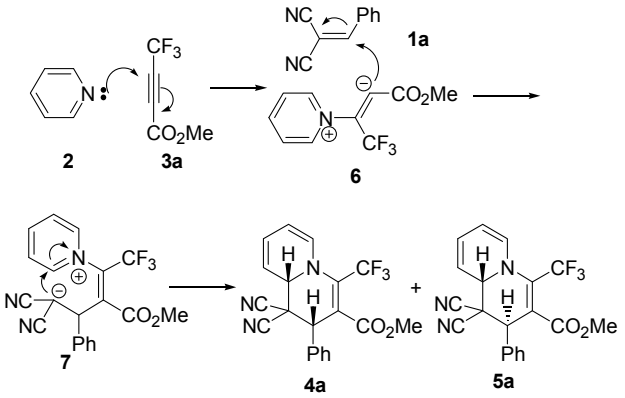
ports,[3a,3c] a plausible mechanism was illustrated in Scheme 1. The reaction occurred through the process of the initial formation of 1,4-dipolar intermediate (**6**) from pyridine **2** and methyl 4,4,4-trifluorobut-2-ynoate (**3a**) followed by its trapping of 2-benzylidenemalononitrile **1a** to generate intermediate **7**. Intramolecular ring closure of the latter yielded **4a** and **5a**.

Scheme 1 Mechanism for the formation of products **4a** and **5a**



Conclusions

In summary, we have developed a facile one-pot process for synthesis of perfluoroalkylated quinolizines **4** and **5**. This method has the advantage of mild condition, moderate yields of product, easy operation and short reaction time. Moreover, all the starting materials are simple and readily available. Further synthetic applications of perfluoroalkylated quinolizines compounds are still being investigated in our laboratory.

Acknowledgement

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[8] CCDC 1044054 (**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=13.647(5) Å, b=8.613(3) Å, c=16.549(6) Å, α=90°, β=90°, γ=90°, space group: $P2_1/n$.

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