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7. Recent Updates on Methyl Fluorosulfonyl Difluoroacetate Mediated Synthesis of Trifluoromethylated Molecules

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Abstract:

Organofluorine compounds have been widely used in pharmaceutical and agrochemical field. Triflurorомethylated compounds particularly show extensive applications in field of life sciences and material sciences. The trifluoromethyl group is used in biologically important molecules due to its enhanced anti-oxidant ability, improved metabolic stability and increased lipophilicity of the compound. MFSI, which was first reported by Chen and Wu in 1989 is used as an efficient, safe, resistant to moisture absorption and economical reagent for trifluoromethylation in synthesizing variety of trifluoromethyl containing heterocycles having great significance in drugs and many bioactive molecules. Contrary to its widespread applications, this reagent has not been exploited much and thus a comprehensive review of MFSI mediated trifluoromethylations is reported here, which we believe will provide further exposure to the chemists about this underutilized reagent.

Keywords:

7.1 Introduction:

In current years, a huge variety of applications[1-5] have been steadily developed in the sphere of organofluorine chemistry. Amongst the fluorinated compounds, trifluoromethyl-substituted molecules have created significant interest. The trifluoromethyl group is most attractive moiety and mostly used in pharmaceutical[6-8]and agrochemical industries.[9-13]

There are many CF_3 containing drugs available in market [14-21] (Figure 7.1). It is used in biological applications because of its high electron withdrawing ability, increased anti-oxidant ability, enhanced metabolic stability and increased lipophilicity of the target molecule.[22-25] The trifluoromethyl group can promote the drug efficacy by enhancing electrostatic interactions with targets, elevate cellular permeability and amplify the power towards oxidative metabolism of drug.[5,26,27]

Trifluoromethyl group is also widely used in dye industries in which trifluoromethylation of chromophore prevents from fading when exposed to light.[28,29] Trifluoromethylated polymers have upgraded chemical and thermal stability, better solubility and improved mechanical properties.[30] It has applications in developing batteries and cells.[31-33]

Ritter et al[34] proposed that if more complex trifluoromethylated compound is needed it is easier to start with simple molecule containing trifluoromethyl moiety and then build structure around it. Nagib et al[35] proposed the direct trifluoromethylation of arenes and heteroarenes by C-H activation through photo redox catalysis.

There are various reagents, which are used for trifluoromethylation. Rupert−Prakash reagent, CF_3SiMe_3 (trifluoromethyl) trimethylsilane is used for trifluoromethylation of heteroarenes and highly electron deficient arenes.[36] For trifluoromethylation of arenes and heteroarenes, trifluoromethanesulfonyl chloride (CF_3SO_2Cl) is also used[35].

Moreover, $PhSOCF_3$ and $PhSO_2CF_3$ are used as a source of trifluoromethyl anions.[37-39] Alkynyl triflones[40,41], Togni's reagent[42] and many more reagents (Sulfides[43,44], Sulfoximines[45], Sulfonium Salts[46], Sulfinate Salts, Sulfonyl Halides[47-49]) were evolved for the trifluoromethylation in different substrates.[50]

