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Synthesis of α-trifluoromethyl piperidine derivatives from tetrahydropyridines via nucleophilic trifluoromethylation of pyridinium cations

Armando Talavera-Alemán, Guillaume Dagousset* and Christine Thomassigny*

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Abstract

The synthesis of α-trifluoromethyl piperidines from tetrahydropyridine derivatives in three steps (the oxidation into the corresponding pyridinium, the nucleophilic trifluoromethylation and then, the hydrogenation) is described. The trifluoromethylation step occurs at the less hindered side of the pyridinium intermediate, with moderate-to-high regioselectivity. The method was also successfully applied to the direct trifluoromethylation of one piperidine derivative.

1. Introduction

Heterocyclic cores are known to play an important role in the design and synthesis of bioactive compounds due to their biological activities [1-3]. Piperidine derivatives are one of the most encountered six-membered *N*-containing heterocycles in natural products and synthetically active derivatives. They have shown a wide variety of biological activities like antibacterial [4,5], antifungal [6,7], antiviral [8,9], anticancer [10], analgesic [11,12], antidepressant [13], antituberculosis agents [14,15]. Consequently, the synthesis and functionalization of piperidine derivatives have gained increased interest in recent years [16-20].

With regard to functionalization of organic compounds, there is a great interest in the introduction of fluorinated substituents [21], and many methodologies have notably been described for the trifluoromethylation of different organic structures [22-29]. Indeed, the

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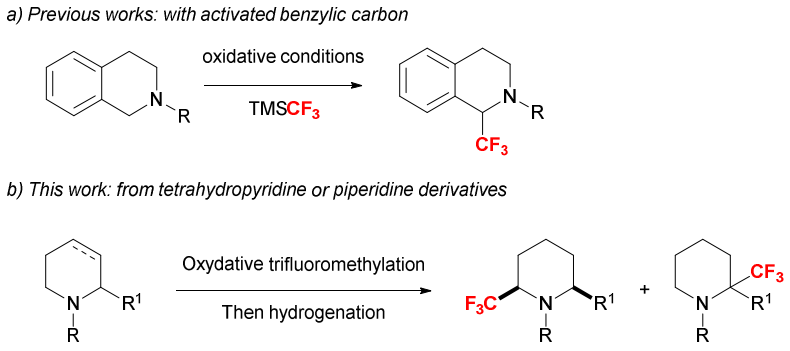
presence of a trifluoromethyl group increases the lipophilicity, bioavailability and the metabolic stability of the molecule, features that have a large impact in pharmaceuticals [30-31] and agrochemicals [32, 33]. In addition, trifluoromethylated compounds are also important in materials industry [34-36].

In this context, α-trifluoromethyl amines have become important cores in synthesis due to their biological activities [37-39]. In particular, different methodologies have been reported for the synthesis of α-trifluoromethyl piperidine derivatives, mostly based on the use of CF_3-containing building blocks [40-49]. A more straightforward synthetic method would be the direct trifluoromethylation of piperidine derivatives, which would be applicable to the late-stage functionalization of relevant heterocycles. However, it is important to mention that such direct trifluoromethylation has only been reported for tetrahydroisoquinolines (Scheme 1a), which have an activated carbon in benzylic position [50-52]. To the best of our knowledge, there are no reports on the direct α-trifluoromethylation of tetrahydropyridine or piperidine derivatives.

We report herein the synthesis of α-trifluoromethyl piperidines from 2-substituted tetrahydropyridines, in three steps, the oxidation of the tetrahydropyridine to its corresponding pyridinium, followed by nucleophilic trifluoromethylation and hydrogenation of the resulting α-trifluoromethyl dihydropyridines (Scheme 1b).

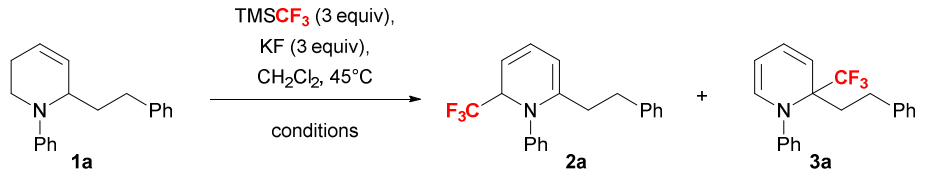


Scheme 1. Direct trifluoromethylation of N-containing six-membered heterocycles.

