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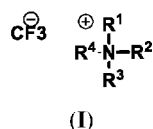
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(57) Abstract: The present invention relates to a new quaternary ammonium trifluoromethyl salts of formula (I), a process for the preparation thereof and its application in trifluoromethylation: (I) wherein, R₁, R₂, R₃ and R₄ are branched or linear C₁-C₄ alkyl, wherein at least one of R₁, R₂, R₃ and R₄ is -OH substituted C₁-C₄ alkyl; preferably, R₁, R₂, R₃ and R₄ are independently selected from -CH₃, -CH₂-C(OH)-(CH₃)₂; provided R₁, R₂, R₃ and R₄ are all not -CH₃ at the same time.



NEW QUATERNARY AMMONIUM SALTS FOR TRIFLUOROMETHYLATION AND PROCESS FOR THE PREPARATION THEREOF

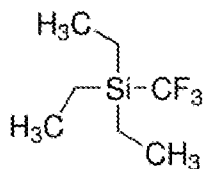
FIELD OF THE INVENTION

The present invention relates to a new quaternary ammonium salt for trifluoromethylation and process for the preparation thereof. More particularly, the present invention relates to a new quaternary ammonium trifluoromethyl salts of formula (I), process for the preparation thereof and its application in trifluoromethylation.

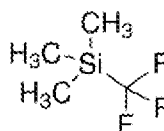
BACKGROUND AND PRIOR ART OF THE INVENTION

Trifluoromethylation (CF_3) containing scaffolds are found in various agrochemicals and pharmaceuticals and material industries. Incorporation of trifluoromethylation (CF_3) group in the drug molecule enhances the lipophilicity, biological activity, metabolic stability of the molecules. Whereas electrophilic or radical trifluoromethylation reagents have been employed with success in many applications, nucleophilic trifluoromethylation appeared poised to provide progress towards facile, catalytic arene trifluoromethylation analogous to well-established, metal-catalyzed cross-coupling reactions. Unfortunately, the use of nucleophilic " CF_3 " sources present difficulties, which has limited their use in metal-catalyzed reactions. The commonly employed Ruppert's reagent (Me_3SiCF_3), which upon exposure to fluoride sources generates trifluoromethyl anion, is prone to decomposition leading to the formation of more stable difluorocarbene and fluorosilicon compounds.

So, there is a need for stable fluorinating agent, having observed that the reported CF_3 agents reported are unstable, costly, hygroscopic and volatile.



Triethyl(trifluoromethyl)silane



Trimethyl(trifluoromethyl)silane

Triethyl(trifluoromethyl)silane, Trimethyl(trifluoromethyl)silane are the two agents known for conducting fluorinating agents, but suffer from severe drawbacks.

Thus, the long felt need for a stable and non-hygroscopic trifluoro methylating agent is fulfilled by the present invention.

OBJECTS OF THE INVENTION

The principal objective of the present invention is to provide a stable, non-hygroscopic quaternary ammonium salt of formula (I) as a trifluoro methylating agent for trifluoromethylation.

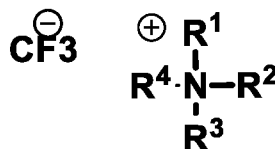
- 5 One more objective of the present invention is to provide a process for the preparation of quaternary ammonium salts of formula (I), wherein said quaternary ammonium salts of formula (I) are for trifluoromethylation.

Yet another objective of the present invention is to provide a process for the trifluoromethylation by using above said quaternary ammonium trifluoromethyl salts of
10 formula (I).

SUMMARY OF THE INVENTION

Accordingly, to accomplish the objectives, the present invention provides a stable, non-hygroscopic quaternary ammonium salts of formula (I) as a trifluoro methylating agent for trifluoromethylation.

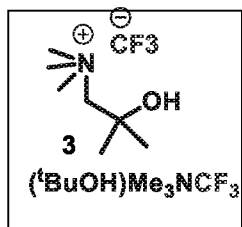
- 15 In an embodiment, the present invention provides quaternary ammonium trifluoromethyl salt of formula (I), wherein the salt acts as a trifluoro methylating agents and remains stable up to 20 minutes at a temperature in the range of 25-30°C.



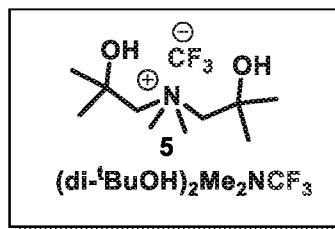
Formula (I)

- 20 wherein, R₁, R₂, R₃ and R₄ are branched or linear C₁-C₄ alkyl, wherein at least one of R₁, R₂, R₃ and R₄ is -OH substituted C₁-C₄ alkyl;
preferably, R₁, R₂, R₃ and R₄ are independently selected from -CH₃, -CH₂-C(OH)-(CH₃)₂;
provided R₁, R₂, R₃ and R₄ are all not -CH₃ at the same time.

- In particularly useful embodiment, the quaternary ammonium salt of formula (I) is
25 selected from below quaternary ammonium trifluoride salt of formula (3), and formula (5).



Formula (3)



Formula (5)

Another embodiment of the present invention provides a process for the preparation of quaternary ammonium trifluoromethyl salt of formula (I), wherein the general process comprises the steps of:

- a) reacting Isobutylene oxide of formula (1) with alkyl amine at a temperature in the range of 25-30 °C for 12 hours and then at 60 °C for 3 days to afford viscous liquid;
- b) dissolving the viscous liquid obtained at step a) in THF and reacting with alkyl halides e at a temperature of 60 °C for 2 hours to get quaternary ammonium iodide salts;
- c) passing the obtained quaternary ammonium iodide salts through the Amberlite® IRA400 in cl form ion exchange resin in HF from H₂O as a solvent and then removing the water at 40 °C to get quaternary ammonium trifluoromethyl salt.

Another aspect of an embodiment, provides an alternative process for the preparation of quaternary ammonium trifluoromethyl salt of formula (I), wherein the process comprises the steps of:

- i. adding alkyl halide into the reaction mixture containing compound of formula (6) and maintaining the reaction mixture at a temperature in the range of 55°C- 60°C for a period in the range of 1-2 hours;
- ii. concentrating the reaction mixture obtained at step i) at reduced pressure to give yellow solid;
- iii. passing the yellow solid obtained at step ii) through Amberlite® IRA400 in chloroform ion exchange resin in HF from H₂O as a solvent;
- iv. removing the water from the reaction mixture obtained at step iii) at a temperature in the range of 40°C-45°C to give quaternary ammonium trifluoride salt (7);
- v. stirring the solution of TMSCF₃ in acetonitrile with quaternary ammonium trifluoride salt (7) obtained at step iv) in acetonitrile at a temperature in the range of -10 to 30 °C for a period in the range of 2-3 hours;

- vi. concentrating the reaction mass obtained at step v) under reduced pressure to obtain quaternary ammonium trifluoromethyl salt of formula (I).

Yet another embodiment of the present invention provides a process for the trifluoromethylation by using quaternary ammonium trifluoromethyl salts of formula (I), wherein said process comprises of reacting a compound of formula (A) with quaternary ammonium trifluoromethyl salt of formula (I) in the presence of metal catalyst/Lewis acid/Bronsted acid in a suitable solvent at a temperature in the range of 30-105 °C for 10-24 hours to get fluorinated products of formula (II) in 55% to 90% yield.

BRIEF DESCRIPTION OF THE DRAWINGS

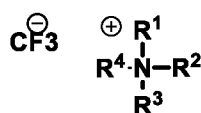
- Figure 1: illustrates hygroscopicity of fluoride salt

DETAILED DESCRIPTION OF THE INVENTION

It is to be understood that the figures and descriptions of the present invention have been simplified to illustrate elements that are relevant for a clear understanding of the invention. The detailed description will be provided herein below with reference to the attached drawing.

The present invention provides a stable, non-hygroscopic quaternary ammonium salts of formula (I) as a trifluoro methylating agent for trifluoromethylation.

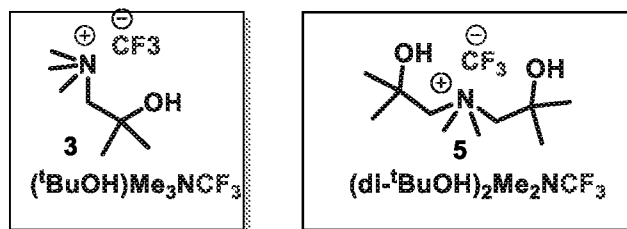
In an embodiment, the present invention provides quaternary ammonium trifluoromethyl salt of formula (I), wherein the salt acts as a trifluoro methylating agents and remains stable up to 20 minutes at a temperature in the range of 25-30°C.



Formula (I)

wherein, R₁, R₂, R₃ and R₄ are branched or linear C₁-C₄ alkyl, wherein at least one of R₁, R₂, R₃ and R₄ is -OH substituted C₁-C₄ alkyl; preferably, R₁, R₂, R₃ and R₄ are independently selected from -CH₃, -CH₂-C(OH)-(CH₃)₂; provided R₁, R₂, R₃ and R₄ are all not -CH₃ at the same time.