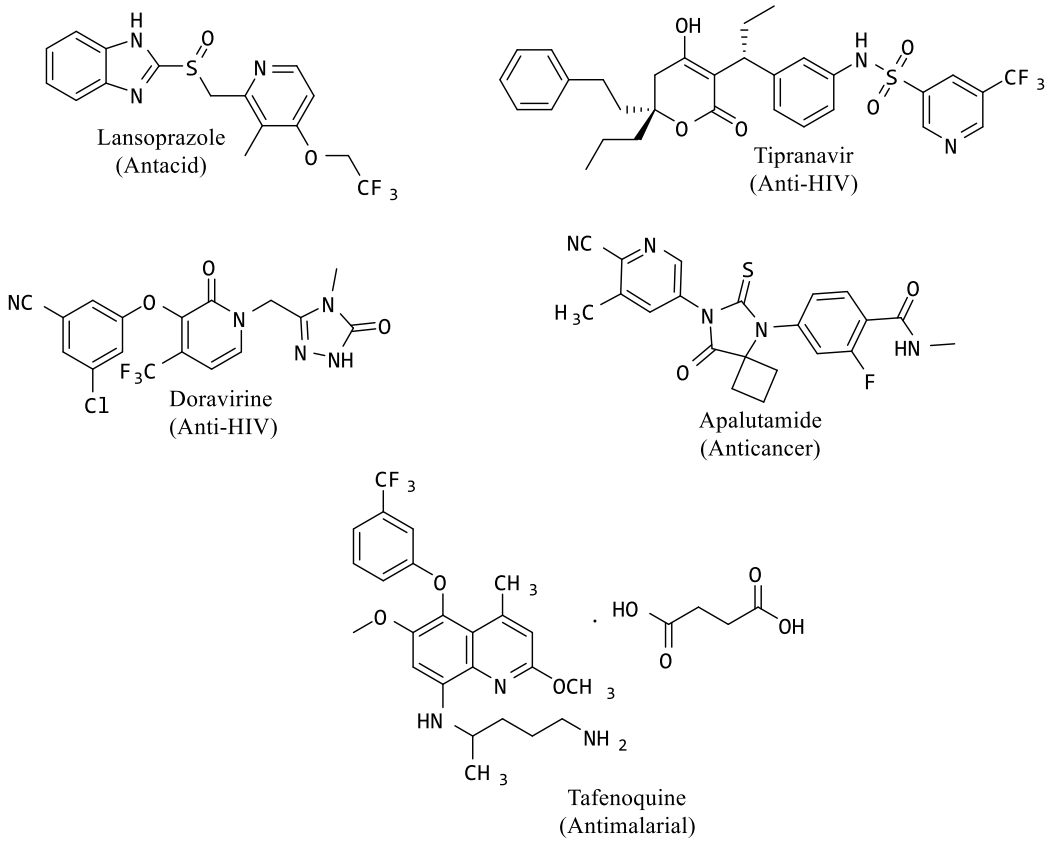


Figure 7.1: CF_3 Containing Drugs

In this chapter, we particularly emphasize on economical and widely used methyl fluorosulfonyldifluoroacetate ($FSO_2CF_2CO_2Me$, MFSDA or MFSI), reagent. We have focused here on summarizing the literature reports involving the synthetic transformations brought about by MFSI in the last one decade.

7.2 Discovery of trifluoromethylating reagent: Methyl fluorosulfonyldifluoroacetate (MFSI):

Methyl fluorosulfonyldifluoroacetate ($FSO_2CF_2CO_2Me$, MFSI) reagent also known as Chen's reagent and was first reported by Chen and Wu in 1989[51] as a trifluoromethylating reagent. It has CAS No. 680-15-9 and b.p. 116–118°C.

It is comparatively economical, safe and convenient to use and resistant to moisture absorption.[52] A number of methods have been developed for the trifluoromethylation of different substrates.[53-56] MFSI is used for the synthesis of a wide variety of trifluoromethyl containing heterocycles that is of greater significance in synthesizing drugs and making many bioactive molecules. MFSI is commercially to be held and purchased from the chemical industries but it can also be prepared within the laboratories by using diverse techniques. For example, MFSI can be synthesised *via* reacting 3,3,4,4-tetrafluoro[1,2]oxathiethane-2,2-dioxide with sodium methoxide[57], in two steps from difluoro(fluorosulfonyl)acetic acid[58] or by the addition of methanol to trimethylsilyl fluorosulfonyldifluoroacetate.[59] Finally, the reaction of tetrafluoroethylene with sulfur trioxide gives a useful cyclic compound tetrafluoroethylene β-sulfone.[60,61] Successive reaction with methanol affords MFSI in 85% yield.[62]

MFSI displays the nucleophilic trifluoromethylation reaction and used for trifluoromethylation of aryl halides, alkyl halides and alkenyl halides for diverse copper mediated reactions. Chen and Wu showed the order of reactivity of halide to be RI>RBr>RCl where the bromo derivatives being more useful and the chloro derivatives is quite slow. Presence of CuI is crucial for the success of reaction. KI can also be used as an alternative of CuI.[9]

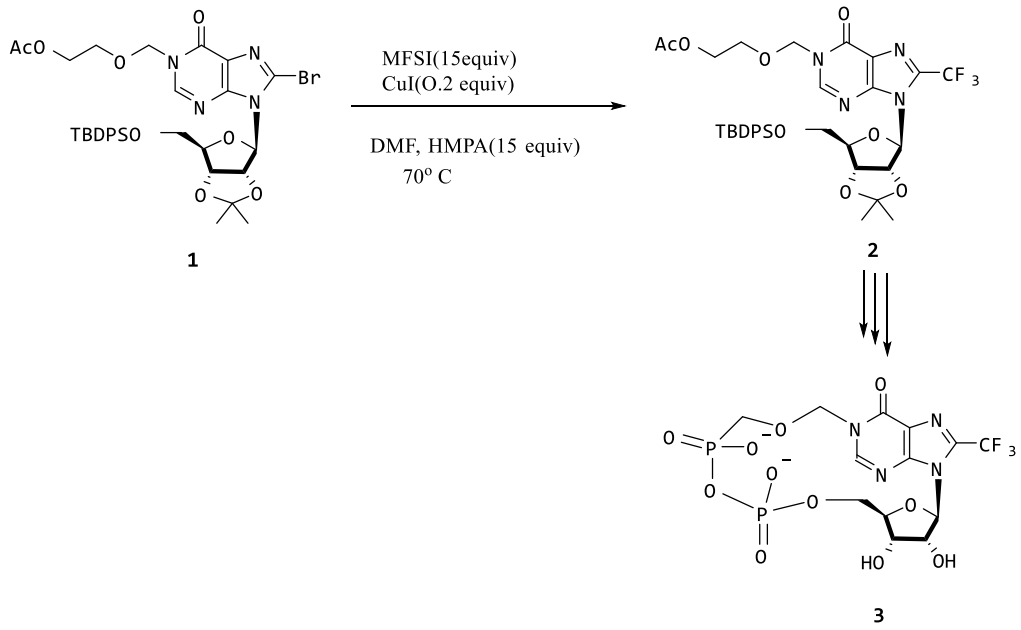
Scope of Methyl Fluorosulfonyldifluoroacetate in Trifluoromethylation reactions