2. Results and discussion

We focused our attention on the direct α-trifluoromethylation of 2-substituted tetrahydropyridines. Indeed, our group has recently gained some expertise in the synthesis of such substrates by aza-silyl Prins cyclization, including under flow conditions [53,54]. Tetrahydropyridine **1a** was chosen as model substrate. Different conditions were tested, particularly by changing the oxidant, the additive, and the solvent (Table 1). Photoredox conditions using an iridium catalyst or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as oxidant in CH_2Cl_2, gave only traces of fluorinated products (entries 1 and 2). The addition of 10 mol% of CuI to DDQ in DMF or the use of (diacetoxyiodo)benzene (PIDA) in CH_2Cl_2 did not work, and only the starting material **1a** was recovered (entries 3 and 4). With oxone as oxidant the conversion of **1a** was complete, but no signal for fluorinated products was observed by ^{19}F NMR (entry 5). To our delight, a change in the oxidant for benzoyl peroxide (BPO) gave a mixture of two products in 37% NMR yield, in proportion (2:1) (entry 6). Interestingly, the NMR analysis of the mixture obtained were in favour of the mixture of the isomeric 1,2-dihydropyridines **2a** and **3a**. No trace of the α-trifluoromethyl tetrahydropyridines was observed. The formation of the products was possibly due to the overoxidation of the tetrahydropyridine core to the corresponding pyridinium salt as intermediate, followed by its regioselective nucleophilic trifluoromethylation. It is important to mention that the 1,4-dihydropyridine isomer was not observed. Once identifying the products of the reaction, we tested different conditions in order to improve the yield (entries 7-10). An increment of BPO to 2.3 equivalents, and 1.5 hour of reaction gave a better conversion of 68% in similar proportion (**2a**:**3a =** 1.9:1, entry 7). Using tetrabutylammonium difluorotriphenylsilicate (TBAT) instead of KF as base, produced a low yield of 7% (entry 8). Then, the one-pot trifluoromethylation in two steps, namely the oxidation followed by addition of $TMCF_3$, gave a good increment in the NMR yield to 75% in proportion (**2a**:**3a =** 2.4:1; entry 9). Finally, in order to avoid the excess of salts in the reaction medium, we decided to perform a filtration over aluminum oxide between the oxidation step and the trifluoromethylation step. Using this two-step procedure, the yield of dihydropyridines **2a** and **3a** was quantitative and in favor of the first one (**2a**:**3a** = 2.3:1; entry 10). Different solvents like 1,2-dichloroethane, chloroform, DMF, acetonitrile, were assayed, obtaining always lower yields.

Table 1. Screening for trifluoromethylation of tetrahydropyridine **1a**

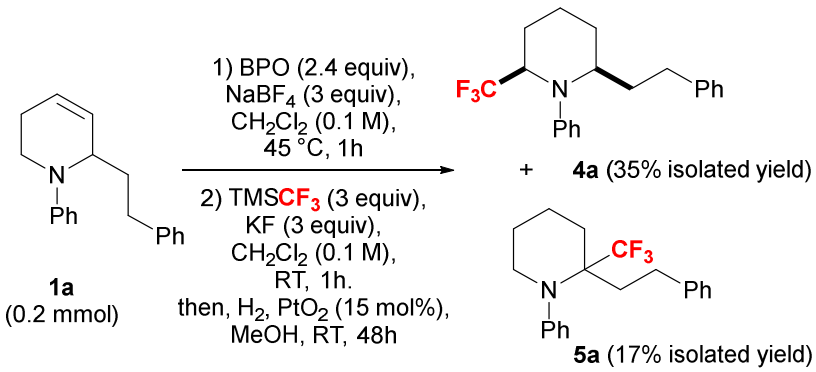


Entry	Conditions	Time (h)	NMR yield[a] % (**2a**:**3a**)
1[b,c]	[Ir{dFCF$_3$ppy}$_2$(bpy)]PF$_6$ (5 mol-%), white light	15	Traces
2	DDQ (2 equiv)	3	Traces
3[c,d]	DDQ (2 equiv), CuI (10 mol-%)	24	0
4	PIDA (2 equiv)	3	0
5[c]	Oxone (2 equiv)	24	0
6	BPO (2 equiv)	1	37 (2:1)
7	BPO (2.3 equiv)	1.5	68 (1.9:1)
8[e]	BPO (2.3 equiv)	2.5	7
9[f]	BPO (2.4 equiv)	1	75 (2.4:1)
10[g]	BPO (2.4 equiv)	1	100 (2.3:1)

[a] Measured by ^{19}F NMR analysis, with CF$_3$OPh as internal reference. [b] MeCN as solvent. [C] Reaction carried out at RT. [d] DMF as solvent. [e] TBAT as base instead of KF. [f] Sequential addition of TMSCF$_3$, RT, 1h. [g] NaBF$_4$ as additive in the oxidation, then filtration, and trifluoromethylation of the crude with TMSCF$_3$, KF, RT, 1h.

The mixture of dihydropyridines **2a** and **3a** was isolated in 82% overall yield, in proportion (68:32). Their separation (**2a** = 40%; **3a** = 20%) has been possible by column chromatography with 15% silver nitrate in silica gel. However, both of them showed a fast

degradation probably due to the conditions used, like acidic solvents, light or even contact with air. In particular, we have been unable to perform a complete analysis of **3a**. In order to obtain more stable compounds, we decided to study the *in situ* hydrogenation of the crude mixture of the trifluoromethylation reaction. The use of platinum oxide (PtO_2) under H_2 atmosphere gave the corresponding *cis*-2,6-disubstituted and 2,2-disubstituted piperidines **4a** and **5a** in almost quantitative NMR yield (94%, **4a**:**5a** = 71:29) (Scheme 2). Their purification was carried out by flash column chromatography, to obtain a good combined yield of 52% (**4a**:**5a** = 67:33). Complete analyses of these two derivatives have been done, and are in favor of the confirmation of structures of the parent compounds **2a** and **3a**.

