



(43) International Publication Date
18 June 2015 (18.06.2015)

(10) International Publication Number
WO 2015/087352 A1

(51) International Patent Classification:

C07C 315/04 (2006.01) C07F 7/08 (2006.01)
C07C 317/14 (2006.01) C07C 313/02 (2006.01)
C07C 317/22 (2006.01)

(21) International Application Number:

PCT/IN2014/000772

(22) International Filing Date:

12 December 2014 (12.12.2014)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

3617/DEL/2013 12 December 2013 (12.12.2013) IN

(71) Applicant: COUNCIL OF SCIENTIFIC AND INDUSTRIAL RESEARCH [IN/IN]; Anusandhan Bhawan, Rafi Marg, New Delhi 110 001 (IN).

(72) Inventors: BABURAO MHASKE, SANTOSH; National Chemical Laboratory, Dr. Homi Bhabha Road, Pune (Maharashtra) 411 008 (IN). PANDYA, Virat; National Chemical Laboratory, Dr. Homi Bhabha Road, Pune (Maharashtra) 411 008 (IN).

(74) Agents: RANJNA MEHTA DUTT et al.; Remfry & Sagar, Attorneys-At-Law, Remfry House At The Millennium Plaza, Sector 27, Gurgaon 122 009 (IN).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY,

BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- of inventorship (Rule 4.17(iv))

Published:

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

(54) Title: A PROCESS FOR THE SYNTHESIS OF ARYL SULFONES

(57) Abstract: The present patent discloses a novel, efficient and transition-metal-free room temperature single step process for synthesis of aryl sulfones and substituted aryl sulfones starting from aryl substrates.



WO 2015/087352 A1

A PROCESS FOR THE SYNTHESIS OF ARYL SULFONES

FIELD OF THE INVENTION

The present invention relates to a novel, efficient and transition-metal-free process for the preparation of aryl sulfones.

BACKGROUND AND PRIOR ART OF THE INVENTION

Arylsulfones are important building blocks in organic chemistry and especially in medicinal chemistry. The arylsulfone fragment is found in various drugs, such as the COX-2 inhibitor Vioxx or the prostaglandin D₂ antagonist Laropiprant. Diarylsulfones have been shown to exhibit antitumor activities or to inhibit HIV-1 reverse transcriptase.

Because of their importance, numerous procedures for the synthesis of arylsulfones have been reported, such as the oxidation of sulfides, the sulfonylation of arenes, or Pd- and Cu-catalyzed coupling reactions as well as transition-metal-free synthesis of diarylsulfones from arylsulfonic acid sodium salts and diaryliodonium salts.

Article titled, "Arylation of Lithium Sulfinates with Diaryliodonium Salts: A Direct and Versatile Access to Arylsulfones" by Natalie Umierski and Georg Manolikakes in Organic Letters 2013, 15, 188 reports an efficient, transition-metal-free arylation of lithium sulfinates, which are readily accessible from reactions of organolithium reagents with sulfur dioxide. Based on this method, it further reports a practical protocol for the direct transformation of (hetero)arenes and (hetero)aromatic halides into diarylsulfones.

US 3,250,812 discloses a process for producing alkyl aryl sulfones which comprises reacting an aryl compound having free hydrogen on the ring with a compound having the formula (R₁SO₂)₂O, wherein R₁ is a lower alkyl radical in a solvent at sufficient temperatures to effect said reaction.

US 4,386,221 disclose a process for the preparation of aryl alkyl sulfones and aryl vinyl sulfones. The process comprises of reacting an aryl compound with an alkyl sulfonyl fluoride or with a vinyl sulfonyl fluoride in the presence of a catalyst selected from AlCl₃ and AlBr₃.

US 5,015,775 discloses Alkyl aryl sulfones of the formula $R-SO_3-Ar-Y_n$, wherein Ar is an aryl compound, Y is a substituent on the aryl compound and R is alkyl or cycloalkyl, and liquid mixtures of positional isomers of the same are prepared by reacting an aryl compound of the formula $Ar-Y_n$, with an alkyl sulfonic acid of the formula $R-SO_3H$ and a phosphorus reagent, preferably under heat.

Article titled, "One-step synthesis of α,β -unsaturated arylsulfones by a novel multicomponent reaction of aromatic aldehydes, chloroacetonitrile, benzenesulfinic acid sodium salt" by Lei Zhang, Mao Hua Ding, Hong Yun Guo in Chinese Chemical Letters, Volume 23, Issue 12, December 2012, Pages 1352–1354 reports a new and green method for the synthesis of α,β -unsaturated arylsulfones through the condensation of aromatic aldehydes, chloroacetonitrile, benzenesulfinic acid sodium salt in the presence of 1-butyl-3-methyl imidazolium hydroxide ([bmim]OH) in EtOH under reflux. The ionic liquid was recovered and recycled for subsequent reactions. The advantages of this protocol were non-toxic, easy work-up and good yields.

Article titled, "A mild and efficient new synthesis of aryl sulfones from boronic acids and sulfinic acid salts" by Christian Beaulieu, Daniel Guay, Zhaoyin Wang and David A. Evans in Tetrahedron Letters 45 (2004) 3233–3236 reports a new efficient and mild preparation of sulfones from boronic acids and sulfinic acid salts. The cross-coupling reaction mediated by cupric acetate gives access to a variety of sulfones in excellent yield.

Article titled, "Synthesis of Aryl Sulfones via l-Proline-Promoted CuI-Catalyzed Coupling Reaction of Aryl Halides with Sulfinic Acid Salts" by Wei Zhu and Dawei Ma in *J. Org. Chem.*, 2005, 70 (7), pp 2696–2700 reports The CuI/l-proline sodium salt catalyzed coupling reaction of aryl halides with sulfinic acid salts readily occurs at 80–95 °C in DMSO to give the corresponding aryl sulfones in good to excellent yields. This process is well-tolerated by a wide range of functional groups including hydroxyl, amino, acetanilide, ketone, ester, and nitrile. Using this method, 4-phenylsulfonyl- and 4-methanesulfonyl-substituted l-phenylalanine derivatives are prepared.