MFSI has been reported in various organic transformations from last so many years and a summary of those reports is being summarised here starting from the year 2010. The triazolylpyridine system are not found in nature in free form but its trifluoromethylated derivatives shows many biological properties like insecticides, antibacterial activity[63], anti-proliferative activity against tumour[64], more cell permeability[65] and many more biological activity[66-70]. Dong et al[71] reported the synthesis of 8- CF_3-cIDPRE **3** (N1 - [(5"-O-Phosphorylethoxy) methyl] -5'-O-phosphoryl -8 - tri-fluoromethylinosine 5", 5"-Cyclic pyrophosphates.

8-CF_3-cIDPRE is agonist and mimics the cADPR (cyclic adenosine 5'-diphosphoribose). 8-CF_3-cIDPRE penetrate the plasma membrane and releases Ca^{2+} which is required in variety of cellular process. Fluorine has strong electron withdrawing property and ability to form hydrogen bonding, it shows metabolic stability and membrane permeability. In this, there is introduction of trifluoromethyl group at 8- position of purine nucleoside, which is important intermediate for synthesis of 8- CF_3-cIDPRE **3**.

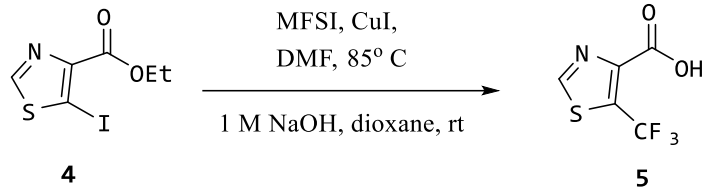
Huang et al[72] also reported the synthesis of trifluoromethylated analogues of cADPR using MFSI. In this, MFSI is used for trifluoromethylation of bromo derivative *viz N*1-[(5``-

Acetoxyethoxy) methyl]-5`- O-TBDPS-2`,3`-O-isopropylidene-8-bromoinosine **1** in the presence of CuI in DMF, HMPA and reaction was stirred for 12hrs at 70° C to form *N*1-[(5``-Acetoxyethoxy) methyl]-5`-O-TBDPS-2`,3`-O-isopropylidene-8-trifluoromethyl inosine **2,** which is an important intermediate and further undergo reaction for synthesis of 8-CF_3-cIDPRE **3** (Scheme 7.1).



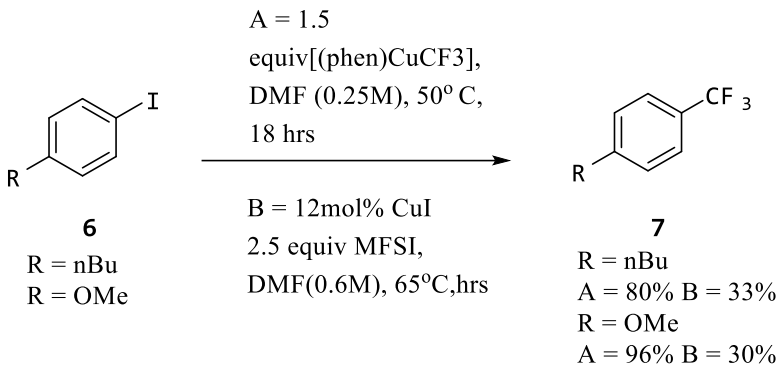
Scheme 7.1: Trifluoromethylation of cyclic adenosine diphosphate ribose.

Hodgetss and his coworker[73] reported that MFSI is used to introduce trifluoromethyl group in thiazole ring **4** to obtain trifluoromethylated product **5**, which is a bioactive molecule. (Scheme 7.2)



Scheme 7.2: Trifluoromethylation of thiazole ring

Boechat et al[74] reported the synthesis of trifluoromethylated derivatives of 1*H*-1,2,4-triazol-3-yl benzenesulfonamide to develop new antimalarial lead compounds with 50%-62% yield. Morimoto et al[75] reported the use of MFSI in copper iodide mediated reactions for the trifluoromethylation of aryl iodides **6** and bromides. The yields of trifluoromethylarene products **7**, which was determined by ^{19}F NMR analysis using 4-$CF_3OC_6H_4OMe$ as internal standard, were much higher (above 80%) under the reaction conditions with 1.5 equiv phen-ligated 1 than with catalytic CuI and 2.5 equiv. $FSO_2CF_2CO_2Me$. (Scheme 7.3).