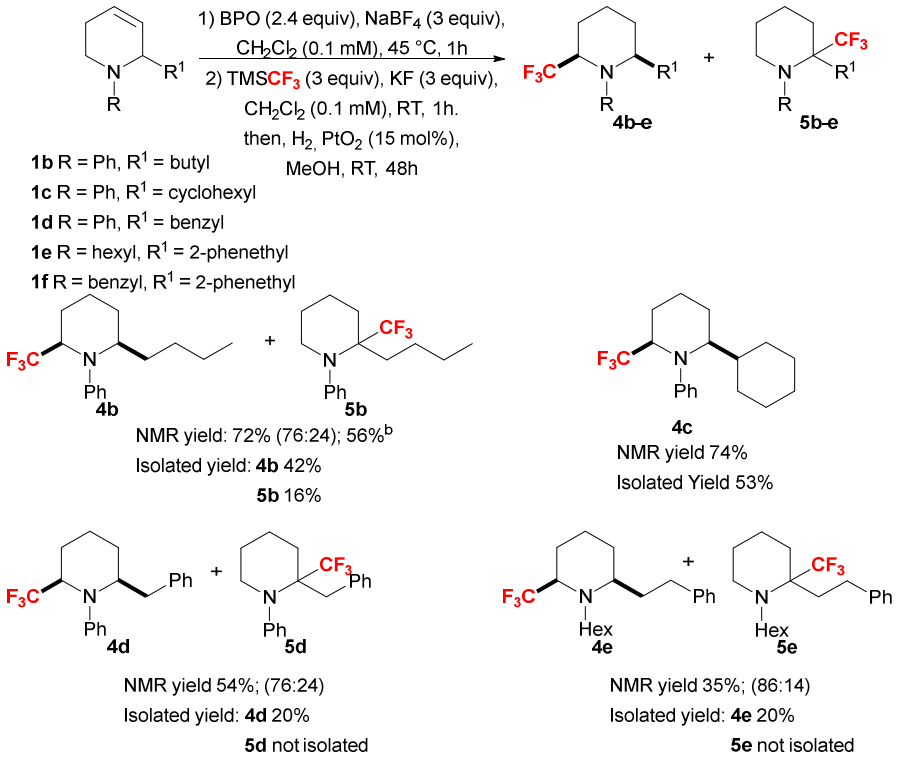


Scheme 2. Synthesis of α-trifluoromethyl piperidines **4a** and **5a**. The reaction could also be performed on a 0.4 mmol scale, with slightly lower NMR yield (80%).

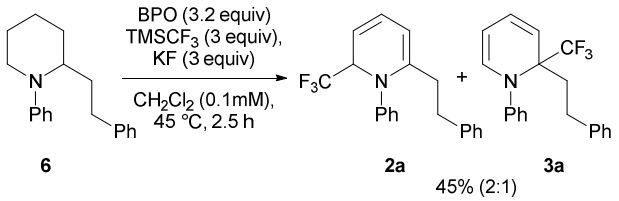
With the optimized conditions for the synthesis of α-trifluoromethyl piperidines, we tested different tetrahydropyridines **1b**-**1e**, bearing various substituents in C-2 as well as different protecting groups (Table 2). The 2,6-disubstituted piperidine **4b-e** was always the main regioisomer in each reaction, and the best results were obtained for *N*-phenyl protected tetrahydropyridines. When the reaction was carried out with substrate **1b** having a butyl group at C-2, the mixture of piperidines **4b**:**5b** were isolated in a good yield of 58% in proportion 81:19. Interestingly, tetrahydropyridine **1c** having a bulkier cyclohexl group at C-2 afforded only one trifluoromethylated isomer (the *cis*-2,6-disubstituted product **4c** in

53% isolated yield), and the 2,2-disubstituted isomer **5c** was not observed, probably due to steric hindrance. In the reaction with a benzyl substituent at C-2, we observed an NMR yield of 54% (**4d**:**5d** 76:24), but after the purification, only **4d** could be isolated in 20% yield. Similarly, *N*-Hexyl protected tetrahydropyridine **1e** gave a lower NMR yield of 35% for the mixture of piperidines **4e**:**5e** (86:14), from which only the 2,6-disubstituted compound **4e** could be isolated in 21% yield. Finally, when the reaction was carried out with the *N*-benzyl protected tetrahydropyridine **1f**, a complex crude mixture was obtained, and no product could be isolated.

Table 2. Scope of the method for the synthesis of α-trifluoromethyl piperidines

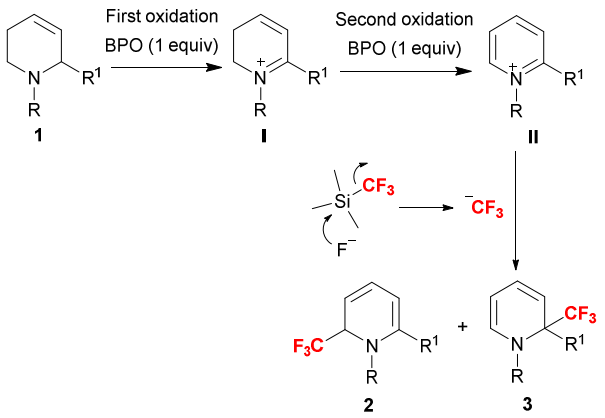


In order to expand the applicability of our methodology, we decided to investigate the trifluoromethylation of a piperidine derivative. Thus, piperidine **6** was treated under our oxidative trifluoromethylative conditions, and we were pleased to see that a 2:1 mixture of dihydropyridines **2a** and **3a** was obtained in 45% NMR yield (Scheme 3).