US 5 468 903 relates to a process for preparing a compound comprising a monocyclic aromatic ring having at least a first substituent and a substituted sulphonyl group at the position para to the first substituent, the process comprising mixing a reactant comprising the

monocyclic aromatic ring with the first substituent and hydrogen in the position of the ring para to the first substituent, with a sulphonic acid halide derivative in the presence of a naturally occurring or synthetic zeolite capable of catalyzing a sulphonylation reaction between the reactant and the sulphonic acid halide.

5

US 6,455,738 B1 relates to a process for the sulfonation of an aromatic compound, said process comprising the steps of:

- 10 a) reacting said aromatic compound with a sulfonating agent, in the presence of a catalytically effective amount of a catalyst which is a mixture of bismuth trihalide and of perfluoroalkanesulfonic acid, with a molar ratio less than the stoichiometry resulting in the complete exchange of the halide by the sulfonic functional group, to obtain a sulfonated aromatic compound, and
- 15 b) recovering the sulfonated aromatic compound obtained in step (a).

US 4,950,793 discloses a process of reacting an aromatic hydrocarbon with a halogenated sulfonic acid in the presence of a Lewis acid to obtain an aromatic sulfone compound.

20

US 5,276,196 relates to the synthesis of bis(haloarylsulfonyl) aromatic compounds and more specifically, bis(chlorophenylsulfonyl) aromatic compounds. A process has been reported wherein product of high purity and minimal iron contamination is produced by reacting haloarylsulfonyl halide with an aromatic compound in the presence of an appropriate catalyst with and without solvent.

25

US 2743290 relates to a process for the production of halogenated thioesters of a sulfonic acid.

30

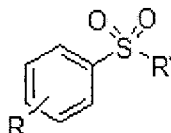
However, till date arynes have not been used for such transformation.

OBJECTIVE OF THE INVENTION

35 The main object of the present invention is to provide a room temperature single step process for synthesis of aryl sulfones and substituted aryl sulfones starting from aryl/aryl substrates.

SUMMARY OF THE INVENTION

The present invention provides a room temperature single step process for synthesis
 5 of compound of Formula I



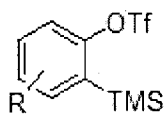
Formula I

wherein, R is selected from H, alkyl (C₁-C₆), aryl, heteroaryl, O-, S-, N-, P-
 10 alkyl/unsubstituted and substituted aryl;

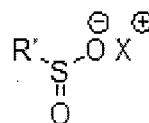
R' is selected from alkyl (C₁-C₆), aryl, heteroaryl, O-, S-, N-, P- alkyl/unsubstituted
 and substituted aryl;

15 comprising the steps of:

- a. adding benzyne precursor of Formula II to a stirred solution of fluoride ion
 source and compound of Formula III in the ratio ranging between 1:1 to 1:1.1
 in anhydrous acetonitrile to obtain a reaction mixture;



Formula II



Formula III

wherein, R is selected from H, alkyl, aryl, heteroaryl, O-, S-, N-, P- alkyl/
 unsubstituted and substituted aryl;

25 R' is selected from, alkyl, aryl, heteroaryl, O-, S-, N-, P- alkyl/ unsubstituted
 and substituted aryl;

X is selected from H, Li, Na, K, Cs;

- b. stirring the reaction mixture of step (a) for the period in the range of 1 to 8 hours followed by purification to obtain the desired product I.

In an embodiment of the present invention, fluoride ion source is selected from the group consisting of TBAF (Tetra-n-butylammonium fluoride), CsF (Cesium fluoride), NaF (Sodium Fluoride), RbF (Rubidium fluoride) or KF (Potassium fluoride).

In yet another embodiment of the present invention, the fluoride ion source is selected from TBAF or CsF.

10

In another embodiment of the present invention, compound of formula I is selected from the group consisting of:

- 1-Phenyl (sulfonyl) benzene (3);
15 1,2-Difluoro-4-(phenylsulfonyl)benzene (5);
1,2-Dimethyl-4-(phenylsulfonyl)benzene (7);
1,4-Dimethyl-2-(phenylsulfonyl)benzene (9);
1-Methoxy-3-(phenylsulfonyl)benzene (11);
1,3-Dimethoxy-5-(phenylsulfonyl)benzene (13);
20 1,2-Dimethoxy-4-(phenylsulfonyl)benzene (15);
5-(Phenylsulfonyl)benzo[d][1,3]dioxole (17);
(Methylsulfonyl)benzene (19);
(Butylsulfonyl)benzene (21);
1-Methyl-4-(phenylsulfonyl)benzene (23);
25 1-(Tert-butyl)-4-(phenylsulfonyl)benzene (25);
1-Methoxy-4-(phenylsulfonyl)benzene (27);
1-(4-(phenylsulfonyl)phenyl)ethan-1-one (29);
1-Nitro-4-(phenylsulfonyl)benzene (31);
1-Fluoro-4-(phenylsulfonyl)benzene (33);
30 2-bromo-5-(phenylsulfonyl)thiophene (35).

In yet another embodiment of the present invention, compound of formula II is selected from the group consisting of:

2-(trimethylsilyl)phenyl trifluoromethane-sulfonate (1)
4,5-difluoro-2-(trimethylsilyl)phenyl trifluoromethane-sulfonate (4)
4,5-dimethyl-2-(trimethylsilyl)phenyl trifluoromethane-sulfonate (6)
3,6-dimethyl-2-(trimethylsilyl)phenyl trifluoromethane-sulfonate (8)
5 3-methoxy-2-(trimethylsilyl)phenyl trifluoromethane-sulfonate (10)
3,5-dimethoxy-2-(trimethylsilyl)phenyl trifluoromethane-sulfonate (12)
4,5-dimethoxy-2-(trimethylsilyl)phenyl trifluoromethane-sulfonate (14)
6-(trimethylsilyl)benzo[d][1,3]dioxol-5-yl trifluoromethane-sulfonate (16)

10 In yet another embodiment of the present invention, compound of formula III is selected from the group consisting of:

sodium benzenesulfinate (2)
sodium methanesulfinate (18)
15 sodium butane-1-sulfinate (20)
sodium 4-methylbenzenesulfinate (22)
sodium 4-(tert-butyl)benzenesulfinate (24)
sodium 4-methoxybenzenesulfinate (26)
sodium 4-acetylbenzenesulfinate (28)
20 sodium 4-nitrobenzenesulfinate (30)
sodium 4-fluorobenzenesulfinate (32)
Sodium 5-bromothiophene-2-sulfinate (34).