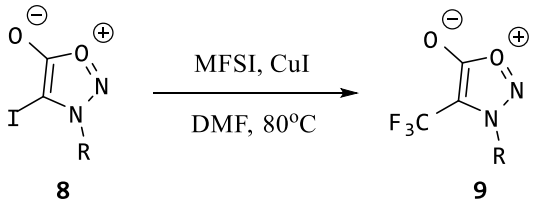


Schemes 7.3: Trifluoromethylation of aryl iodides

Foster et al[76] designed more efficient policy for trifluoromethylation of pyrazoles using MFSI. He reported the trifluoromethylation of 4-iodosyndones **8** to synthesize bioactive 5-trifluoromethylpyrazoles **9** with good yield in the presence of MFSI, CuI and DMF, which was further used as an intermediate to synthesize herbicide fluazolate.

He suggested that when the reaction was accomplished with 4-iodo-*N*-phenylsyndone, the yield of trifluoromethylated product is 79%. When electron-donating substituent like p-methoxyphenyl group is present, the obtained yield is similar (80%).

When the reaction was executed with electron- withdrawing like p-nitro phenyl group, the time taken for trifluoromethylation was increased with comparatively low yield (55%). Non-aromatic group on nitrogen were also accepted under same reaction conditions. (Scheme 7.4).



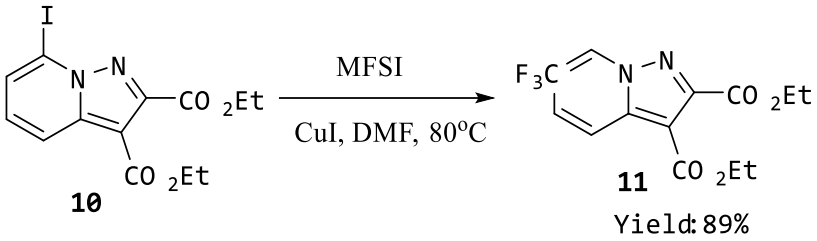
R= Ph

R= Me, Bn, Ph, 4-OMeC_6H_4, 4-$NO_2C_6H_4$

Scheme 7.4: Trifluoromethylation of 4-iodosyndones.

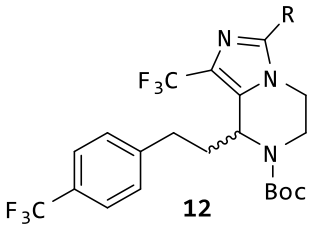
Chong and Bullock[77,79] synthesized 7-Trifluoromethylpyrazolo[1,5-*a*]-pyridinedicarboxylate **11** which is an important intermediate for a potential drug candidate.

MFSI reacted with iodide derivative of pyrazolo[1,5-*a*] pyridine dicarboxylates **10** in the presence of CuI in DMF at 80° C to give trifluoromethylated pyrazolopyridinecarboxylate **11** with 89% yield. (Scheme 7.5)



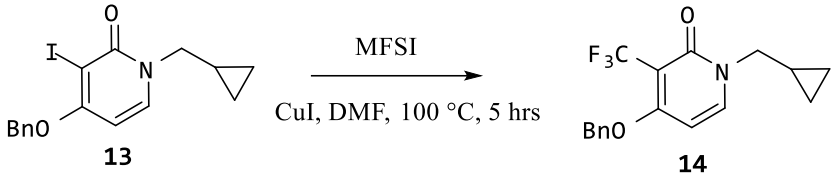
Scheme 7.5: Trifluoromethylation of iodo derivative of pyrazolopyridine dicarboxylates

Sifferlen[79] et al has been reported the incorporation of trifluoromethyl moiety using MFSI in synthesis of bioactive intermediate **12** which was further used in synthesis of 5,6,7,8-tetrahydroimidazo[1,5-*a*] pyrazines which is an orexin receptor antagonist.



Cid et al[80] discovered a novel bioactive derivative of phenylpiperidine substituted pyridones which act as an allosteric modulator of glutamate receptor.