Scheme 3. Direct trifluoromethylation of piperidine **6**

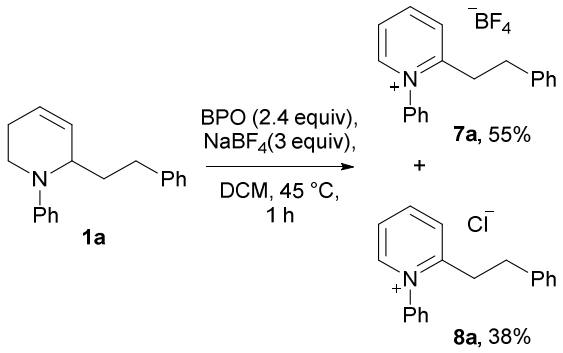
We proposed a mechanism (Scheme 4) that starts with the oxidation of the tetrahydropyridine **1** with one equivalent of BPO into the iminium ion **I**. Then, a second oxidation of cation **I** yields the corresponding pyridinium **II**. Finally, pyridinium **II** undergoes the addition of the trifluoromethyl anion, leading to the corresponding α-trifluoromethyl dihydropyridines **2** and **3**. Nucleophilic trifluoromethylation of the pyridinium cation was in favor of the more activated position and the less hindered carbon, in concordance with previous report by Li [55].



Scheme 4. Putative mechanism for the trifluoromethylation of tetrahydropyridines.

To confirm the mechanism, we decided to isolate the pyridinium cation. Then, the oxidation step of tetrahydropyridine **1a** was carried out according to the described conditions, and after its purification we isolated two main products, which corresponded to the pyridinium cation with two different counterions, namely the tetrafluoroboride anion

(BF_4^-) **7a** and the chloride anion (Cl^-) **8a** (presumably coming from the solvent, Scheme 5). It is important to mention that the synthesis of pyridinium salts is reported mainly from pyridine derivatives [56,57], and they are important reagents in organic synthesis [58-60]. The mixture of pyridiniums **7a** and **8a**, were then subjected to the trifluoromethylation conditions, and the mixture of tetrahydropyridines **2a** and **3a** was obtained in an analogous manner to the one-pot procedure of Table 1 (quantitative NMR yield in proportion 2.3:1).



Scheme 5. Synthesis of pyridinium ions from tetrahydropyridine **1a**.

Finally, pyridinium **7a** was treated with HCl, and after 24 hours we obtained a mixture 1:1 of **7a**:**8a**, demonstrating that the counter ion in **8a** was the chloride anion.

3. Conclusion

In conclusion we have developed a methodology for the synthesis of 2-trifluoromethyl piperidines from tetrahydropyridine derivatives. This synthesis was performed in three steps, via a pyridinium cation as intermediate. The main product in all cases was the 2-trifluoromethyl-6-disubstituted piperidine. Reaction with a tetrahydropyridine bearing a branched substituent at C-2 such as cyclohexane gave the corresponding 2-trifluoromethyl-6-disubstituted piperidine with complete regioselectivity.

4. Experimental part

DCM was distilled over calcium hydride and stored with calcium chloride under Ar. ^{1}H NMR spectra were recorded in a Bruker AV-I 300 MHz spectrometer at 298 K, and were calibrated using residual $CHCl_3$ (δ = 7.26 ppm) or acetone (δ = 2.05). ^{13}C NMR spectra were recorded with a Bruker Avance 300 spectrometer at 75 MHz and 298 K, and were calibrated using $CDCl_3$ (δ = 77.16 ppm) or acetone (δ = 29.84). ^{19}F NMR were recorded with a Bruker Avance 300 spectrometer at 282 MHz and $CFCl_3$ (δ = 0.00 ppm) was used as reference. ^{1}H NMR spectroscopic data are reported as follows: chemical shift δ [ppm] (multiplicity, coupling constant [Hz], integration). Multiplicities are reported as follows: s = singlet, brs = broad singlet, d = doublet, dd = doublet of doublets, t = triplet, dt = doublet of triplets, m = multiplet. High-resolution mass spectra (HRMS) were obtained with a Waters Xevo QTOF instrument with an electrospray ionisation source (ESI+), using enkephaline leucine as internal calibrant. Benzoyl peroxide was purified by dissolving in chloroform and precipitating with MeOH, and drying it in vacuum at room temperature, it was kept in the dark at 4 °C. Reagents were purchased from Sigma–Aldrich, Alfa Aesar, or Fluorochem and were used as received unless otherwise stated. Tetrahydropyridines **1a**-**f** were synthesized according with previous reports [54,59].