In yet another embodiment of the present invention, the yield of the compound of
25 formula I is in the range of 45-96%.

DETAILED DESCRIPTION OF THE INVENTION

For the purposes of this patent application, "Room temperature" means temperature in the range of 20-30°C.

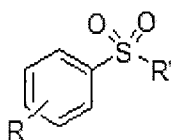
30

Present invention provides a transition metal free process for the synthesis of arylsulfones, wherein sulfinic acid/sulfinic acid salt is treated with arynes to obtain arylsulfones under mild reaction condition, in high yields.

Further, the present invention provides a process for the synthesis of arylsulfones which works with all kinds of aryl substrates having electron donating or withdrawing functional groups.

5 The process of the present invention provides aryl-aryl sulfones as well as aryl-alkyl sulfones.

Present invention provides a room temperature single step process for synthesis of aryl sulfones and substituted aryl sulfones compound of Formula I

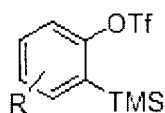


Formula I

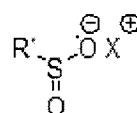
wherein, R is selected from H, alkyl, aryl, heteroaryl, O-, S-, N-, P- alkyl/unsubstituted and substituted aryl;

15 R' is selected from alkyl, aryl, heteroaryl, O-, S-, N-, P- alkyl/unsubstituted and substituted aryl,

starting from compounds of Formula II and Formula III,



Formula II



Formula III

Wherein, R is selected from H, alkyl, aryl, heteroaryl, O-, S-, N-, P- alkyl/unsubstituted and substituted aryl;

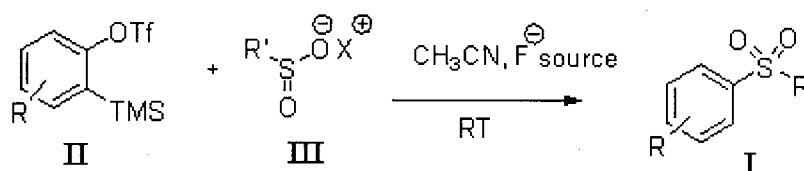
25 R' is selected from, alkyl, aryl, heteroaryl, O-, S-, N-, P- alkyl/ unsubstituted and substituted aryl; and

X is selected from H, Li, Na, K, Cs;

comprising the steps of:

- a. adding benzyne precursor of Formula **II** to a stirred solution of fluoride ion source and compound of Formula **III** in anhydrous acetonitrile to obtain a reaction mixture;
- b. stirring the reaction mixture of step (a) followed by purification affords a solid or thick oil sulfone **I**.

The process is shown below in Scheme A:



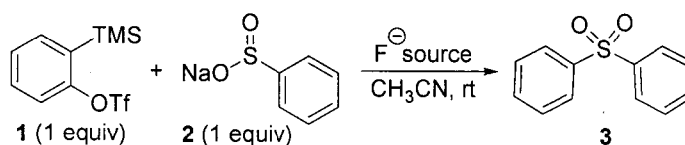
Scheme: A

The present invention provides a room temperature single step process for synthesis of aryl sulfones and substituted aryl sulfones compounds of Formula **I** wherein the fluoride ion source is selected from TBAF, CsF, NaF, RbF, KF and preferably from TBAF or CsF.

The present invention provides a room temperature single step process for synthesis of sulfones and substituted sulfones compounds of Formula **I** wherein the yield is more than 45% and preferably more than 80%.

In an aspect, the present invention provides the optimization results of fluoride source, various silyl triflate and sulfonates substrates selected which are summarized below in table 1, 2 and 3:

Table 1: Optimization studies^a

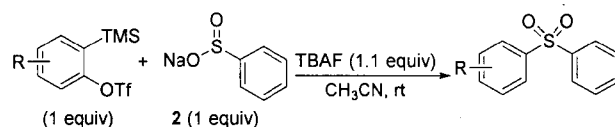


entry	F ⁻ source (equiv)	additive ^b	time	Yield
1	CsF (5.5)	-	6.0 h	86%
2	CsF (2.5)	A	6.0 h	88%
3	CsF (2.0)	A	7.0 h	82%
4	CsF (1.5)	A	7.0 h	56%
5	KF (2.0)	A	6.0 h	67%
6	TBAF (2.5)	-	1.5 h	95%
7	TBAF (1.5)	-	2.5 h	94%
8	TBAF (1.1)	-	3.0 h	94%
9	TBAF (1.0)	-	5.0 h	72%

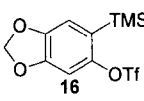
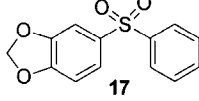
^aAll the reactions were performed on 25 mg scale of *o*-silyl aryl triflate **1**. ^bA = 18-crown-6-ether (5 mol %).

5

Table 2: Preparation of sulfones from various silyl triflates^a



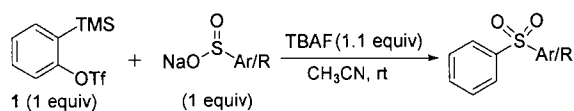
entry	silyl triflate	Product	Time	yield
1 ^b			3 h	95%
2			6 h	76%
3			4 h	92%
4			8 h	55%
5			4 h	64%
6			4 h	86%
7			3 h	60%

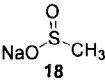
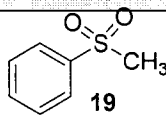
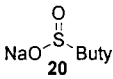
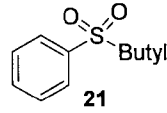
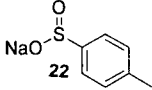
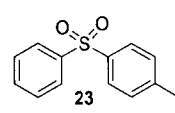
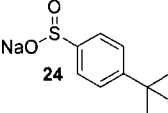
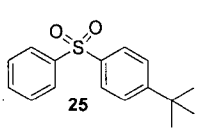
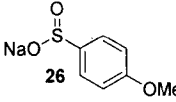
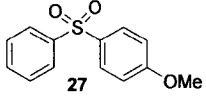
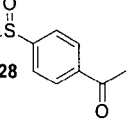
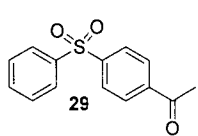
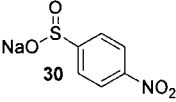
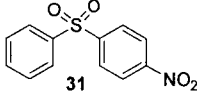
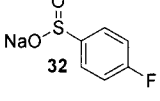
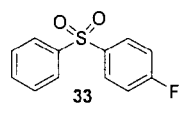
8			6 h	96%
---	---	---	-----	-----