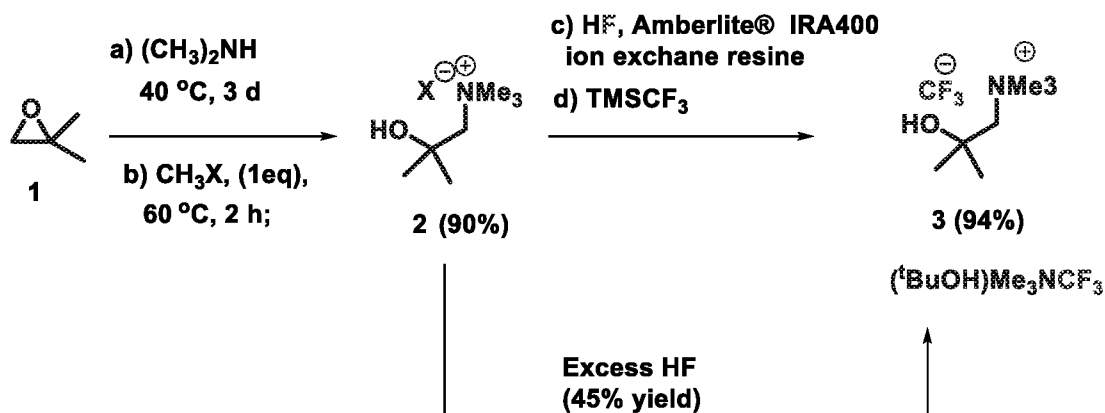
In particularly useful embodiment, the quaternary ammonium salt of formula (I) is selected from below quaternary ammonium trifluoride salt of formula (3), and formula (5).



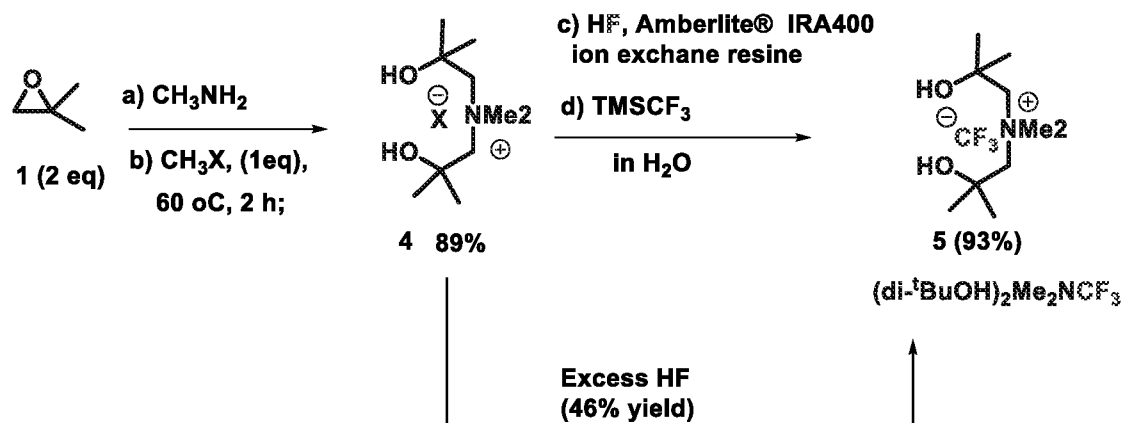
Another embodiment of the present invention provides a process for the preparation of quaternary ammonium trifluoromethyl salt of formula (I), wherein the general process comprises the steps of:

- 5 a) reacting Isobutylene oxide of formula (1) with alkyl amine at a temperature in the range of 25-30 °C for 12 hours and then at 60 °C for 3 days to afford viscous liquid;
- b) dissolving the viscous liquid obtained at step a) in THF and reacting with alkyl iodide at a temperature of 60 °C for 2 hours to get quaternary ammonium iodide salts;
- 10 c) passing the obtained quaternary ammonium iodide salts at step c) through the Amberlite® IRA400 in cl form ion exchange resin in HF (excess) from H₂O as a solvent and then removing the water at 40°C to get quaternary ammonium trifluoromethyl salt (I).

The process for the synthesis of quaternary ammonium salt of formula (3) and
 15 formula (5) is depicted below in Scheme-1a and Scheme-1b, respectively.



Scheme-1a



Scheme-1b

Alkyl amine at step a) is selected from C₁-C₁₀ alkyl amine or C₁-C₁₀ dialkyl amine.

- 5 In a particularly useful embodiment, methyl amine is used to prepare salt of formula (3) and dimethyl amine is used to prepare salt of formula (5).

Alkyl halide at step b) is methyl iodide, methyl bromide.

Another aspect of an embodiment, provides an alternative process for the preparation of quaternary ammonium trifluoromethyl salt of formula (I), wherein the

10 process comprises the steps of:

- i. adding alkyl iodide into the reaction mixture containing compound of formula (6) and maintaining the reaction mixture at a temperature in the range of 55°C- 60°C for a period in the range of 1-2 hours;
- ii. concentrating the reaction mixture obtained at step i) at reduced pressure to give yellow solid;
- 15 iii. passing the yellow solid obtained at step ii) through Amberlite® IRA400 in chloroform ion exchange resin in HF from H_2O as a solvent;
- iv. removing the water from the reaction mixture obtained at step iii) at a temperature in the range of 40°C-45°C to give quaternary ammonium fluoride salt (7);
- 20 v. stirring the solution of TMSCF_3 in acetonitrile with quaternary ammonium fluoride salt (7) obtained at step iv) in acetonitrile at a temperature in the range of -10 to 30 °C for a period in the range of 2-3 hours;
- vi. concentrating the reaction mass obtained at step v) under reduced pressure to obtain quaternary ammonium trifluoromethyl salt of formula (I).

Alkyl iodide at step i) is methyl iodide.

The process is depicted below in scheme-2 generically:



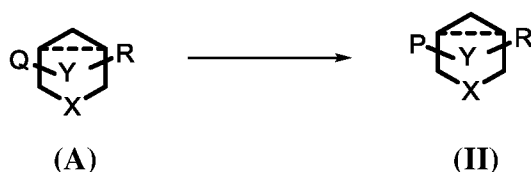
wherein, R₁, R₂, R₃ and R₄ are branched or linear C₁-C₄ alkyl, wherein at least one of R₁, R₂, R₃ and R₄ is -OH substituted C₁-C₄ alkyl; preferably, R₁, R₂, R₃ and R₄ are independently selected from -CH₃, -CH₂-C(OH)-(CH₃)₂; provided R₁, R₂, R₃ and R₄ are all not -CH₃ at the same time; X= I, Br, Cl

Yet another embodiment of the present invention provides a process for the trifluoromethylation by using quaternary ammonium trifluoromethyl salts of formula (I), wherein said process comprises of reacting compound of formula (A) with quaternary ammonium trifluoromethyl salt of formula (I) in the presence of metal catalyst /Lewis acid/ Bronsted acid in a suitable solvent at a temperature in the range of 30-105 °C for 10-24 h to get fluorinated products of formula (II) in 55% to 90% yield.

Lewis acid/ Bronsted acid is selected from (M(OTf)₂/ M(OTf)₃ (wherein, M= Any metal selected from Ag, Bi, Cu, Fe, Ni, In, Sc), BF₃·OEt₂, Tf₂NH, PTSA, carboxylic acids.

Suitable solvent is selected from toluene, xylene, hexane, heptane, octane, methyl isobutyl ketone, dimethylformamide, dimethyl sulfoxide, dichloroethane, fluorobenzene, dioxane. In particularly useful embodiment, toluene or THF is used as a solvent.

The process for trifluoromethylation is depicted below in Scheme-3:



wherein,
ring 'Y' is aromatic, 5-membered or 6-membered;
X= C, N, O or S;
Q= F, Cl, Br, I, OTf or -R_a-C(O)-;

wherein, R_a = H or C₁-C₁₀ (un)substituted alkyl, C₁-C₆ cycloalkyl, aryl;

R = same or different and selected from the group comprising of C₁-C₁₀ alkyl, C₁-C₁₀ cycloalkyl, aryl, alkoxy, cyano, -COOR_b, ketone, aldehyde, NO₂;

wherein, R_b is C₁-C₁₀ alkyl or aryl;

5 **P** = CF₃ or -R_a-C(OH)-CF₃-;

or any two or more adjacent carbon atoms of ring 'Y' may form 5-6 membered aromatic ring.