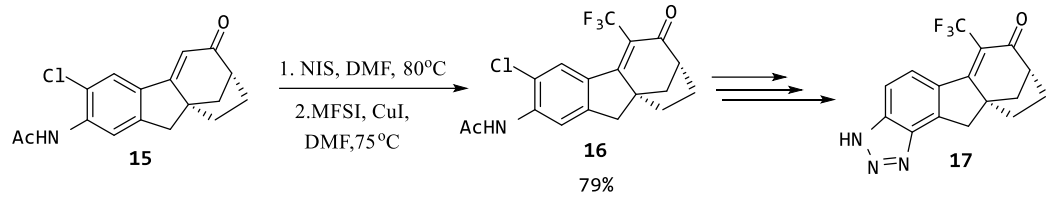
MFSI used for trifluoromethylation of 3-iodopyridones i.e., 4-Benzyloxy-1-cyclopropylmethyl-3-iodo-1*H*-pyridin-2-one **13** to synthesize 3-trifluoromethylpyridone i.e., 4-Benzylox-1-cyclopropylmethyl-3-trifluoromethyl-1*H*-pyridin-2-one **14** which is a key intermediate to form the bioactive molecules. (Scheme 6).



Scheme 6. Trifluoromethylation of 3-iodopyridones

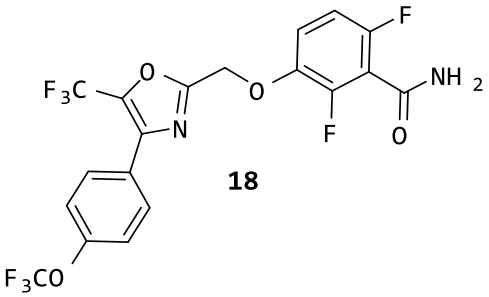
Madess et al[81] discovered derivatives of tetrahydrofluoroene which act as beta agonist for estrogen receptors used in therapy of postmenopausal women for treating the symptoms related with decreased oestrogen level.

Compound **15** undergo iodination followed by trifluoromethylation using MFSI, CuI in DMF to synthesize the compound **16** with high yield which on further transformation give desirable bioactive molecule i.e., tetrahydrofluoroene **17** (Schemes 7.7)

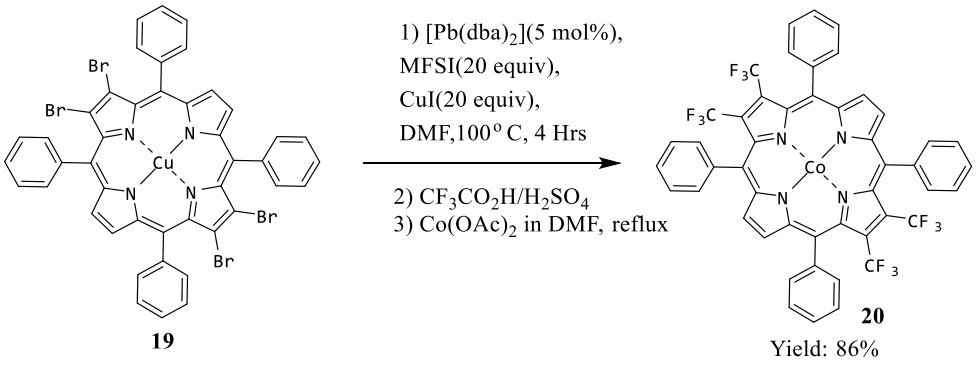


Schemes 7.7: Trifluoromethylation of intermediate in the synthesis of tetrahydrofluoroene

Stokes and coworkers[82] suggested the synthesis of bioactive intermediate **18** by the trifluoromethylation of its oxazolyl iodide intermediate using MFSI.



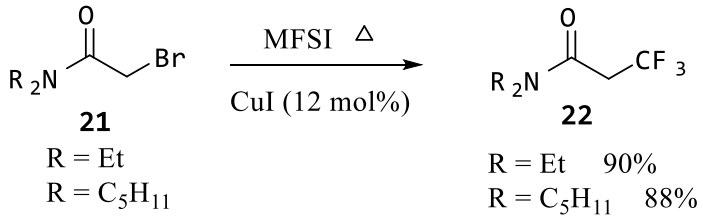
Zhao et al[83] reported that cobalt (II) β-tetrakis- (trifluoromethyl)-meso-tetraphenylporphyrin ($CoTPP(CF_3)_4$) exhibited excellent catalytic selectivity as well as conversion of benzylamines to imines through oxidative coupling with the product yield of 52–89% . He prepared $[Co\{TPP(CF_3)_4\}]$ **19** by the trifluoromethylation of $[Cu(TPPBr_4)]$ **20** in good yield using MFSI and subsequent insertion of Co^{II}. (Schemes 8)



Schemes 7.8: Synthesis of $[Co\{TPP(CF_3)_4\}]$

Zhang et al [84] reported the wide use of MFSI for various copper mediated reactions in a review published in 2014. MFSI was used for trifluoromethylation of aryl halides, alkyl halides and alkenyl halides and trifluoromethylthiolation of aryl halides. Alonso et al [85] reported in their review that MFSI was used as trifluoromethylation of various substrate in presence of CuI.