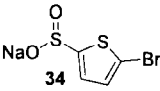
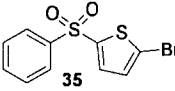
^aAll the reactions were performed on 50 mg scale of *o*-silyl aryl triflates. ^bThis reaction was also performed on 500 mg scale of *o*-silyl aryl triflate **1**.

5

Table 3: Preparation of sulfones from various sulfonates^a



Example	NaO-SO ₂ -Ar/R	product	time	yield
1			4 h	75%
2			8 h 3 h	45% ^b 86% ^c
3			3 h	68%
4			4 h	85%
5			1 h	61%
6			4 h	54%
7			3 h	74%
8			3 h	86%

9			3 h	73%
---	---	---	-----	-----

^aAll the reactions were performed on 50 mg scale of *o*-silyl aryl triflate **1**. ^bTBAF (6 equiv). ^cCsF (4 equiv), 18-crown-6-ether.

5 EXAMPLES

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

GENERAL INFORMATION

10 All reagents and solvents were used as received from commercial sources unless and otherwise noted. Acetonitrile was dried and stored over 4 Å molecular sieves. All experiments were carried out under an atmosphere of Argon. *o*-Silyl aryl triflates were synthesized by known procedures. Sodium sulfinates **2** and **18** were purchased from commercial sources and rest of the sodium sulfinates were prepared using known literature
15 procedures. Pre-coated plates (silica gel 60 PF254, 0.25 mm or 0.5 mm) were utilized for Thin Layer Chromatography (TLC). Column chromatographic purifications were carried out on flash silica-gel (240-400 mesh) using petroleum ether and ethyl acetate as eluents. The ¹H, ¹³C, NMR spectra were recorded on 200/400/500 MHz, 50/100/125 MHz NMR spectrometer respectively in CDCl₃. Chemical shifts were reported as δ values from standard
20 peaks. Melting point was recorded on Buchi instrument. Mass spectra were taken on LC-MS (ESI) mass spectrometer. HRMS were scanned at NCL, Pune.

EXAMPLE 1

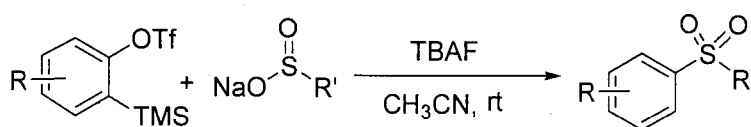
25 EXPERIMENTAL PROCEDURE FOR THE PREPARATION OF SODIUM SULFINATES

4-Methoxybenzenesulfinic acid sodium salt (**26**) was prepared by heating of sodium sulfite (2.5 g, 20 mmol), 4-methoxybenzenesulfonyl chloride (2.06 g, 10 mmol) and sodium bicarbonate (1.68 g, 20 mmol) in water (9.6 mL) at 70-80 °C for 4 h. After cooling to room
30 temperature (20-30°C), water was removed under vacuum and the residue was extracted in

ethanol. Recrystallization from ethanol furnished sodium sulfinate **26** (1.34 g, 67%) as a white solid.

The other sodium sulfonates **20**, **22**, **24**, **28**, **30**, **32** and **34** were prepared similarly from their corresponding sulfonyl chlorides using known methods.

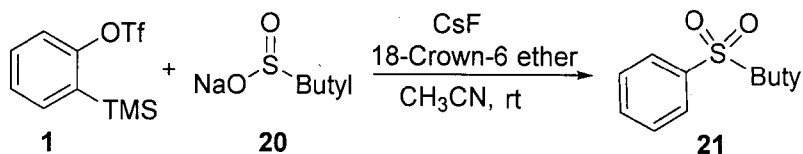
GENERAL EXPERIMENTAL PROCEDURE FOR THE SYNTHESIS OF SULFONES



To a round-bottom flask containing TBAF (1.10 equiv) and sodium sulfinate (1.0 equiv) was added *o*-silylaryl triflate (1.00 equiv) in acetonitrile (1 mL) at room temperature (20-30°C), under Argon atmosphere. The reaction mixture was stirred at room temperature (20-30°C) and the progress was monitored by TLC. After completion of the reaction, acetonitrile was removed on rotary evaporator and the crude product was purified by flash silica gel column using a gradient of ethyl acetate-petroleum ether to afford the corresponding diaryl/aryl-alkyl/aryl-heteroaryl sulfones in good to excellent yields.

Example 2

Experimental Procedure using CsF: (Butylsulfonyl)benzene (**21**)

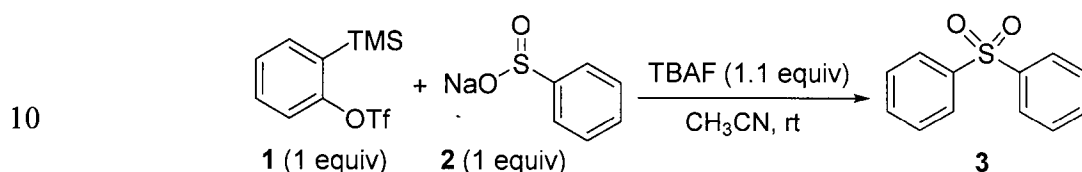


To a round-bottom flask containing CsF (101 mg, 670 mmol) butyl sulfinic acid sodium salt (36.2 mg, 251 mmol) and 18-Crown-6-ether (4.4 mg, 16.7 mmol) was added *o*-silyl aryl triflate (50 mg, 167.5 mmol) in acetonitrile (2 mL) at room temperature (25°C), under Argon atmosphere. The reaction mixture was stirred at room temperature (25°C) and the progress was monitored by TLC. After completion of the reaction (3 h), acetonitrile was

removed on rotary evaporator and the crude product was purified by flash silica gel column using a gradient of ethyl acetate-petroleum ether (1:4) to afford the sulfone **21** (29 mg, 86%) as a yellow thick oil.