Compound of formula (A) is selected from ethyl 4-iodobenzoate, 1-chloro-4-iodobenzene, 1-(tert-butyl)-4-iodobenzene, 2-chloro-5-iodopyridine, 2-bromoquinolin, 5-
10 Methyl-2-trifluoromethylthiophene, 3-bromopyridine, 4-iodopyridine, 2-Chloro-6-bromopyridine, 2-Bromo-6-iodopyridine, 5-Bromo-2-iodopyridine, 2-Bromo-5-bromopyridine, 2-Chloro-3-bromopyridine 1-(naphthalen-2-yl)ethan-1-one, 1-(4-bromophenyl)ethan-1-one, 1-(4-methoxyphenyl)ethan-1-one, 1-(4-chlorophenyl)ethan-1-one, 1-(4-fluorophenyl)ethan-1-one.

15 Compounds of formula (II) is selected from 4-Trifluoromethylbenzonitrile, Ethyl 4-Trifluoromethylbenzoate: 4 Chloro(trifluoromethyl)benzene, 4-Butyl(trifluoromethyl)benzene, 2-Chloro-5-(trifluoromethyl)pyridine, 2-Trifluoromethylquinoline 5-Methyl-2-trifluoromethylthiophene, 3-(Trifluoromethyl)pyridine, 4-(Trifluoromethyl)pyridine: 2-Chloro-6-
20 (trifluoromethyl)pyridine, 2-Bromo-6-(trifluoromethyl)pyridine 5-Bromo-2-(trifluoromethyl)pyridine, 2-Bromo-5-(trifluoromethyl)pyridine, 3-Bromo-5-(trifluoromethyl)pyridine, 2-Chloro-3-(trifluoromethyl)pyridine, 2-Chloro-4-(trifluoromethyl)pyridine, 3,5-Dibromo-2-(trifluoromethyl)pyridine 1,1,1-trifluoro-2-(naphthalen-2-yl)propan-2-ol, 2-(4-bromophenyl)-1,1,1-trifluoropropan-2-ol, 1,1,1-trifluoro-
25 2-(4-methoxyphenyl)propan-2-ol, 2-(4-chlorophenyl)-1,1,1-trifluoropropan-2-ol: 1,1,1-trifluoro-2-(4-fluorophenyl)propan-2-ol.

Figure 1 depicts the hygroscopicity of the quaternary ammonium trifluoromethyl salts of formula (3) and formula (5). The trifluoro methylating agents of this invention remain non-hygroscopic for 15-20 minutes at 25-30 °C and it takes around 30 minutes for the salt to
30 turn into a liquid. The salts have a charge on CF₃, so there is no need to generate anion. The -OH group in the compound is necessary for their stability and so also at least one butyl group.

For fluorination, if equivalents of epoxide are increased, the step b) does not proceed. Other amberlites are also being tried and more molecules are being attempted for

synthesis. The present process provides 82-93% yield, comparable to existing processes, but with a more stable and non-hygroscopic and economically more favourable agent. Thermal stability of the trifluoro methylating agents is also good.

EXAMPLES

- 5 Following examples are given by way of illustration and therefore should not be construed to limit the scope of the invention.

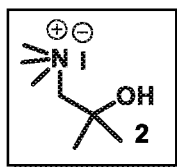
Example 1: General process for the synthesis of quaternary ammonium trifluoromethyl salt (I)

- 10 **Step-1:** Isobutylene oxide and respective amine were added into a sealed tube. The mixture was stirred at 25 °C for 12 hours and then heated at 60 °C for 3 days. The compounds were concentrated at reduced pressure to give viscous liquid.

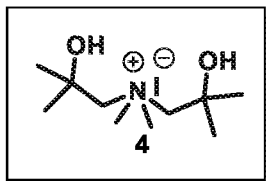
Step-2: In the sealed tube viscous liquid was dissolved in THF then methyl iodide (3mmol) was added and heated at 60 °C for 2 hours. The compounds were concentrated at reduced pressure to give yellow solid.

- 15 **Characterization:**

2-hydroxy-N, N, N,2-tetramethylpropan-1- ammonium iodide (2):¹H NMR (400MHz, MeOD-d₄) δ4.75 (br s, 11 H), 2.82 (s, 6 H) ¹³C NMR (101MHz, MeOD-d₄) 74.9, 71.0, 56.4, 31.0



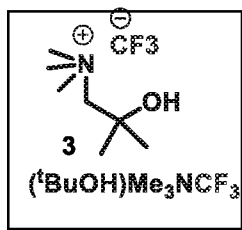
- 20 **2-hydroxy-N-(2-hydroxy-2-methylpropyl)-N,N,2-trimethylpropan-1- ammonium iodide (4):** ¹H NMR (400MHz, MeOD-d₄) 5.20 (s, 4 H), 4.99 (s, 6 H), 3.00 (s, 9 H) ¹³C NMR (101MHz, MeOD-d₄) 75.0, 71.2, 55.5, 5, 31.3



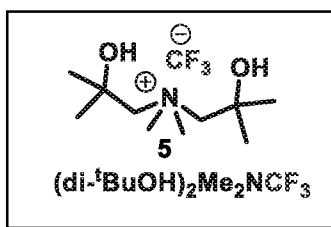
- 25 **Step-3:** The yellow solid then pass through Amberlite® IRA400 in cl form ion exchange resin in HF from H₂O as a solvent. Water was removed at 40 °C to get quaternary ammonium trifluoro methyl salt.

Characterization:

2-hydroxy-N, N, N,2-tetramethylpropan-1- ammonium Trifluomethy (3): ^1H NMR (400MHz, $\text{CH}_3\text{CN-d}_3$) δ 3.62 (br. s., 4 H), 3.29 (s, 6 H), 1.33 (s, 9 H) ^{13}C NMR (101MHz, $\text{CH}_3\text{CN-d}_3$) δ , 73.3, 70.2, 55.7, 31.2, 2.0, ^{19}F NMR (376 MHz, CDCl_3) δ 127;



2-hydroxy-N-(2-hydroxy-2-methylpropyl)-N,N,2-trimethylpropan-1-ammonium Trifluomethyl (5): ^1H NMR (400MHz, $\text{CH}_3\text{CN-d}_3$) δ 3.62 (br. s., 4 H), 3.29 (s, 6 H), 1.33 (s, 9 H) ^{13}C NMR (100MHz, $\text{CH}_3\text{CN-d}_3$) δ 73.3, 70.2, 55.7, 31.2, 2.0, ^{19}F NMR (376 MHz, CDCl_3) δ 129;



Example-2: Alternative general process for the synthesis of quaternary ammonium trifluoromethyl salt (I)

Step-1: In the sealed tube viscous liquid 6 and alkyl iodide (3mmol) was added and heated at 60 °C for 2 hours. The compounds were concentrated at reduced pressure to give yellow solid.

Step-2: The yellow solid then pass through Amberlite® IRA400 in cl form ion exchange resin in HF from H_2O as a solvent. Water was removed at 40 °C to gave quaternary ammonium trifluoride salt.

Step-3. In dry round bottom flask stirred solution of TMSCF_3 was dissolved in acetonitrile under argon then compound 3 was dissolved in acetonitrile add to the RB stirred for 3 hours. Concentrate under reduced pressure.

Example-2: General process for the trifluoromethylation aryl halides and triflates

In a flame dried reaction vials or round bottom flask halide precursor (A) (1mmol), ($\text{di-}^t\text{BuOH}$) $_2\text{Me}_2\text{NCF}_3$ or ($^t\text{BuOH}$) Me_3NCF_3 (3mmol) and $\text{Pd}(\text{OAc})_2$ or $\text{Ni}(\text{COD})$, (10% mmol) was added in a toluene and stirred at 100°C for 12h. After completion of reaction mixture was concentrated under reduced pressure. The crude product was purified by flash

column chromatography using EtOAc/hexane to give fluorinated products in 55% to 90% yield.

Characterization of synthesized compound:

4-Trifluoromethylbenzonitrile:

5 ¹H NMR (400 MHz, CDCl₃) δ 7.75 (d, *J* = 8.4 Hz, 2H), 7.81 (d, *J* = 8.4 Hz, 2H);
¹⁹F NMR (376 MHz, CDCl₃) δ 98.2 (s, 3F); EI-MS *m/z* (%) 171 (M⁺, 100), 152 (33), 121 (41).

Ethyl 4-Trifluoromethylbenzoate:

10 ¹H NMR (400 MHz, CDCl₃) δ 1.42 (t, *J* = 7.2 Hz, 3H), 4.45 (q, *J* = 7.2 Hz, 2H),
7.70 (d, *J* = 8.0 Hz, 2H), 8.18 (d, *J* = 8.0 Hz, 2H); ¹⁹F NMR (376 MHz, CDCl₃) δ 98.8

4-Chloro(trifluoromethyl)benzene:

¹H NMR (400 MHz, CDCl₃) δ 7.46 (d, *J* = 8.3 Hz, 2H), 7.57 (d, *J* = 8.3 Hz, 2H);
¹⁹F NMR (376 MHz, CDCl₃) δ 99.3.