4.1 Synthesis of dihydropyridines 2a and 3a

Tetrahydropyridine **1a** (0.3 mmol, 1 equiv) was added to a mixture of BPO (0.72 mmol, 2.4 equiv) and $NaBF_4$ (0.9 mmol, 3 equiv) in CH_2Cl_2 (2 mL, 0.1mM) in a bath of ice, then the resulting mixture was stirred at 45 °C for 1 h, once the reaction finished, the crude was filtered over a path of aluminum oxide with CH_2Cl_2 (10 mL) and CH_2Cl_2-MeOH (5:1, 20 mL), the solvent of this second fraction was evaporated. The resulting crude was dissolved in CH_2Cl_2 (3 mL, 0.1 mM) and KF (0.9 mmol, 3 equiv) and $TMSCF_3$ (0.9 mmol, 3 equiv) were added. The mixture was stirred until complete consumption of the pyridiniums (followed by TLC), to obtain a quantitative NMR yield, in proportion (7:3; **2a**:**3a**). The solvent was evaporated and the crude filtered over a path of aluminum oxide with 20 ml of a pentane-diethyl ether mixture (49:1) to obtain the pure mixture of dihydropyridines **2a** and **3a** in 82% yield (2.1:1). This mixture was purified by column chromatography with 15% silver nitrate in silica gel (w/w) and a mixture of pentane-acetone (99:1) as eluent.

The reaction could also be carried out on a 0.6 mmol scale with a slightly lower yield (43%, 85 mg of isolated product).

4.1.1 6-phenethyl-1-phenyl-2-(trifluoromethyl)-1,2-dihydropyridine (2a): isolated as colorless oil (40 mg; 40%) R_f= 0.44 (pentane-acetone 49:1). ^{1}H NMR (300 MHz, Acetone-d_6) δ 7.39 (t, *J* = 7.5 Hz, 2H), 7.27-7.08 (m, 6H), 7.00 (d, *J* = 7.5 Hz, 1H), 6.33 (dd, *J* = 9.2, 5.6 Hz, 1H), 5.67 (d, *J* = 5.6 Hz, 1H), 5.22 (t, 7.1 Hz, 1H), 4.83 (p, *J* = 7.8 Hz, 1H), 2.86 – 2.55 (m, 2H), 2.63 – 2.31 (m, 2H). ^{13}C NMR (75 MHz, Acetone d_6) δ 147.3 (Cq), 143.8 (Cq), 142.4 (Cq), 130.1 (CH), 129.1 (CH), 128.9 (CH), 128.4 (CH), 126.7 (CH), 126.4 (q, *J* = 286.1 Hz, CF_3)125.9 (CH), 125.6 (CH), 108.0 (CH), 107.3 (CH), 63.1 (q, 31.1 Hz, CH), 36.4 (CH_2), 35.6 (CH_2). ^{19}F NMR (282 MHz, Acetone-d_6) δ -78.08 (d, 8.1 Hz). IR ATR: 3027, 2929, 1643, 1572, 1490, 1454, 1407, 1382, 1256, 1154, 1132, 1114. HRMS TOF ES$^+$ calcd. for $C_{20}H_{17}NF_3$ $[M-H]^+$ 328.1313; found 328.1308.

4.1.2 2-phenethyl-1-phenyl-2-(trifluoromethyl)-1,2-dihydropyridine (3a). Isolated as colorless oil (20 mg; 20%). ^{1}H NMR (300 MHz, Acetone-d6) δ 7.50-7.33 (m, 5H), 7.23-7.07 (m, 3H), 6.79 (d, J = 7.1 Hz, 2H), 6.40-6.29 (m, 2H), 5.09 (d, J = 8.1 Hz, 2H), 2.67 (td, J = 13.2, 5.1 Hz, 1H), 2.45 (t, J = 13.3 Hz, 1H), 2.31 (t, J = 13.4 Hz, 1H), 1.92 (td, J = 13.6, 5.1 Hz, 1H). 13C NMR (75 MHz, Acetone d6) δ 145.1 (Cq), 142.1 (Cq), 137.3 (CH), 129.9 (CH), 129.2 (CH), 128.9 (CH), 128.84 (CH), 128.81 (CH) 128.6 (CH), 127.5 (q, J = 292.5 Hz, CF3) 127.3 (CH), 126.8 (CH), 112.4 (CH), 98.9 (CH), 66.5 (q, J = 27.0 Hz, Cq) 34.4 (CH2), 30.9 (CH2). 19F NMR (282 MHz, Acetone-d6) δ -79.78 (s). IR ATR: 3060, 3029, 2929, 1690, 1598, 1564, 1492, 1454, 1245, 1151, 1031, 734, 696. HRMS TOF ES$^+$ not found, chemically correlated with **5a**.

4.2 General procedure for the synthesis of trifluoromethyl piperidines:

Tetrahydropydridines **1a**-**f** (0.2 mmol, 1 equiv), were treated according with the procedure for the synthesis of dihydropyridines. Once the reaction finished, PtO_2 (15 mol-%) and MeOH (2 mL) were added and the mixture was stirred under H_2 atmosphere, after the

reaction finished (followed by ^{19}F NMR), the crude was filtered over a path of celite, the solvent evaporated and the crude purified by flash column chromatography.