5 Example 3

Large Scale Experiment (sulfone **3**, table 2, entry 1)



15 To a round-bottom flask containing TBAF (581 mg, 1.84 mol, 1.10 equiv) and aryl sulfinic acid sodium salt (275 mg, 1.67 mol, 1.0 equiv) was added *o*-silyl aryl triflate (500 mg, 1.67 mol, 1.0 equiv) in acetonitrile (10 mL) at room temperature (30°C), under Argon atmosphere. The reaction mixture was stirred at room temperature (30°C) and the progress was monitored by TLC. After completion of the reaction (3 h), acetonitrile was removed on rotary evaporator and the crude product was purified by flash silica gel column using a gradient of ethyl acetate-petroleum ether (3:17) to afford the sulfone **3** (260 mg, 95%) as a white solid.

20

CHARACTERIZATION DATA OF COMPOUNDS

All reactions were performed on 50 mg scale of *o*-silyl aryl triflates. Representative large scale experiment was performed on 500 mg scale of *o*-silyl aryl triflates.

25

EXAMPLE 4

1-Phenyl (sulfonyl) benzene (**3**)

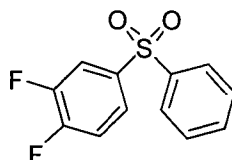


Reaction Time: 3 h; R_f: 0.3 (1:4 EtOAc: Pet Ether); White solid; 34 mg, 94%; mp 120 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.88 (d, *J* = 8.0 Hz, 4H), 7.50 (t, *J* = 8.0 Hz, 2H), 7.44 (t, *J*

= 8.0 Hz, 4H); ^{13}C NMR (125 MHz, CDCl_3) δ 141.6, 133.2, 129.3, 127.7; HRMS-ESI (m/z) calcd $[\text{C}_{12}\text{H}_{10}\text{O}_2\text{S} + \text{H}]^+$: 219.0474, found : 219.0474.

EXAMPLE 5

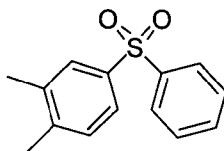
1,2-Difluoro-4-(phenylsulfonyl)benzene (5)



Reaction Time: 6 h; Rf: 0.3 (1:4 EtOAc:Pet Ether); White solid; 28.9 mg, 76%; mp 179-181 °C ^1H NMR (400 MHz, CDCl_3) δ 7.86 (d, J = 8.2 Hz, 2H), 7.75-7.65 (m, 2H), 7.54 (t, J = 8.0 Hz, 1H), 7.47 (t, J = 8.0 Hz, 2H), 7.18-7.28 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 153.6 (dd, J = 257.8, 12.4 Hz), 150.3 (dd, J = 255.9, 17.2 Hz), 140.8, 138.5 (t, J = 7.6 Hz), 133.7, 129.5, 127.7, 124.8 (q, J = 3.84 Hz), 118.4 (d, J = 18.2 Hz), 111.7 (d, J = 18.2 Hz); HRMS-ESI (m/z) calcd $[\text{C}_{12}\text{H}_8\text{O}_2\text{SF}_2\text{Na}]^+$: 277.0105 found: 277.0100

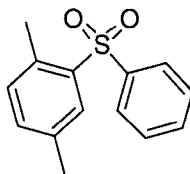
EXAMPLE 6

1,2-Dimethyl-4-(phenylsulfonyl)benzene (7)



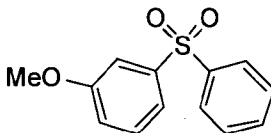
Reaction Time: 4 h; Rf: 0.3 (1:4 EtOAc:Pet Ether); White solid; 34.7 mg, 92%; mp 114-116 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.86 (d, J = 7.3 Hz, 2H), 7.63-7.58 (m, 2H), 7.50-7.38 (m, 3H), 7.17 (s, 1H), 2.23 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 142.9, 142.1, 138.7, 138.1, 132.9, 130.4, 129.2, 128.4, 127.5, 125.2, 20.0, 19.8; HRMS-ESI (m/z) calcd $[\text{C}_{14}\text{H}_{14}\text{O}_2\text{S} + \text{H}]^+$: 247.0787, found : 247.0786.

Example 7

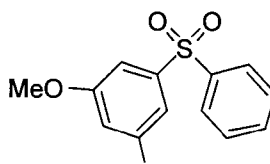
1,4-Dimethyl-2-(phenylsulfonyl)benzene (9)

Reaction Time: 8 h; Rf: 0.3 (1:4 EtOAc:Pet Ether); White solid; 20.7 mg, 55%; mp 111-113 °C;

¹H NMR (500 MHz, CDCl₃) δ 7.98 (s, 1H), 7.79 (d, *J* = 7.6 Hz, 2H), 7.52-7.38 (m, 3H), 7.21 (d, *J* = 7.6 Hz, 1H), 7.04 (d, *J* = 7.6 Hz, 1H), 2.35 (s, 3H), 2.30 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 141.5, 138.4, 136.5, 134.8, 134.3, 132.9, 132.6, 129.7, 128.9, 127.6, 20.9, 19.7; HRMS-ESI (*m/z*) calcd [C₁₄H₁₄O₂S + H]⁺: 247.0787, found: 247.0786.

Example 8**1-Methoxy-3-(phenylsulfonyl)benzene (11)**

Reaction Time: 4 h; Rf: 0.3 (1:4 EtOAc:Pet Ether); White solid; 24.2 mg, 64%; mp 82 °C; ¹H NMR (500 MHz, CDCl₃) δ 7.88 (d, *J* = 7.6 Hz, 2H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.46-7.40 (m, 3H), 7.38 (t, *J* = 2.2 Hz, 1H), 7.34 (t, *J* = 8.0 Hz, 1H), 7.01 (dd, *J* = 2.2, 2.2 Hz, 1H), 3.77 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 160.0, 142.7, 141.5, 133.2, 130.4, 129.5, 127.6, 119.9, 119.5, 112.2, 55.7; HRMS-ESI (*m/z*) calcd [C₁₃H₁₂O₃S + H]⁺: 249.0580, found: 249.0579.