(a) trifluoromethylation of bromomethyl amide **21** to synthesize parallel trifluoromethyl derivatives **22** with excellent yield. (Schemes 7.9)

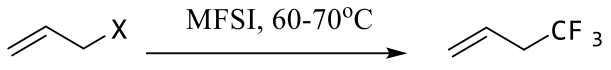


21
R = Et
R = C_5H_{11}

22
R = Et 90%
R = C_5H_{11} 88%

Schemes 7.9: Trifluoromethylation of bromomethyl amide

(b) trifluoromethylation of allyl halide **23** to give trifluoromethylated derivative **24** in high yield. (Schemes 7.10)

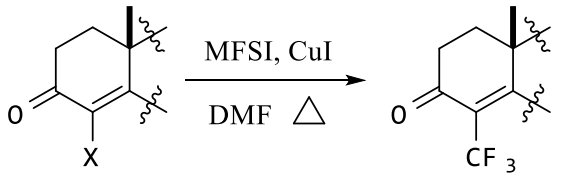


23
X = Br, I

24
Yield :68-70%

Schemes 7.10: Trifluoromethylation of allyl halide

(c) trifluoromethylation of iodo- steroidal molecule **25** to give trifluoromethyl steroids **26** with good yield. Trifluoromethylated flavonoid and antitumor trifluoromethylated flavonoid derivatives were also prepared using this methodology[86] (Schemes 11).



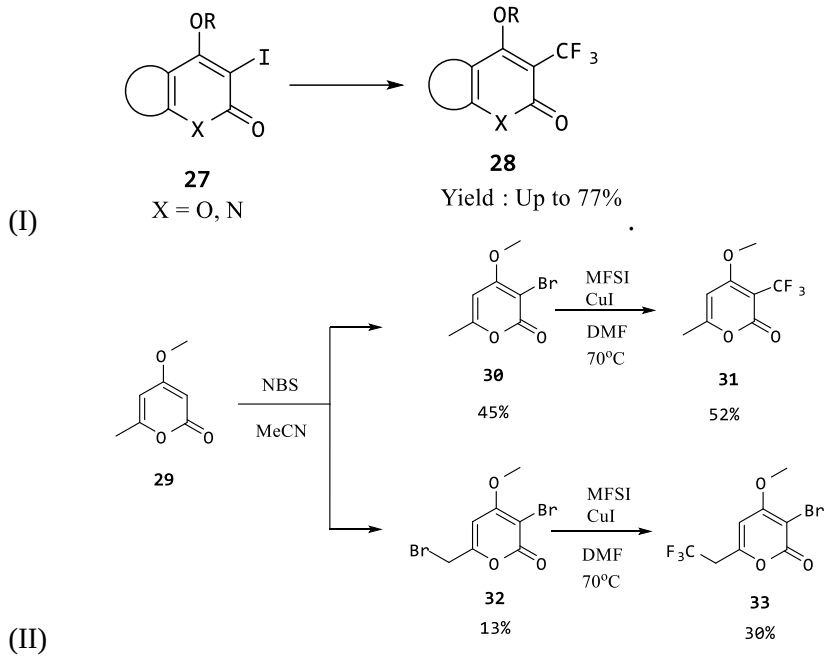
25
X = Br, I

26
Yield : 70-91%

Schemes 7.11: Trifluoromethylation of iodo-steroids

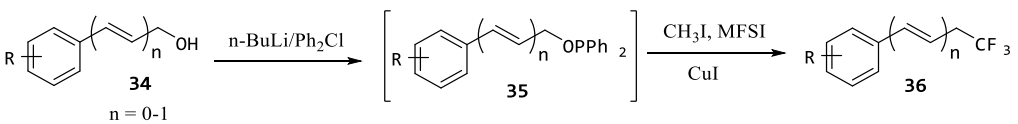
Clarke et al[87] developed the trifuoromethylated series of 4-alkoxy -2-pyrones, pyridones and quinolone using MFSI. These compounds have special biological properties.

They reported that when 1.2 equivalents of MFSI with 1.2 equivalents of copper iodide in DMF were used, good yields were obtained. As shown in scheme 7.12 (I), trifluoromethylation of iodinated starting material **27** gave **28**.

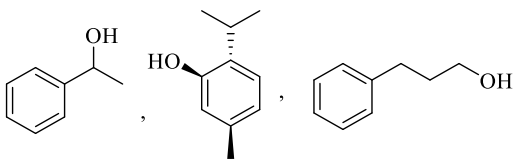


Scheme 7.12: Trifluoromethylation of pyrones, pyridones and quinolones

whereas mono **30** and di brominated **32** products were obtained by the bromination of 4-methoxy -6-methyl -2- pyrones **29**. The bromo derivative further underwent trifluoromethylation to yield product **31** and **33**. [Scheme 7.12(II)]. Li et al[88] suggested an efficient method for the trifluoromethylation of benzyl alcohol or allyl alcohol **34** to obtain various trifluoromethylated compound **36**. Derivatives of **35** were formed by reacting compound **34** (benzyl or allyl alcohol) with *n*-BuLi, Ph_2Cl. Intermediate **35** undergo trifluoromethylation in the presence of methyl iodide and MFSI in the presence of copper iodide when stirred at 80° for 15 hrs to obtain compound **36**. A variety of compounds were prepared from this method. (Scheme 7.13). Electronic density of alcohols affects the yield of reactions. Electron-donating groups such as methoxy and methyl group gave good yield whereas halide-substituted alcohols gave the moderate yield and low yields were observed with secondary alcohols because of steric hindrance.