4-Butyl(trifluoromethyl)benzene:

15 ¹H NMR (400 MHz, CDCl₃) δ 0.52 (t, *J* = 8.0 Hz, 3H), 1.31-1.36 (m, 2H), 1.54-
1.61 (m, 2H), 2.67 (t, *J* = 7.8 Hz, 2H), 7.28 (d, *J* = 8.6 Hz, 2H), 7.51 (d, *J* = 8.6 Hz, 2H);
¹⁹F NMR (376 MHz, CDCl₃) δ 99.4

2-Chloro-5-(trifluoromethyl)pyridine:

20 ¹H NMR (400 MHz, CDCl₃) δ 7.48 (d, *J* = 8.5 Hz, 1H), 7.89 (d, *J* = 8.5 Hz, 1H),
8.67 (s, 1H); ¹⁹F NMR (376 MHz, CDCl₃) δ 99.5

2-Trifluoromethylquinoline:

¹H NMR (400 MHz, CDCl₃) δ 7.68 (t, *J* = 7.6 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 1H),
7.85 (t, *J* = 7.6 Hz, 1H), 7.91 (d, *J* = 8.8 Hz, 1H), 8.24 (d, *J* = 8.4 Hz, 1H), δ 8.37 (d, *J* = 8.8
Hz, 1H); ¹⁹F NMR (376 MHz, CDCl₃) δ 94.3

25 ⁵-Methyl-2-trifluoromethylthiophene:

¹H NMR (400 MHz, CDCl₃) δ 2.41 (s, 3H), 6.63-6.67 (m, 1H), 7.15 (d, *J* = 4.0 Hz,
1H); ¹⁹F NMR (376 MHz, CDCl₃) δ 107

3-(Trifluoromethyl)pyridine:

30 ¹H NMR: δ 8.92 (s, 1 H), 8.81 (d, *J* = 4.8 Hz), 7.94 (d, *J* = 8.0 Hz), 7.87 (dd, *J* =
7.9, 4.9 Hz). ¹³C NMR: δ 153.4, 146.9 (q, *J* = 4.0 Hz), 133.1 (q, *J* = 3.0 Hz), 127.8 (q, *J* =
33.0 Hz), 123.5 (q, *J* = 273 Hz), 123.6.

4-(Trifluoromethyl)pyridine:

¹H NMR: δ 8.81 (d, *J* = 5.1 Hz, 1 H), 7.54 (d, *J* = 5.2 Hz, 1 H). ¹³C NMR: δ 150.4,
138.3 (q, *J* = 34.0 Hz), 122.4 (q, *J* = 273 Hz), 119.1.

2-Chloro-6-(trifluoromethyl)pyridine:

¹H NMR: δ 5 7.9 (m, 1 H), 7.65 (d, J 5 7.5 Hz, 1 H), 7.54 (d, J 5 8.1 Hz, 1 H). ¹³C NMR: δ 5 152.0, 148.3 (q, J 5 36.0 Hz), 141.0, 127.6, 120.6 (q, J 5 274 Hz), 119.0. ¹⁹F NMR: 5268.7.

5 2-Bromo-6-(trifluoromethyl)pyridine:

¹H NMR: δ 5 7.77 (t J 5 7.9 Hz, 1 H), 7.70 (d, J 5 7.7 Hz, 1 H), 7.67 (dd, J 5 7.7, 1.0 Hz, 1 H). ¹³C NMR: δ 5 148.8 (q, J 5 36.0 Hz), 142.4, 139.6, 131.4, 120.4 (q, J 5 274 Hz), 119.4. ¹⁹F NMR: 5 268.7

5-Bromo-2-(trifluoromethyl)pyridine:

10 ¹H NMR: δ 5 8.79 (d, J 5 1.9 Hz, 1 H), 8.02 (dd, J 5 8.3, 1.9 Hz, 1 H), 7.59 (d, J 5 8.3 Hz, 1 H). ¹³C NMR: δ 5 151.3, 146.6 (q, J 5 35.0 Hz), 140.0, 124.0, 121.7, 121.3 (q, J 5 274 Hz). ¹⁹F NMR: 5 268.4 (s).

2-Bromo-5-(trifluoromethyl)pyridine:

15 ¹H NMR: δ 5 8.66 (s, 1 H), 7.80 (dd, J 5 8.5, 2.5 Hz, 1 H), 7.66 (d, J 5 8.4 Hz, 1 H). ¹³C NMR: δ 5 147.1 (q, J 5 4.0 Hz), 145.9, 135.3 (q, J 5 3.0 Hz), 128.3, 126.0 (q, J 5 33.0 Hz), 123.1 (q, J 5 273 Hz). ¹⁹F NMR: 5263.0

3-Bromo-5-(trifluoromethyl)pyridine:

20 ¹H NMR: δ 5 8.88 (s, 1 H), 8.82 (s, 1 H), 8.08 (s, 1 H). ¹³C NMR: δ 5 154.4, 144.9 (q, J 5 4.0 Hz), 135.8 (q, J 5 3.0 Hz), 128.0 (q, J 5 34.0 Hz), 122.6 (q, J 5 273 Hz), 120.7. ¹⁹F NMR: 5262.0

2-Chloro-3-(trifluoromethyl)pyridine:

¹H NMR: δ 5 8.58 (dd, J 5 4.8, 1.3 Hz, 1 H), 8.04 (dd, J 5 7.8, 1.9 Hz, 1 H), 7.40 (dd, J 5 7.4, 4.8 Hz, 1 H). ¹³C NMR: δ 5 152.4, 149.1, 136.8 (q, J 5 5.0 Hz), 125.5 (q, J 5 33.0 Hz), 122.3 (q, J 5 273 Hz), 122.1. ¹⁹F NMR: 5 264.4

25 2-Chloro-4-(trifluoromethyl)pyridine:

¹H NMR: δ 5 8.60 (d, J 5 5.1 Hz, 1 H), 7.58 (dq, J 5 1.5, 0.8 Hz, 1 H), 7.48 (dm, J 5 5.1 Hz, 1 H). ¹³C NMR: δ 5 152.7, 151.0, 141.1 (q, J 5 35.0 Hz), 122.2 (q, J 5 273 Hz), 120.7 (q, J 5 4.0 Hz), 118.3 (q, J 5 3.0 Hz). ¹⁹F NMR: 5265.4

3,5-Dibromo-2-(trifluoromethyl)pyridine:

30 ¹H NMR: δ 5 8.68 (d, J 5 1.8 Hz, 1 H), 8.2 (m, 1 H). ¹³C NMR: δ 5 148.3, 144.8, 144.7 (q, J 5 35.0 Hz), 123.7, 120.9 (q, J 5 275 Hz), 118.4. ¹⁹F NMR: 5 266.4

Example-3: General process for the trifluoromethylation of aldehydes or ketones:

In a flame dried reaction vials or round bottom flask Aldehyde and ketones (A) (1mmol), (di-^tBuOH)R₂NCF₃ and Lewis acid/ Bronsted acid (10% mmol) was added dry

THF and stirred at for 12h. After completion of reaction mixture was concentrated under reduced pressure. The crude product was purified by flash column chromatography using EtOAc/hexane to give fluorinated products in 55% to 91% yield.

Characterization of synthesized compound:

5 **1,1,1-trifluoro-2-(naphthalen-2-yl)propan-2-ol:** ¹H NMR (CDCl₃) δ 1.88 (s, 3H), 2.50 (s, 1H), 7.46.7.54 (m, 2H), 7.66 (d, *J* = 8.4Hz, 1H), 7.78.7.92 (m, 3H), 8.05 (s, 1H); ¹³C NMR (CDCl₃) δ 24.2, 75.0 (q, *J* = 29.1 Hz), 123.3 (d, *J* = 1.6 Hz), 125.4 (d, *J* = 1.2Hz), 125.46 (q, *J* = 284.5Hz), 126.2, 126.8, 127.3, 127.9, 128.2, 132.6, 132.8, 135.5; ¹⁹F NMR (CDCl₃) δ .80.7

10 **2-(4-bromophenyl)-1,1,1-trifluoropropan-2-ol:** ¹H NMR (CDCl₃) δ 1.75 (s, 3H), 2.64 (br s, 1H), 7.38.7.55 (m, 4H); ¹³C NMR (CDCl₃) δ 24.0, 74.6 (q, *J* = 29.1 Hz), 122.8, 125.1 (q, *J* = 284.1 Hz), 127.7, 131.2, 137.1; ¹⁹F NMR (CDCl₃) δ 81.1

15 **1,1,1-trifluoro-2-(4-methoxyphenyl)propan-2-ol:** ¹H NMR (CDCl₃) δ 1.75 (s, 3H), 2.42 (br s, 1H), 3.81 (s, 3H), 6.90 (dt, *J* = 1.6, 8.8 Hz, 2H), 7.48 (d, *J* = 9.0 Hz, 2H); ¹³C NMR (CDCl₃) δ 24.0, 55.3, 74.6 (q, *J* = 29.1 Hz), 113.5, 125.4 (q, *J* = 284.1 Hz), 127.2, 130.3, ¹⁹F NMR (CDCl₃) δ .81.3