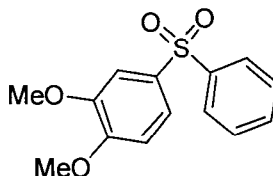
Example 9**1,3-Dimethoxy-5-(phenylsulfonyl)benzene (13)**

Reaction Time: 4 h; Rf: 0.2 (1:4 EtOAc:Pet Ether); Yellow solid; 33.4 mg, 86%; mp 92-94 °C; ¹H NMR (500 MHz, CDCl₃) δ 7.87 (d, *J* = 7.3 Hz, 2H), 7.49 (t, *J* = 7.6 Hz, 1H),

7.44 (t, $J = 7.9$ Hz, 2H), 6.99 (d, $J = 2.8$ Hz, 2H), 6.52 (t, $J = 2.5$ Hz, 1H), 3.74 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 161.2, 143.3, 141.5, 133.2, 129.2, 127.6, 105.5, 105.4, 55.80; HRMS-ESI (m/z) calcd $[\text{C}_{14}\text{H}_{14}\text{O}_4\text{S} + \text{H}]^+$: 279.0686, found : 279.0682.

5 Example 10

1,2-Dimethoxy-4-(phenylsulfonyl)benzene (15)



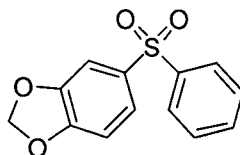
10

Reaction Time: 3 h; Rf: 0.4 (3:7 EtOAc:Pet Ether); Red solid; 23.3 mg, 60%; mp 118-119 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.85 (d, $J = 7.3$ Hz, 2H), 7.54-7.40 (m, 4H), 7.32 (s, 1H), 6.86 (d, $J = 8.5$ Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 153.0, 149.3, 142.2, 133.0, 132.9, 129.2, 127.3, 121.9, 110.8, 109.9, 56.3, 56.2; ESI-Mass ($\text{M} + \text{Na}$) 301. HRMS-ESI (m/z) calcd $[\text{C}_{14}\text{H}_{14}\text{O}_4\text{S} + \text{H}]^+$: 279.0686, found : 279.0678.

15

Example 11

20 5-(Phenylsulfonyl)benzo[d][1,3]dioxole (17)

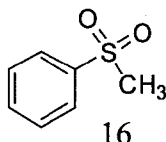


25 Reaction Time: 6 h; Rf: 0.2 (1:4 EtOAc:Pet Ether); White solid; 37 mg, 96%; mp 102-104 °C; ^1H NMR (500 MHz, CDCl_3) δ 7.84 (d, $J = 7.3$ Hz, 2H), 7.51-7.40 (m, 4H), 7.24 (d, $J = 1.8$ Hz, 1H), 6.80 (d, $J = 8.2$ Hz, 1H), 5.97 (s, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 151.9, 148.4, 142.0, 134.9, 133.0, 129.2, 127.4, 123.6, 108.5, 107.8, 102.4; HRMS-ESI (m/z) calcd $[\text{C}_{13}\text{H}_{10}\text{O}_4\text{S} + \text{H}]^+$: 263.0373, found: 263.0371.

30

Example 12

(Methylsulfonyl)benzene (19)

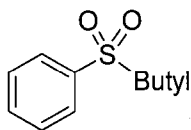


16

Reaction Time: 4 h; Rf: 0.2 (1:4 EtOAc:Pet Ether); Yellow solid; 19.6 mg, 75%; mp 256-258 °C; ^1H NMR (500 MHz, CDCl_3) δ 7.89 (d, J = 7.6 Hz, 2H), 7.60 (t, J = 7.6 Hz, 1H), 7.52 (t, J = 7.6 Hz, 2H), 2.99 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 140.6, 133.7, 129.4, 127.3, 44.5; HRMS-ESI (m/z) calcd $[\text{C}_7\text{H}_8\text{O}_2\text{S} + \text{H}]^+$: 157.0318 found: 157.0319.

Example 13

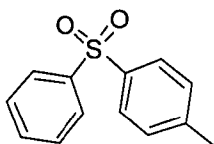
(Butylsulfonyl)benzene (21)



Reaction Time: 3 h; Rf: 0.5 (1:4 EtOAc:Pet Ether); thick oil; 28.9 mg, 86%; ^1H NMR (400 MHz, CDCl_3) δ 7.84 (d, J = 7.5 Hz, 2H), 7.59 (t, J = 7.5 Hz, 1H), 7.50 (t, J = 7.8 Hz, 2H), 3.02 (t, J = 8.0 Hz, 2H), 1.67-1.58 (m, 2H), 1.38-1.27 (m, 2H), 0.82 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 139.2, 133.6, 129.2, 128.1, 56.1, 24.6, 21.5, 13.5; HRMS-ESI (m/z) calcd $[\text{C}_{10}\text{H}_{14}\text{O}_2\text{S} + \text{H}]^+$: 199.0787 found: 199.0788.

Example 14

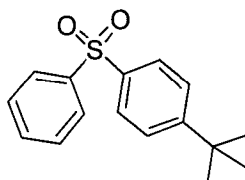
1-Methyl-4-(phenylsulfonyl)benzene (23)



Reaction Time: 3 h; Rf: 0.5 (1:4EtOAc:Pet Ether); White solid; 26.5 mg, 68%; mp 198-200 °C; ^1H NMR (500 MHz, CDCl_3) δ 7.86 (d, J = 7.3 Hz, 2H), 7.47 (d, J = 7.9 Hz, 2H), 7.47 (t, J = 7.3 Hz, 1H), 7.42 (t, J = 7.6 Hz, 2H), 7.23 (d, J = 7.9 Hz, 2H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 144.1, 141.9, 138.6, 133.0, 129.9, 129.2, 127.7, 127.5, 21.5; HRMS-ESI (m/z) calcd $[\text{C}_{13}\text{H}_{12}\text{O}_2\text{S} + \text{H}]^+$: 233.0631 found: 233.0630.