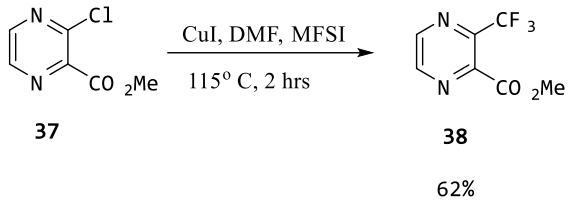
R= p-CF_3, -OMe, p-Me, p-Br, o-Cl, p-Cl,



n= 0,1

Scheme 7.13: Trifluoromethylation of benzyl alcohol or allyl alcohol

Oda et al[89] suggested the application of MFSI for the trifluoromethylation of methyl 3-chloropyrazine-2-carboxylate **37** in the presence of CuI in DMF, toluene and converted into methyl 3-(trifluoromethyl) pyrazine-2-carboxylate **38** which is a key intermediate to synthesize pyraziflumid and many other derivatives. Pyraziflumid shows excellent fungicidal activity partiparticularly against gray mold, Brown rust and powdery mildew. (Scheme 7.14). Sharma et al[90] described the successful nucleophilic trifluoromethylation of differently substituted α-iodinated oxoketene dithioacetals **39** *via* using MFSI in presence of CuI and DMF which provided α-trifuoromethylated oxoketene dithioacetals **40** with good to outstanding yield. Those synthons were further utilized for the synthesis of biologically important diversely substituted trifluoromethylated pyrazoles. (Scheme 7.15).

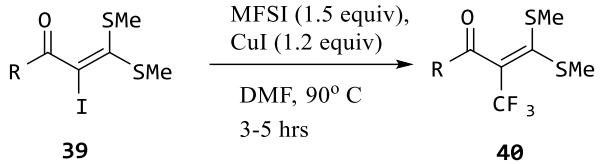


37 **38**

62%

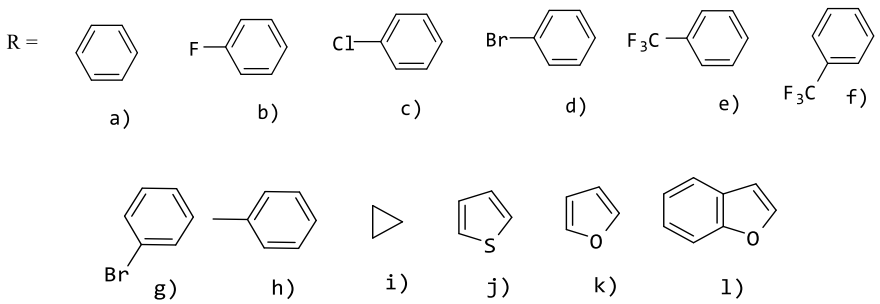
Scheme 7.14. Trifluoromethylation of methyl 3-chloropyrazine-2-carboxylate

Electron withdrawing group present at the *m*- and *p*- position in the α-iodinated oxoketene dithioacetals (b-g) contributed good yield of α-trifuoromethylated oxoketene dithioacetals. Though, electron releasing group in substrarte with *p*-CH_3 gave decent yield. On the other hand, with *o*-CH_3 in α-iodo oxoketene dithioacetals at -*o* or -*p* positions were confirmed unproductive due to incapability towards nucleophilic substitution. High yield was obtained with cyclopropyl substituted substrate. Heteroaromatic substituted α-iodo oxoketene dithioacetals (j – l) produced good to excellent yield.