20 **2-(4-chlorophenyl)-1,1,1-trifluoropropan-2-ol:** ¹H NMR (CDCl₃) δ 1.77 (s, 3H), 2.45 (s, 1H), 7.35 (dt, *J* = 1.8, 8.6 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 2H); ¹³C NMR (CDCl₃) δ 24.1, 74.5 (q, *J* = 29.1 Hz), 125.1 (q, *J* = 284.1 Hz), 127.4, 128.3, 134.5, 136.6; ¹⁹F NMR (CDCl₃) δ .81.2

25 **1,1,1-trifluoro-2-(4-fluorophenyl)propan-2-ol:** ¹H NMR (CDCl₃) δ 1.78 (s, 3H), 2.43 (br s, 1H), 7.02.7.12 (m, 2H), 7.52.7.59 (m, 2H); ¹⁹F NMR (CDCl₃) δ 113.1.113.2 (m, 1F); ¹³C NMR (CDCl₃) δ 24.1, 74.5 (q, *J* = 29.1 Hz), 115.0(q, *J* = 21.5 Hz), 125.3 (q, *J* = 284.9 Hz), 127.89 (d, *J* = 8.4 Hz), 127.92 (d, *J* = 8.0 Hz), 134.0 (d, *J* = 3.2 Hz), 162.5 (d, *J* = 246.6); ¹⁹F NMR (CDCl₃) δ .81.1

ADVANTAGES OF THE INVENTION

- stable, non-hygroscopic and cheap trifluoro methylating agents are provided.
- simple and easy method to prepare these trifluoro methylating agents is provided.
- simple and easy method of trifluoromethylation of the compounds.

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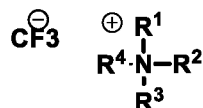
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Claims:

1. A quaternary ammonium trifluoromethyl salt of formula (I);



(I)

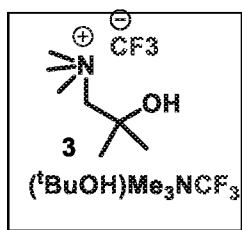
wherein, R₁, R₂, R₃ and R₄ are C₁-C₄ alkyl, wherein at least one of R₁, R₂, R₃ and R₄ is -OH substituted C₁-C₄ alkyl;

preferably, R₁, R₂, R₃ and R₄ are independently selected from -CH₃, -CH₂-C(OH)-(CH₃)₂;

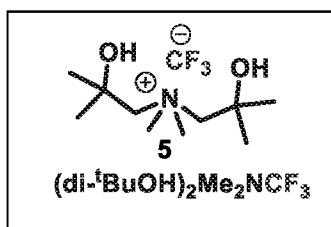
provided R₁, R₂, R₃ and R₄ are all not -CH₃ at the same time;

wherein, said quaternary ammonium salt of formula (I) remains stable up to 20 minutes at a temperature in the range of 25-30°C.

2. The quaternary ammonium salt of formula (I) as claimed in claim 1, is selected from quaternary ammonium salts of formula (3) and formula (5);



(3)



(5).

3. A process for the preparation of quaternary ammonium salt of formula (I) as claimed in claim 1, wherein the process comprising the steps of:
- reacting Isobutylene oxide of formula (1) with alkyl amine at a temperature in the range of 25-30 °C for 12 hours and then at 60 °C for 3 days to afford viscous liquid;

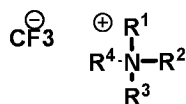
- b) dissolving the viscous liquid obtained at step a) in THF and reacting with alkyl iodide at a temperature of 60 °C for 2 hours to get quaternary ammonium iodide salts;
- c) passing the obtained quaternary ammonium iodide salts at step c) through the Amberlite® IRA400 in cl form ion exchange resin in HF from H₂O as a solvent and then removing the water at 40 °C to get quaternary ammonium trifluoromethyl salt (I).
4. The process as claimed in claim 3, wherein said alkyl amine at step a) is selected from methyl amine and dimethyl amine, and wherein said alkyl iodide at step b) is methyl iodide.
5. A process for the preparation of quaternary ammonium salt of formula (I) as claimed in claim 1, wherein the process comprising the steps of:
- adding alkyl iodide into the reaction mixture containing compound of formula (6) and maintaining the reaction mixture at a temperature in the range of 55°C- 60°C for a period in the range of 1-2 hours;
 - concentrating the reaction mixture obtained at step i) at reduced pressure to give yellow solid;
 - passing the yellow solid obtained at step ii) through Amberlite® IRA400 in chloroform ion exchange resin in HF from H₂O as a solvent;
 - removing the water from the reaction mixture obtained at step iii) at a temperature in the range of 40°C-45°C to give quaternary ammonium trifluoride salt (7);
 - stirring the solution of TMSCF₃ in acetonitrile with quaternary ammonium trifluoride salt (7) obtained at step iv) in acetonitrile at a temperature in the range of -10 °C to 30 °C for a period in the range of 2-3 hours;
 - concentrating the reaction mass obtained at step v) under reduced pressure to obtain quaternary ammonium trifluoromethyl salt of formula (I).
6. A process for the trifluoromethylation by using quaternary ammonium salts of formula (I) as claimed in claim 1, wherein said process comprises of reacting compound of formula (A) with quaternary ammonium trifluoromethyl salt of formula (I) in the presence of metal catalyst /Lewis acid/ Bronsted acid in a suitable solvent at a temperature in the range of 30-105 °C for 10-12 hours to get fluorinated products of formula (II).

7. The process for the trifluoromethylation as claimed in claim 6, wherein said compound of formula (A) is selected from ethyl 4-iodobenzoate, 1-chloro-4-iodobenzene, 1-(tert-butyl)-4-iodobenzene, 2-chloro-5-iodopyridine, 2-bromoquinolin, 5-Methyl-2-trifluoromethylthiophene, 3-bromopyridine, 4-iodopyridine, 2-Chloro-6-bromopyridine, 2-Bromo-6-iodopyridin, 5-Bromo-2-iodopyridine, 2-Bromo-5-bromopyridine, 1-(naphthalen-2-yl)ethan-1-one, 1-(4-bromophenyl)ethan-1-one, 1-(4-methoxyphenyl)ethan-1-one, 1-(4-chlorophenyl)ethan-1-one, 1-(4-fluorophenyl)ethan-1-one.
8. The process for the trifluoromethylation as claimed in claim 6, wherein said compound of formula (II) is selected from 4-Trifluoromethylbenzonitrile, Ethyl 4-Trifluoromethylbenzoate: 4-Chloro(trifluoromethyl)benzene, 4-Butyl(trifluoromethyl)benzene, 2-Chloro-5-(trifluoromethyl)pyridine, 2-Trifluoromethylquinoline 5-Methyl-2-trifluoromethylthiophene, 3-(Trifluoromethyl)pyridine, 4-(Trifluoromethyl)pyridine: 2-Chloro-6-(trifluoromethyl)pyridine, 2-Bromo-6-(trifluoromethyl)pyridine 5-Bromo-2-(trifluoromethyl)pyridine, 2-Bromo-5-(trifluoromethyl)pyridine, 3-Bromo-5-(trifluoromethyl)pyridine, 2-Chloro-3-(trifluoromethyl)pyridine: 2-Chloro-4-(trifluoromethyl)pyridine, 3,5-Dibromo-2-(trifluoromethyl)pyridine 1,1,1-trifluoro-2-(naphthalen-2-yl)propan-2-ol 2-(4-bromophenyl)-1,1,1-trifluoropropan-2-ol: 1,1,1-trifluoro-2-(4-methoxyphenyl)propan-2-ol: 2-(4-chlorophenyl)-1,1,1-trifluoropropan-2-ol: 1,1,1-trifluoro-2-(4-fluorophenyl)propan-2-ol.
9. The process for the trifluoromethylation as claimed in claim 6, wherein said metal catalyst or Lewis acid or Bronsted acid is selected from $M(OTf)_2$ / $M(OTf)_3$; wherein M (metals) is selected from Ag, Bi, Cu, Fe, Ni, In, Sc, $BF_3 \cdot OEt_2$, Tf_2NH , PTSA, carboxylic acids; and wherein said suitable solvent is selected from toluene and THF.
10. The process for the trifluoromethylation as claimed in claim 6, wherein said fluorinated product is obtained in 55% to 90% yield.

AMENDED CLAIMS

received by the International Bureau on 30 May 2022 (30.05.2022)

1. A quaternary ammonium trifluoromethyl salt of formula (I);



(I)

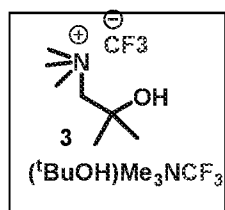
wherein, R₁, R₂, R₃ and R₄ are C₁-C₄ alkyl, wherein at least one of R₁, R₂, R₃ and R₄ is -OH substituted C₁-C₄ alkyl;

preferably, R₁, R₂, R₃ and R₄ are independently selected from -CH₃, -CH₂-C(OH)-(CH₃)₂;

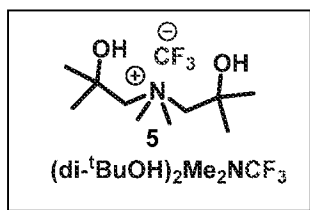
provided R₁, R₂, R₃ and R₄ are all not -CH₃ at the same time;

wherein, said quaternary ammonium salt of formula (I) remains stable up to 20 minutes at a temperature in the range of 25-30°C.