4.2.1 *Cis*-2-phenethyl-1-phenyl-6-(trifluoromethyl)piperidine (4a)

Prepared from tetrahydropyridine **1a** by the general procedure, the hydrogenation was carried out under 7 bar of pressure in 24 hours. Purified by flash column chromatography with the mixture pentane-CH_2Cl_2 (250:1) as colorless oil (23 mg; 35%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.20 (m, 7H), 7.05-6.90 (m, 3H), 4.30 (m, 1H), 3.70 (m, 1H), 2.89-2.62 (m, 2H), 2.15-1.76 (m, 7H), 1.64 (brs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.9 (Cq), 142.0 (Cq), 129.2 (CH), 128.6 (CH), 128.5 (CH), 126.8 (q, J = 287.2 Hz, CF_3), 126.0 (CH), 120.2 (CH), 117.5 (CH), 56.0 (q, J = 28.5 Hz, CH) 54.1 (CH), 34.2 (CH_2), 32.8 (CH_2), 27.7 (CH_2), 24.0 (CH_2), 17.2 (CH_2). ^{19}F NMR (282 MHz, $CDCl_3$) δ -70.55 (d, J = 8.6 Hz). IR ATR: 3027, 2949, 2863, 1596, 1503, 1451, 1259, 1220, 1172, 1132, 1120, 1078, 745, 695. HRMS TOF ES$^+$ calcd. for $C_{20}H_{23}NF_3$ $[M+H]^+$ 334.1783; found 334.1774.

4.4.4 2-phenethyl-1-phenyl-2-(trifluoromethyl)piperidine (5a)

Prepared from tetrahydropyridine **1a** by the general procedure, the hydrogenation was carried out under 7 bar of pressure in 24 hours. Purified by flash column chromatography with the mixture pentane-CH_2Cl_2 (500:1) as colorless oil (11 mg; 17%). ^1H NMR (300 MHz, Acetone-d_6) δ 7.31-7.15 (m, 6H), 7.15-6.98 (m, 4H), 3.9 (brs, 1H), 3.05 (d, J = 12.1 Hz, 1H), 2.74 (td, J = 13.0, 2.8 Hz, 1H), 2.60 (td, J = 13.0, 5.5 Hz, 1H), 2.10 (d, J = 13.8 Hz, 1H), 1.99-1.61 (m, 7H). ^{13}C NMR (75 MHz, Acetone-d_6) δ 150.4 (Cq), 142.7 (Cq), 130.3 (q, J = 296.4 Hz, CF_3) 129.58 (CH), 129.56 (CH), 129.29 (CH), 129.27 (CH), 129.1 (CH), 126.7 (CH), 126.3 (CH), 63.6 (q, J = 21.4 Hz, Cq), 51.6 (CH_2), 36.6 (CH_2), 30.6 (CH_2), 30.3 (CH_2), 26.6 (CH_2), 20.7 (CH_2). ^{19}F NMR (282 MHz, Acetone-d_6) δ -64.64 (s). IR ATR: 3063, 3030, 2932, 2860, 1598, 1491, 1454, 1139, 1126, 1111, 1069, 766, 725, 697. HRMS TOF ES$^+$ calcd. for $C_{20}H_{23}NF_3$ $[M+H]^+$ 334.1783; found 334.1798.

4.2.3 *Cis*-2-butyl-1-phenyl-6-(trifluoromethyl)piperidine (4b)

Prepared from tetrahydropyridine **1b** by the general procedure, the hydrogenation was carried out in 48 hours with a balloon of hydrogen. Purified by flash column

chromatography with the mixture pentane-CH_2Cl_2 (250:1) as colorless oil (24 mg; 42%).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.30 (m, 2H), 7.08-6.91 (m, 3H), 4.27 (brs, 1H), 3.56 (brs, 1H), 2.08-1.93 (m, 3H), 1.86-1.69 (m, 2H), 1.64-1.49 (m, 3H), 1.39-1.25 (m, 4H), 1.02-0.84 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.9 (Cq), 129.3 (CH), 126.8 (q, J = 287.0 Hz, CF_3), 120.0 (CH), 117.4 (CH), 55.7 (q, J = 28.6 Hz, CH), 55.3 (CH), 32.0 (CH_2), 28.9 (CH_2), 27.8 (CH_2), 24.1 (CH_2), 22.9 (CH_2), 17.3 (CH_2), 14.2 (CH_3). ^{19}F NMR (282 MHz, $CDCl_3$) δ -70.02 (d, J = 6.5 Hz). IR ATR: 2954, 2863, 1596, 1502, 1258, 1221, 1188, 1161, 1130, 1100, 1080, 930, 745, 688. HRMS TOF ES$^+$ calcd. for $C_{16}H_{23}NF_3$ $[M+H]^+$ 286.1783; found 216.1779.