Example 15

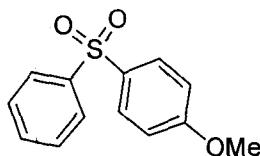
1-(Tert-butyl)-4-(phenylsulfonyl)benzene (25)



Reaction Time: 4 h; Rf: 0.5 (1:4 EtOAc:Pet Ether); White solid; 38.7 mg, 85%; mp 129-130 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.88 (d, J = 7.0 Hz, 2H), 7.79 (d, J = 8.8 Hz, 2H), 7.52-7.40 (m, 5H), 1.24 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 157.1, 141.9, 138.5, 133.0, 129.2, 127.6, 127.5, 126.3, 35.2, 31.0; HRMS-ESI (m/z) calcd $[\text{C}_{16}\text{H}_{18}\text{O}_2\text{S} + \text{H}]^+$: 275.1100
5 found: 275.1099.

Example 16

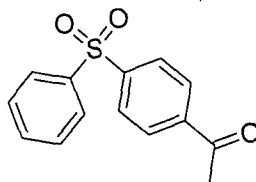
1-Methoxy-4-(phenylsulfonyl)benzene (27)



Reaction Time: 1 h; Rf: 0.2 (1:4 EtOAc:Pet Ether); White solid; 25.4 mg, 61%; mp 90-91 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.87-7.78 (m, 4H), 7.50-7.38 (m, 3H), 6.92-6.87 (m, 2H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 163.3, 142.3, 133.1, 132.8, 129.9, 129.2, 127.3, 114.5, 55.6; HRMS-ESI (m/z) calcd $[\text{C}_{13}\text{H}_{12}\text{O}_3\text{S} + \text{H}]^+$: 249.0580 found: 249.0579.

Example 17

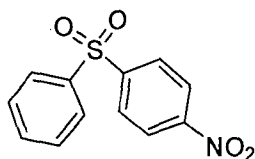
1-(4-(phenylsulfonyl)phenyl)ethan-1-one (29)



Reaction Time: 4 h; Rf: 0.2 (1:4 EtOAc:Pet Ether); Yellow solid; 22.5 mg, 54%; mp 132-134 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.98 (s, 4H), 7.89 (d, J = 8.5 Hz, 2H), 7.53 (t, J = 8.5 Hz, 1H), 7.46 (t, J = 8.5 Hz, 2H), 2.55 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 196.7, 145.4, 140.7, 140.3, 133.6, 129.5, 129.0, 128.0, 127.8, 26.9; ESI-Mass ($M + 1$) 261. HRMS-ESI (m/z) calcd $[\text{C}_{14}\text{H}_{12}\text{O}_3\text{S} + \text{H}]^+$: 261.0580, found : 261.0573.

Example 18

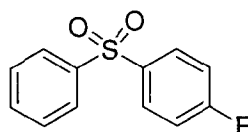
1-Nitro-4-(phenylsulfonyl)benzene (31)



Reaction Time: 3 h; Rf: 0.5 (1:4 EtOAc:Pet Ether); White solid; 32.6 mg, 74%; mp 144-145 °C ^1H NMR (400 MHz, CDCl_3) δ 8.28 (d, $J = 9$ Hz, 2H), 8.07 (d, $J = 9$ Hz, 2H), 7.90 (d, $J = 7.3$ Hz, 2H), 7.57 (t, $J = 7.3$ Hz, 1H), 7.49 (t, $J = 7.3$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 150.3, 147.3, 140.0, 134.1, 129.7, 129.0, 128.0, 124.5; ESI-Mass ($\text{M} + \text{Na}$) 209;

Example 19

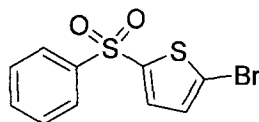
1-Fluoro-4-(phenylsulfonyl)benzene (33)



Reaction Time: 3 h; Rf: 0.5 (1:4 EtOAc:Pet Ether); White solid; 34 mg, 86%; mp 113-115 °C; ^1H NMR (500 MHz, CDCl_3) δ 7.93-7.83, (m, 4H), 7.55-7.41 (m, 3H), 7.22-7.08 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 165.4 (d, $J = 255.8$ Hz), 141.5, 137.7, 133.3, 130.5 (d, $J = 9.2$ Hz), 129.4, 127.6, 116.6 (d, $J = 32.1$ Hz); HRMS-ESI (m/z) calcd $[\text{C}_{12}\text{H}_9\text{O}_2\text{SF} + \text{H}]^+$: 237.0380 found: 237.0379.

Example 20

2-bromo-5-(phenylsulfonyl)thiophene (35)



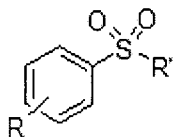
Reaction Time: 3 h; Rf: 0.5 (1:4 EtOAc:Pet Ether); White solid; 37.09 mg, 73%; mp 105-107 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.90 (d, $J = 6.8$ Hz, 2H), 7.54 (t, $J = 7.7$ Hz, 1H), 7.46 (t, $J = 7.5$ Hz, 2H), 7.39 (d, $J = 4.1$ Hz, 1H), 6.99 (d, $J = 4.1$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 143.8, 141.5, 133.6, 133.4, 130.8, 129.5, 127.3, 122.1; HRMS-ESI (m/z) calcd $\text{C}_{10}\text{H}_7\text{O}_2\text{S}_2^{81}\text{Br} + \text{Na}]^+$: 326.8943, found: 326.8936.

ADVANTAGES OF THE INVENTION

The process of the invention works with very simple reagents at very mild reaction condition which can be very useful industrially. Also the process can be applied for large scale synthesis.