2. The quaternary ammonium trifluoromethyl salt of formula (I) as claimed in claim 1, is selected from quaternary ammonium salts of formula (3) and formula (5);



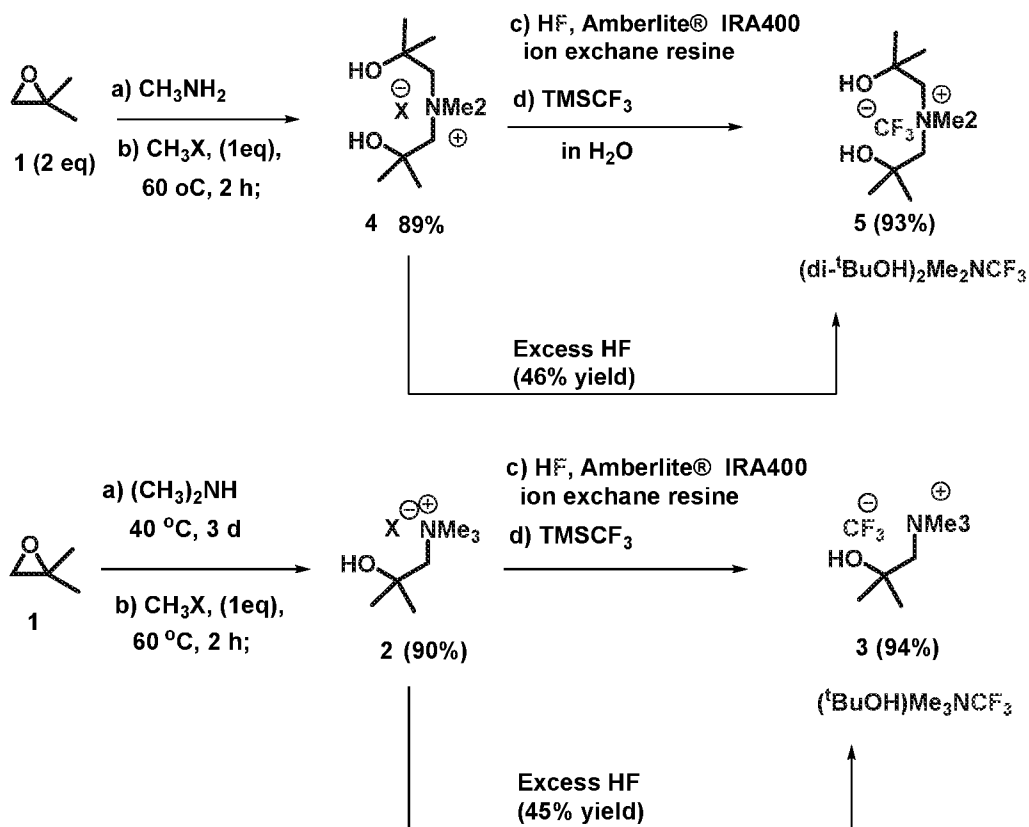
(3)



(5).

3. A process for the preparation of quaternary ammonium trifluoromethyl salt of formula (I) as claimed in claim 2, wherein the process comprises the steps of:

- reacting Isobutylene oxide of formula (1) with alkyl amine at a temperature in the range of 25-30 °C for 12 hours and then at 60 °C for 3 days to afford viscous liquid;
- dissolving the viscous liquid obtained at step a) in THF and reacting with alkyl iodide at a temperature of 60 °C for 2 hours to get quaternary ammonium iodide salts;
- passing the obtained quaternary ammonium iodide salts at step b) through the Amberlite® IRA400 in cl form ion exchange resin in HF from H₂O as a solvent followed by addition of a solution of TMSCF₃ in a solvent or HF in excess, and then removing the water at 40 °C to get quaternary ammonium trifluoromethyl salt (I);



wherein said alkyl amine at step a) is selected from methyl amine and dimethyl amine, and wherein said alkyl iodide at step b) is methyl iodide.

4. A process for the preparation of quaternary ammonium trifluoromethyl salt of formula (I) as claimed in claim 1, wherein the process comprises the steps of:

- i. adding alkyl iodide into the reaction mixture containing compound of formula (6) and maintaining the reaction mixture at a temperature in the range of 55°C-60°C for a period in the range of 1-2 hours;
- ii. concentrating the reaction mixture obtained at step i) at reduced pressure to give yellow solid;
- iii. passing the yellow solid obtained at step ii) through Amberlite® IRA400 in chloroform ion exchange resin in HF from H₂O as a solvent;
- iv. removing the water from the reaction mixture obtained at step iii) at a temperature in the range of 40°C-45°C to give quaternary ammonium fluoride salt (7);
- v. stirring the solution of TMSCF₃ in acetonitrile with quaternary ammonium fluoride salt (7) obtained at step iv) in acetonitrile at a temperature in the range of -10 °C to 30 °C for a period in the range of 2-3 hours;
- vi. concentrating the reaction mass obtained at step v) under reduced pressure to obtain quaternary ammonium trifluoromethyl salt of formula (I);



wherein, R₁, R₂, R₃ and R₄ are branched or linear C₁-C₄ alkyl,

wherein at least one of R₁, R₂, R₃ and R₄ is -OH substituted C₁-C₄ alkyl;

preferably, R₁, R₂, R₃ and R₄ are independently selected from -CH₃,

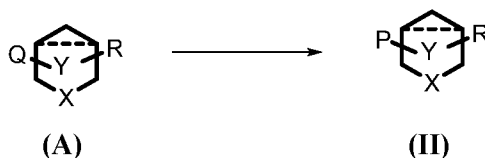
and CH₂C(OH)-(CH₃)₂;

provided R₁, R₂, R₃ and R₄ are all not -CH₃ at the same time;

wherein X= I, Br, or Cl.

5. A process for the trifluoromethylation by using quaternary ammonium trifluoromethyl salts of formula (I) as claimed in claim 1, wherein said process comprises of reacting compound of formula (A) with quaternary ammonium trifluoromethyl salt of formula (I) in the presence of metal catalyst /Lewis acid/ Bronsted acid in a suitable solvent at

a temperature in the range of 30-105 °C for 10-12 hours to get fluorinated products of formula (II);



wherein,

ring 'Y' is aromatic and 5-membered or 6-membered;

X= C, N, O or S;

Q= F, Cl, Br, I, OTf or -R_a-C(O)-;

wherein, R_a= H or C₁-C₁₀ (un)substituted alkyl, C₁-C₆ cycloalkyl, aryl;

R= same or different and selected from the group comprising of C₁-C₁₀ alkyl, C₁-C₁₀ cycloalkyl, aryl, alkoxy, cyano, -COOR_b, ketone, aldehyde, NO₂;

wherein, R_b is C₁-C₁₀ alkyl or aryl;

P= CF₃ or -R_a-C(OH)-CF₃;

or any two or more adjacent carbon atoms of ring 'Y' form 5-6 membered aromatic ring.

6. The process for the trifluoromethylation as claimed in claim 5, wherein said compound of formula (A) is selected from ethyl 4-iodobenzoate, 1-chloro-4-iodobenzene, 1-(tert-butyl)-4-iodobenzene, 2-chloro-5-iodopyridine, 2-bromoquinolin, 5-Methyl-2-trifluoromethylthiophene, 3-bromopyridine, 4-iodopyridine, 2-Chloro-6-bromopyridine, 2-Bromo-6-iodopyridin, 5-Bromo-2-iodopyridine, 2-Bromo-5-bromopyridine, 1-(naphthalen-2-yl)ethan-1-one, 1-(4-bromophenyl)ethan-1-one, 1-(4-methoxyphenyl)ethan-1-one, 1-(4-chlorophenyl)ethan-1-one, 1-(4-fluorophenyl)ethan-1-one.
7. The process for the trifluoromethylation as claimed in claim 5, wherein said compound of formula (II) is selected from 4-Trifluoromethylbenzonitrile, Ethyl 4-Trifluoromethylbenzoate: 4-Chloro(trifluoromethyl)benzene, 4-Butyl(trifluoromethyl)benzene, 2-Chloro-5-(trifluoromethyl)pyridine, 2-Trifluoromethylquinoline 5-Methyl-2-trifluoromethylthiophene, 3-(Trifluoromethyl)pyridine, 4-(Trifluoromethyl)pyridine: 2-Chloro-6-(trifluoromethyl)pyridine, 2-Bromo-6-(trifluoromethyl)pyridine 5-Bromo-2-

(trifluoromethyl)pyridine, 2-Bromo-5-(trifluoromethyl)pyridine, 3-Bromo-5-(trifluoromethyl)pyridine, 2-Chloro-3-(trifluoromethyl)pyridine, 2-Chloro-4-(trifluoromethyl)pyridine, 3,5-Dibromo-2-(trifluoromethyl)pyridine, 1,1,1-trifluoro-2-(naphthalen-2-yl)propan-2-ol, 2-(4-bromophenyl)-1,1,1-trifluoropropan-2-ol, 1,1,1-trifluoro-2-(4-methoxyphenyl)propan-2-ol, 2-(4-chlorophenyl)-1,1,1-trifluoropropan-2-ol, and 1,1,1-trifluoro-2-(4-fluorophenyl)propan-2-ol.