4.2.4 2-butyl-1-phenyl-2-(trifluoromethyl)piperidine (5b)

Prepared from tetrahydropyridine **1b** by the general procedure, the hydrogenation was carried out in 48 hours with a balloon of hydrogen. Purified by flash column chromatography with the mixture pentane-CH_2Cl_2 (500:1) as colorless oil (9 mg; 16%). ^{1}H NMR (300 MHz, Acetone-d_6) δ 7.32-7.23 (m, 4H), 7.14 (t, J = 7.6 Hz, 1H), 3.54 (brs, 1H), 3.01 (d, J = 12.0 Hz, 1H), 1.85-1.46 (m, 8H), 1.38-1.18 (m, 4H), 0.87 (t, J = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, Acetone-d_6) δ 150.5 (Cq), 130.4 (q, J = 296.7 Hz, CF_3), 129.5 (CH), 129.4 (CH), 129.2 (CH), 126.2 (CH), 63.6 (q, J = 20.9 Hz, Cq), 51.4 (CH_2), 34.2 (CH_2), 30.5 (CH_2), 26.7 (CH_2), 26.1 (CH_2), 23.9 (CH_2), 20.8 (CH_2), 14.3 (CH_3). ^{19}F NMR (282 MHz, Acetone) δ -64.64 (s). IR ATR: 2957, 2874, 1597, 1492, 1223, 1188, 1117, 1084, 944, 764, 699. HRMS TOF ES$^+$ calcd. for $C_{16}H_{23}NF_3$ $[M+H]^+$ 286.1783; found 216.1772.

4.2.5 *Cis*-2-cyclohexyl-1-phenyl-6-(trifluoromethyl)piperidine (4c)

Prepared from tetrahydropyridine **1c** by the general procedure, but the trifluoromethylation reaction (second step) was performed in two hours, and the hydrogenation in 48 h under 7 bar of pressure. Isolated by flash column chromatography with a mixture pentane-CH_2Cl_2 (500:1), as colorless oil (33 mg, 53%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (t, J = 7.5 Hz, 2H), 7.13 (d, J = 7.5 Hz, 2H), 7.01 (t, J = 7.5 Hz, 1H), 4.00-3.97 (m, 1H), 3.38 (d, J = 6.0 Hz, 1H), 2.0-1.43 (m, 12H), 1.17-1.12 (m, 2H), 0.95 (brs, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.1(Cq), 129.1 (CH), 126.7 (q, J = 285.1 Hz, CF_3), 121.5 (CH), 120.6 (CH), 61.4 (CH), 59.9 (q, J = 28.4 Hz, CH) 39.9 (CH), 30.9 (CH_2), 29.1 (CH_2), 26.8 (CH_2), 26.7 (CH_2), 26.5 (CH_2), 24.7 (CH_2), 24.0 (CH_2), 18.2 (CH_2). ^{19}F NMR (282 MHz, $CDCl_3$) δ -70.94 (d, J =

8.5 Hz). IR ATR: 3063, 3024, 2930, 2860, 1612, 1456, 1084, 1035, 944, 851, 793, 698. HRMS TOF ES$^+$ calcd. for $C_{18}H_{25}NF_3$ $[M+H]^+$ 312.1939; found 312.1933.

4.2.6 *Cis*-2-benzyl-1-phenyl-6-(trifluoromethyl)piperidine (4d)

Prepared from tetrahydropyridine **1d** by the general procedure with the next changes: the oxidation reaction (first step) was carried out in 6 h at 60 °C, and the hydrogenation was performed in 48 h with a balloon of hydrogen. Purified by flash column chromatography with the mixture pentane-CH_2Cl_2 (250:1) as colorless oil (13 mg; 20%). ^{1}H NMR (300 MHz, Acetone-d_6) δ 7.40-7.18 (m, 9H), 6.95 (t, J = 7.2 Hz, 1H), 4.47-4.35 (m, 1H), 3.75-3.65 (m, 1H), 2.81 (m, 1H), 2.63 (m, 1H), 2.02-1.85 (m, 3H), 1.60-1.45 (m, 3H). ^{13}C NMR (75 MHz, Acetone-d_6) δ 150.6 (Cq), 140.4 (Cq), 130.0 (CH), 129.3 (CH), 127.8 (q, J = 286.2 Hz, CF_3), 127.0 (CH), 122.0 (CH), 120.0 (CH), 58.8 (CH), 57.1 (q, J = 27.6 Hz, CH), 39.4 (CH_2), 27.9 (CH_2), 25.0 (CH_2), 18.3 (CH_2). ^{19}F NMR (282 MHz, Acetone-d_6) δ -69.21 (d, J = 8.5 Hz). IR ATR: 3024, 2949, 2866, 1597, 1504, 1259, 1136, 1122, 1078, 1034, 944, 744, 699. HRMS TOF ES$^+$ calcd. for $C_{19}H_{21}NF_3$ $[M+H]^+$ 320.1626; found 320.1618.