CLAIMS

1. A room temperature single step process for synthesis of compound of Formula I



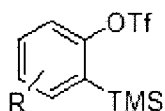
Formula I

wherein, R is selected from H, alkyl (C₁-C₆), aryl, heteroaryl, O-, S-, N-, P-alkyl/unsubstituted and substituted aryl;

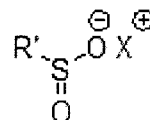
R' is selected from alkyl (C₁-C₆), aryl, heteroaryl, O-, S-, N-, P-alkyl/unsubstituted and substituted aryl;

comprising the steps of:

- a. adding benzyne precursor of Formula II to a stirred solution of fluoride ion source and compound of Formula III in the ratio ranging between 1:1 to 1:1.1 in anhydrous acetonitrile to obtain a reaction mixture;



Formula II



Formula III

wherein, R is selected from H, alkyl, aryl, heteroaryl, O-, S-, N-, P-alkyl/ unsubstituted and substituted aryl;

R' is selected from, alkyl, aryl, heteroaryl, O-, S-, N-, P- alkyl/ unsubstituted and substituted aryl;

X is selected from H, Li, Na, K, Cs;

b. stirring the reaction mixture of step (a) for the period in the range of 1 to 8 hours followed by purification to obtain the desired product I.

2. The process according to claim 1, wherein the fluoride ion source is selected from the group consisting of TBAF (Tetra-n-butylammonium fluoride), CsF (Cesium fluoride), NaF (Sodium Fluoride), RbF (Rubidium fluoride) or KF (Potassium fluoride).

3. The process according to claim 1, wherein the fluoride ion source is selected from TBAF or CsF.

4. The process according to claim 1, wherein the compound of formula I is selected from the group consisting of:

1-Phenyl (sulfonyl) benzene (3);

1,2-Difluoro-4-(phenylsulfonyl)benzene (5);

1,2-Dimethyl-4-(phenylsulfonyl)benzene (7);

1,4-Dimethyl-2-(phenylsulfonyl)benzene (9);

1-Methoxy-3-(phenylsulfonyl)benzene (11);

1,3-Dimethoxy-5-(phenylsulfonyl)benzene (13);

1,2-Dimethoxy-4-(phenylsulfonyl)benzene (15);

5-(Phenylsulfonyl)benzo[d][1,3]dioxole (17);

(Methylsulfonyl)benzene (19);

(Butylsulfonyl)benzene (21);

1-Methyl-4-(phenylsulfonyl)benzene (23);

1-(Tert-butyl)-4-(phenylsulfonyl)benzene (25);

1-Methoxy-4-(phenylsulfonyl)benzene (27);

1-(4-(phenylsulfonyl)phenyl)ethan-1-one (29);

1-Nitro-4-(phenylsulfonyl)benzene (31);

1-Fluoro-4-(phenylsulfonyl)benzene (33);

2-bromo-5-(phenylsulfonyl)thiophene (35).

5. The process according to claim 1, wherein the compound of formula II is selected from the group consisting of:

2-(trimethylsilyl)phenyl trifluoromethane-sulfonate (1)
4,5-difluoro-2-(trimethylsilyl)phenyl trifluoromethane-sulfonate (4)
4,5-dimethyl-2-(trimethylsilyl)phenyl trifluoromethane-sulfonate (6)
5 3,6-dimethyl-2-(trimethylsilyl)phenyl trifluoromethane-sulfonate (8)
3-methoxy-2-(trimethylsilyl)phenyl trifluoromethane-sulfonate (10)
3,5-dimethoxy-2-(trimethylsilyl)phenyl trifluoromethane-sulfonate (12)
4,5-dimethoxy-2-(trimethylsilyl)phenyl trifluoromethane-sulfonate (14)
6-(trimethylsilyl)benzo[d][1,3]dioxol-5-yl trifluoromethane-sulfonate (16)

10

6. The process according to claim 1, wherein the compound of formula III is selected from the group consisting of:

sodium benzenesulfinate (2)
15 sodium methanesulfinate (18)
sodium butane-1-sulfinate (20)
sodium 4-methylbenzenesulfinate (22)
sodium 4-(tert-butyl)benzenesulfinate (24)
sodium 4-methoxybenzenesulfinate (26)
20 sodium 4-acetylbenzenesulfinate (28)
sodium 4-nitrobenzenesulfinate (30)
sodium 4-fluorobenzenesulfinate (32)
Sodium 5-bromothiophene-2-sulfinate (34).

20

- 25 7. The process according to claim 1, wherein the yield of the compound of formula I is in the range of 45-96%.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2014/000772

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07C315/04 C07C317/14 C07C317/22 C07F7/08 C07C313/02
ADD.

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 C07F

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)

EP0-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SANDRO CACCHI ET AL: "Unsymmetrical diaryl sulfones and arylvinylsulfones through Palladium-catalyzed coupling of aryl and vinyl halides or triflates with sulfinic acid salts", JOURNAL OF ORGANIC CHEMISTRY., vol. 69, 2004, pages 5608-5614, XP002737436, USAMERICAN CHEMICAL SOCIETY, WASHINGTON, DC. ISSN: 0022-3263 Scheme 4, entries 4,20,21,28 on Table 4; table 4 ----- -/--	1-7



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

"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

"T" 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

18 March 2015

Date of mailing of the international search report

07/04/2015

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Voyiazoglou, D

INTERNATIONAL SEARCH REPORT

International application No

PCT/IN2014/000772

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CHUANFA NI ET AL: "Nucleophilic fluoroalkylation of alpha,beta-enones,arynes and activated alkynes with fluorinated sulfones: probing the hard/soft nature of fluorinated carbanions", JOURNAL OF ORGANIC CHEMISTRY., vol. 73, 2008, pages 5699-5713, XP002737437, USAMERICAN CHEMICAL SOCIETY, WASHINGTON, DC. ISSN: 0022-3263 Scheme 5; page 5705, last paragraph; table 8	1-7
A	EITO YOSHIOKA ET AL: "Insertion of arynes into the carbonooxygen double bond of amides and its application into the sequential reactions", TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 68, no. 1, 20 October 2011 (2011-10-20), pages 179-189, XP028125992, ISSN: 0040-4020, DOI: 10.1016/J.TET.2011.10.072 [retrieved on 2011-10-28] compounds 18,25,Scheme 1; page 183, left column, second paragraph; page 179, left column, first paragraph; figure 1; table 5	1-7
T	VIRAT G. PANDYA ET AL: "Transition-Metal free C-S bond formation: a facile access to aryl sulfones from sodium sulfinates via arynes", ORGANIC LETTERS, vol. 16, 2014, pages 3836-3838, XP002737438, USACS, WASHINGTON, DC. ISSN: 1523-7060 abstract	1-7