8. The process for the trifluoromethylation as claimed in claim 5, wherein said metal catalyst or Lewis acid or Bronsted acid is selected from $M(OTf)_2$ / $M(OTf)_3$; wherein M (metals) is selected from Ag, Bi, Cu, Fe, Ni, In, Sc, $BF_3 \cdot OEt_2$, Tf_2NH , PTSA, carboxylic acids; and wherein said suitable solvent is selected from toluene and THF.
9. The process for the trifluoromethylation as claimed in claim 5, wherein said fluorinated product is obtained in 55% to 90% yield.

STATEMENT UNDER ARTICLE 19 (1)**STATEMENT OF SUPPORT PROVIDING REASONS AND BASIS OF AMENDMENTS**

Claims 1-9 (amended) are presently pending. The preamble of dependent claims have been amended for clarity. Claims 3, 5 and 6 have been amended to overcome objection of clarity. Claim 3 has been further amended by introducing features of claim 4, results in deletion of claim 4. Pending claims have been renumbered and amended for change in dependencies accordingly. No new matter has been added by way of present amendments.

Clarity under PCT Article 6:

1. The Examiner objected that claim 5 does not meet the requirements of Article 6 PCT as the matter for which protection is sought is not clearly defined. The compound of formula (6) is not defined anywhere in the claim or the previous claims.

Our Submission:

The Applicant has amended claim 5 by defining compound of formula (6), rendering the objection moot. Support is available on page 7 of the specification.

2. The Examiner objected that claim 3 does not meet the requirements of PCT Article 6 as it lacks clarity and is not supported by specification. It is not clear how trifluoromethyl salt of the compound is to be obtained in step (c) as the suitable reagent is not mentioned therein. Further, the process steps are not consistent with corresponding scheme 1a, 1b of the description as they provide a further step (d) incorporating reagent TMSCF₃ in H₂O for introducing CF₃ group in the salt form.

Our Submission:

The Applicant has amended claim 3 by incorporating reagent TMSCF₃ in solvent for introduction of CF₃ group in the salt form, rendering the objection moot. The alternate embodiment of adding excess HF is also covered. Support is available in scheme 1a and 1b of the description.

3. The Examiner objected that the application does not disclose the invention sufficiently clear and complete for it to be carried out by any person skilled in the art (Article 5 PCT). Example 1 of the specification is not consistent with the corresponding scheme 1a, 1b on pages 5-6 as the step (d) incorporating reagent TMSCF₃ in H₂O for introducing the CF₃ group in the salt form is not specified in the example. So, it is not clear how CF₃ salt of compound of formula (I) is obtained.

Our Submission:

The Applicant respectfully disagrees with the assertion of the Examiner. However, without prejudice, the Applicant has amended claim 3 by incorporating reagent TMSCF₃ in solvent for introduction of CF₃ group in the salt form, rendering the objection moot. Support is available in scheme 1a and 1b of the description.

4. The Examiner objected that contrary to the requirements of Rule 5.1 (a) (ii) PCT, the relevant background art is not mentioned in the description.

Our Submission:

The Applicant submits that the present invention is novel, and the Examiner has also acknowledged the same. In view thereof, there is no relevant background art to be mentioned in the description.

Moreover, Rule 5.1 (a) (ii) PCT mentioned that “indicate the background art which, as far as known to the applicant, can be regarded as useful for the understanding, searching and examination of the invention, and, preferably, cite the documents reflecting such art”.

Said rule specify disclosing the prior-art documents known to the Applicant. The Applicant is unknown to any document which directly or indirectly relates to the present invention. In view thereof, the Applicant requests reconsideration and withdrawal of the objection.

5. The Examiner objected that claim 3 is not clear (Article 6 PCT) as step (c) derives dependency from step (c) itself.

Our Submission:

The Applicant has corrected the dependency, rendering the objection moot.

6. The Examiner objected that claim 6 does not meet the requirements of Article 6 PCT as the matter for which protection is sought is not clearly defined. The compound of formula (A), formula (II) is not defined anywhere in the claim or the previous claims.

Our Submission:

The Applicant respectfully disagrees with the assertion of the Examiner. However, without prejudice, the applicant has defined the compounds of formula (A) and formula (II) in claim 6 having support on pages 7-8 of the present application. Reconsideration and withdrawal of the objection respectfully requested.

Lacking unity under Rule 13.1 of PCT:

The Examiner objected that the present application consists of the following group of inventions:

Group I: Claims 1-2 (partly); Claims 3-4 (fully) related to quaternary ammonium salt of formula I and a process for its preparation comprising starting material isobutylene oxide and alkyl amine

Group II: Claims 1-2 (partly); Claim 5 (fully) related to quaternary ammonium salt of formula I and a process for its preparation comprising starting materials formula (6) and alkyl iodide.

Group III: Claims 1-2 (partly); Claims 6-10 (fully) related to quaternary ammonium salt of formula I and a process of trifluoromethylation using quaternary ammonium salts of formula I.

The Examiner highlighted that these groups of inventions are not so linked as to form a single general inventive concept as required under Rule 13.1 of PCT for the following reasons. These groups of inventions are not linked by any common technical feature.

Our Submission:

The Applicant respectfully disagree with the assertion of the Controller and submits that the present invention discloses a quaternary ammonium trifluoromethyl salts of formula (I), a process for the preparation of a quaternary ammonium trifluoromethyl salts of formula (I) and an application of a quaternary ammonium trifluoromethyl salts of formula (I) in trifluoromethylation. In view thereof, the Applicant has highlighted said underlined common feature in the pending claims. Reconsideration and withdrawal of the objection respectfully requested.

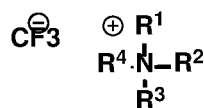
Inventive step under PCT Article 33(3):

The Examiner objected that the pending claims lack inventive step.

At the outset, the Applicant appreciated the Examiner for acknowledging the novelty of the present invention.

Further, the applicant most respectfully disagrees with the above assertion of the Examiner regarding inventive step of the invention and without acquiescing to the validity of the objection, submits that the amended claims submitted herewith are clearly inventive over the cited prior arts, taken either alone or in combination with each-other.

The present invention discloses a quaternary ammonium trifluoromethyl salt of formula (I);



(I)

wherein, R₁, R₂, R₃ and R₄ are C₁-C₄ alkyl, wherein at least one of R₁, R₂, R₃ and R₄ is -OH substituted C₁-C₄ alkyl;

preferably, R₁, R₂, R₃ and R₄ are independently selected from -CH₃, -CH₂-C(OH)-(CH₃)₂;

provided R₁, R₂, R₃ and R₄ are all not -CH₃ at the same time;

wherein, said quaternary ammonium salt of formula (I) remains stable up to 20 minutes at a temperature in the range of 25-30°C.

None of the cited documents D1-D7 discloses a quaternary ammonium trifluoromethyl salt of formula (I) as disclosed in the present invention.

D1 discloses quaternary ammonium halide salts. It describes “wherein X represents an anion such as the halides, e.g., chloride, bromide; hydroxide; methylsulfate; and the like” (on col. 3, lines 65-68), which does not clearly define trifluoromethyl salt, whereas the present invention provides quaternary ammonium trifluoromethyl salt which acts as a trifluoromethylating agent. Moreover, the important element of claim 1 of the present invention is “the quaternary ammonium trifluoromethyl salt of formula (I) remains stable up to 20 minutes at a temperature in the range of 25-30°C”. D1 does not talk anything about stability of quaternary ammonium halide salts as described.

Compound of formula (II) disclosed by D2 is altogether different than the quaternary ammonium trifluoromethyl salt of formula (I) of the present invention. D2 defines X⁻ anion in para [0042] as:

[0042] X⁻ is an anion and present in the amount equal to the cations present in Formula I and/or Formula II. In some embodiments, Formula I may not have any cations and X⁻ is not present as a counter anion. In some embodiments, Formula II may have 1, 2, or 3 cations and X⁻ is present as an anion equal to the amount of cation charges. In some embodiments, X⁻ may be a halide, sulfate, methosulfate, carbonate, carboxylate, phosphate, or hydroxide. In some embodiments, X⁻ may be a halide or hydroxide. In some embodiments, X⁻ may be a hydroxide.