4.2.7 1-hexyl-2-phenethyl-6-(trifluoromethyl)piperidine (4e)

Prepared from tetrahydropyridine **1e** by the general procedure in which the first step (oxidation) was done in 18 h at 80 °C, the trifluoromethylation in 3 h and the hydrogenation in 18 h with a balloon of hydrogen. purified by flash column chromatography with the mixture pentane-CH_2Cl_2 (500:1) as colorless oil (14 mg; 21%). ^{1}H NMR (300 MHz, Acetone-d_6) δ 7.39-7.10 (m, 5H), 3.36 (brs, 1H), 2.72-2.67 (m, 5H), 1.96-1.20 (m, 16H), 0.89 (t, J = 6.0 Hz, 3H). ^{13}C NMR (75 MHz, Acetone-d_6) δ 143.6 (Cq), 129.2 (CH), 129.1 (CH), 127.9 (q, J = 286.0 Hz, CF_3), 126.5 (CH), 61.1 (q, J = 27.3 Hz, CH), 58.8 (CH), 52.0 (CH_2), 36.8 (CH_2), 33.4 (CH_2), 32.5 (CH_2), 29.5 (CH_2), 27.5 (CH_2), 27.1 (CH_2), 23.4 (CH_2), 21.9 (CH_2), 20.3 (CH_2), 14.3 (CH_2). ^{19}F NMR (282 MHz, Acetone-d_6) -71.16 (d, J = 5.0 Hz). IR ATR: 2931, 2858, 1615, 1454, 1084, 1035, 944, 852, 793, 698. HRMS TOF ES$^+$ calcd. for $C_{20}H_{31}NF_3$ $[M+H]^+$ 342.2409; found 342.2415.

4.3 General procedure for the synthesis of pyridiniums 7 and 8

Tetrahydropyridine **1a** (0.3 mmol) was added to a mixture of BPO (0.72 mmol) and $NaBF_4$ (0.9 mmol) in CH_2Cl_2 (final volume of 3 mL) in a bath of ice, then the resulting mixture was stirred at 45 °C for 1 h, once the reaction finished, the solvent was evaporated and the crude was purified by column chromatography with aluminum oxide as support and mixtures CH_2Cl_2-MeOH as eluent.

4.3.1 2-phenethyl-1-phenylpyridin-1-ium tetrafluoroborate (7a): Isolated in fractions eluted with mixtures of CH_2Cl_2-MeOH (99:1 to 49:1), as brown oil, 76 mg (55%) Rf = 0.36 (CH_2Cl_2-MeOH, 10:1). ^{1}H NMR (300 MHz, Acetone-d_6) δ 9.06 (d, J = 6.2 Hz, 1H), 8.82 (t, J = 7.9 Hz, 1H), 8.49 (d, J = 8.1 Hz, 1H), 8.24 (t, J = 7.0 Hz, 1H), 7.86-7.71 (m, 5H), 7.26-7.15 (m, 3H), 7.06 (d, 7.1 Hz, 2H), 3.27 (dd, J = 9.6, 6.5 Hz, 2H), 3.07 (dd, J = 8.9, 6.5 Hz, 2H). ^{13}C NMR (75 MHz, Acetone-d_6) δ 159.6 (Cq), 148.0 (CH), 147.3 (CH), 141.9 (Cq), 140.3 (Cq), 132.3 (CH), 131.2 (CH), 130.2 (CH), 129.4 (CH), 129.3 (CH), 127.5 (CH), 127.0 (CH), 126.7 (CH), 36.2 (CH_2), 35.0 (CH_2). ^{19}F NMR (282 MHz, Acetone-d_6) δ -150.26 (s), -150.31 (s). IR ATR: HRMS TOF ES$^+$ calcd. for $C_{19}H_{18}N$ [M]$^+$ 260.1439; found 260.1434.

4.3.2 2-phenethyl-1-phenylpyridin-1-ium chloride (8a): isolated in fractions eluted with the mixture CH_2Cl_2-MeOH (47:3), as yellow oil, 45 mg (38%), Rf = 0.28 (DCM-MeOH, 10:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.92 (d, J = 6.1 Hz, 1H), 8.75 (t, J = 8.0 Hz, 1H), 8.39 (d, J = 8.4 Hz, 1H), 8.36 (t, J = 7.0 Hz, 1H), 7.67-7.55 (m, 3H), 7.37 (d, J = 7.5 Hz, 2H), 7.18 (brs, 3H), 6.87 (brs, 2H), 3.24 (t, J = 7.6 Hz, 2H), 2.99 (t, J = 7.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1 (Cq), 147.0 (CH), 146.3 (CH), 140.1 (Cq), 138.1 (Cq), 131.5 (CH), 130.4 (CH), 129.6 (CH), 128.7 (CH), 128.3 (CH), 126.9 (CH), 126.7 (CH), 125.5 (CH), 35.2 (CH_2), 34.8 (CH_2). IR ATR: HRMS TOF ES$^+$ calcd. for $C_{19}H_{18}N$ [M]$^+$ 260.1439; found 260.1436.

Declaration of competing interest

There are no conflicts to declare.

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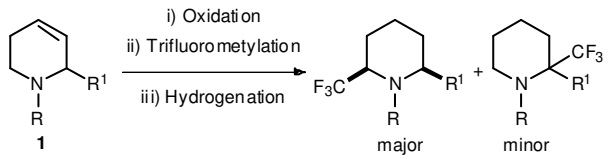

Pyridinium salt as the key intermediate

No trifluoromethylation at C-4

Applicable to piperidines as starting materials