It does not include trifluoromethyl anion. Thus, quaternary ammonium salts described in the D2 are different than the present invention. As salts described by D2 are different than the quaternary ammonium trifluoromethyl salt of formula (I) of the present invention, their chemical and physical properties including stability also differ from each other.

The important element of claim 1 of the present invention is “the quaternary ammonium trifluoromethyl salt of formula (I) remains stable up to 20 minutes at a temperature in the range of 25-30°C”. D2 does not talk anything about stability of quaternary ammonium salts as described.

As the quaternary ammonium trifluoromethyl salt of formula (I) of the present invention is novel and inventive, the dependent claims covering process for the preparation thereof also become novel and inventive for the same reason at least.

Subject matter of the claim 1 of the present invention appears to be different than the subject matter of the documents D3 and D4. Thus, documents D3 and D4 appear to be irrelevant in view of teaching of the present invention.

D5 discloses use of anion exchange resin Amberlite IRA-400 and IRA-410 for anion exchange. However, the present invention uses Amberlite resin in order to obtain quaternary ammonium fluoride salt and not trifluoromethyl salt, which is stable up to 20 minutes at a temperature in the range of 25-30°C. Thus, D5 does not disclose or teach subject matter of claim 1 or the process to achieve it of the present invention.

D6 discloses trifluoromethylation process of aldehydes and ketones in the presence of TMSCF₃ and quaternary ammonium salt. However, it fails to disclose the trifluoromethylation by using isolated, stable quaternary ammonium trifluoromethyl salt of formula (I) as disclosed in the present invention.

D6 also does not talk about the stable quaternary ammonium trifluoromethyl salt of formula (I) or the process for its preparation. Moreover, as discussed above, process disclosed for trifluoromethylation by D6 is also altogether different than the trifluoromethylation process of the present invention.

Thus, the subject matter of claim 1 of the present invention is different than the subject matter of D6, making the document D6 irrelevant in view of the teachings of the present invention.

D7 discloses trifluoromethylation of oximes providing cyclised product by using copper catalyst and Togni's reagent as a trifluoromethylating agent. Here, the starting material, reagent and product everything is altogether different than the present invention. Subject matter of D7 is altogether different than the subject matter of claim 1 of the present invention. Thus, it appears that D7 is also irrelevant to the present invention.

In view of the above, it is respectfully submitted that the present invention does not fall under the purview of the cited documents D1-D7. All of the cited documents D1-D7, either individually or in combination with each-other, do not teach or suggest or motivates a person skilled in the art to arrive at the present invention. Thus, the present invention is novel as well as inventive over the cited documents D1-D7. The Examiner is respectfully requested to reconsider and waive the objection.

1/1

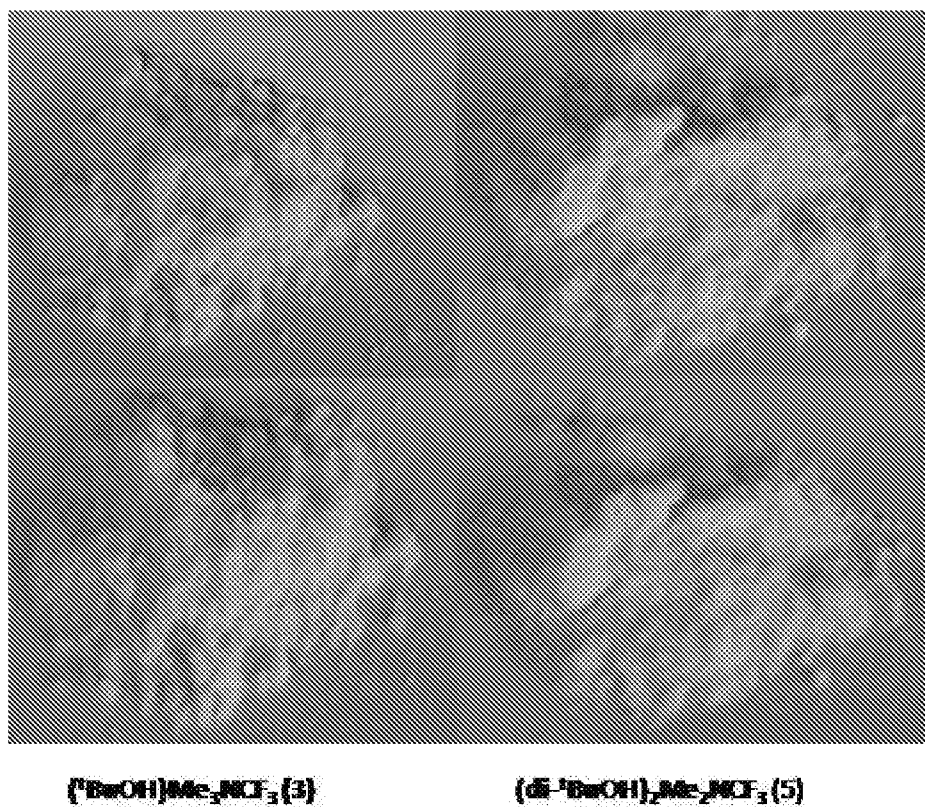


Figure 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2021/051167

A. CLASSIFICATION OF SUBJECT MATTER

C07C215/08, C07C215/12, C07C211/03, C07C17/093 Version=2022.01

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 3954873A (ROBERT M. GIPSON) 04 MAY 1976 (04.05.1976) *col.3, lines 52-61; col.4, lines 36-42* Family: [NONE]	1-10
Y	WO 2020/214692 A1 (ANGUS CHEMICAL COMPANY) 22 OCTOBER 2020 (22.10.2020) *para 1; para 70; example 2*	1-10
Y	JUKES, T. H., & WELCH, A. D., (1942), "THE EFFECT OF CERTAIN ANALOGUES OF CHOLINE ON PEROSIS", JOURNAL OF BIOLOGICAL CHEMISTRY, 146(1), 19-24 *pg. 21, para2, Table 1*	1-10
Y	MENGE, G. A., (1911), "SOME NEW COMPOUNDS OF THE CHOLINE TYPE", JOURNAL OF THE WASHINGTON ACADEMY OF SCIENCES, 1(8), 223-224 *pg. 404*	1-10
Y	LOPEZ, M., COCA, J., & SASTRE, H. (1992), "ANION EXCHANGE IN AMBERLITE IRA-400 AND AMBERLITE IRA-410 ION EXCHANGE RESINS", JOURNAL OF CHEMICAL	1-10



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"D" document cited by the applicant in the international application

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"I" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

28-03-2022

Date of mailing of the international search report

28-03-2022

Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/IN2021/051167

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	& ENGINEERING DATA, 37(2), 274-277 *pg. 274, Experimental Section* ----- JOHNSTON, C. P., WEST, T. H., DOOLEY, R. E., REID, M., JONES, A. B., KING, E. J., & LLOYD-JONES, G. C., (2018), ANION-INITIATED TRIFLUOROMETHYLATION BY TMSF ₃ : DECONVOLUTION OF THE SILICONATE-CARBANION DICHOTOMY BY STOPPED-FLOW NMR/IR. JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, 140(35), 11112-11124 *pg. 11112, Introduction; Fig. 4,7* -----	1-10
	HE, Y. T., LI, L. H., YANG, Y. F., WANG, Y. Q., LUO, J. Y., LIU, X. Y., & LIANG, Y. M., (2013), "COPPER-CATALYZED SYNTHESIS OF TRIFLUOROMETHYL-SUBSTITUTED ISOXAZOLINES", CHEMICAL COMMUNICATIONS, 49(50), 5687-5689 *Table 1*	6-10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2021/051167

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Group I: Claims 1-2 (partly); Claims 3-4 (fully) related to quaternary ammonium salt of formula I and a process for its preparation comprising starting material isobutylene oxide and alkyl amine

Group II: Claims 1-2 (partly); Claim 5 (fully) related to quaternary ammonium salt of formula I and a process for its preparation comprising starting materials formula (6) and alkyl iodide.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

Continuation of Observations where unity of invention is lacking (Box III)

Group III: Claims 1-2 (partly); Claims 6-10 (fully) related to quaternary ammonium salt of formula I and a process of trifluoromethylation using quaternary ammonium salts of formula I.

These groups of inventions are not so linked as to form a single general inventive concept as required under Rule 13.1 of PCT for the following reasons. These groups of inventions are not linked by any common technical feature. The processes differ in terms of reactants employed, intermediates involved, reagents used and consequently, the reaction sites and reaction mechanism. Thus, no relationship could be established between the said inventions. There is no single general concept that links the different methods as claimed. Therefore, the above mentioned groups lack a common feature which could be regarded as the special technical feature providing unity to the claims. Consequently, the application may be objected for lacking unity a priori.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IN2021/051167

Citation	Pub.Date	Family	Pub.Date
WO 2020/214692 A1	22-10-2020	EP 3956291 A1	23-02-2022