39 **40**

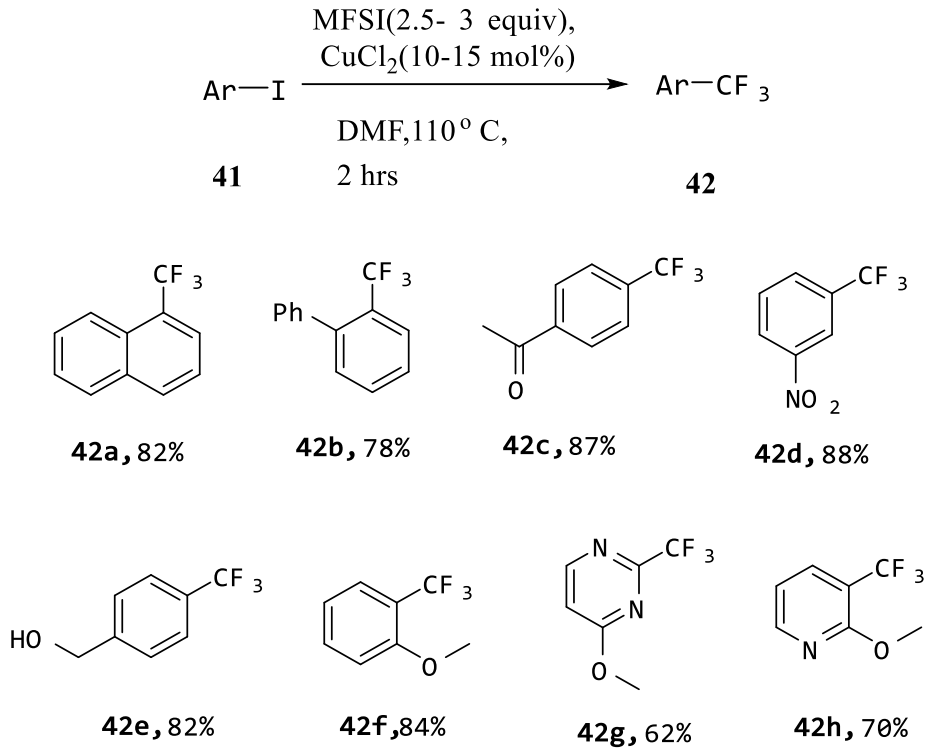
80% - 93%



Scheme 7.15: Trifluoromethylation α - iodinated oxoketene dithioacetals

Zhao and coworkers[91] proposed the nucleophilic trifluoromethylation of various aryl and heteroaryl iodides **4** using MFSI, and carried in the presence of $CuCl_2$ with excellent yield. In their review, they started with the trifluoromethylation of 1- iodonapthalene.

After the successful trifluoromethylation of iodonapthalene, they further synthesized a number of structurally diverse trifluoromethylated (hetero) aryl derivatives **42(a-h)** in the presence of $CuCl_2$ as catalyst at 110°C when stirred for 2 hrs. Effect of others salts of Cu on the yield, were also studied. (Scheme 7.16)

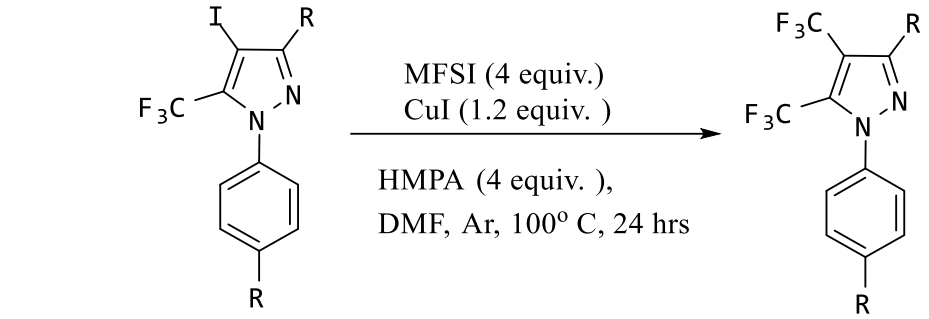


Scheme 7.16: Trifluoromethylation of aryl and heteroaryl iodides

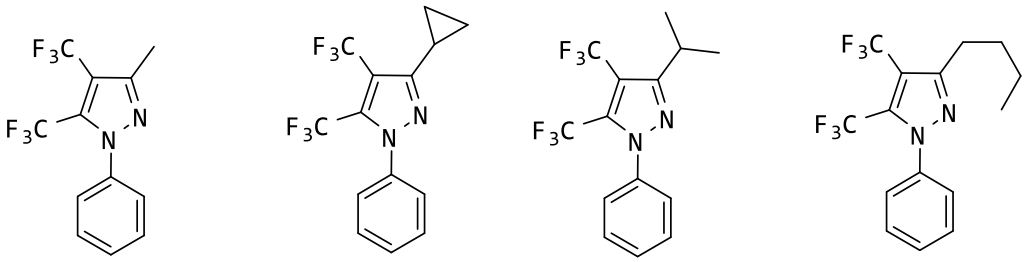
Junges et al[92] reported the trifluoromethylation of 1-aryl-3-alkyl(aryl)-5-trifluoromethyl-4-iodo-1*H*-pyrazoles **43** in CuI, MFSI and HMPA under anhydrous DMF for 24 hrs at 80°C to obtained a chain of 1-aryl-3-alkyl(aryl)-4,5-bis(trifluoromethyl)-1*H*-pyrazoles **44(a-h)** in good yield which showcased the insecticidal property. (Scheme 7.17).

Recently Xie and Hu[93] posted an article on huge application of MFSI in area of organic chemistry wherein they mentioned about the discovery, applications and reactions of Chen's reagent.

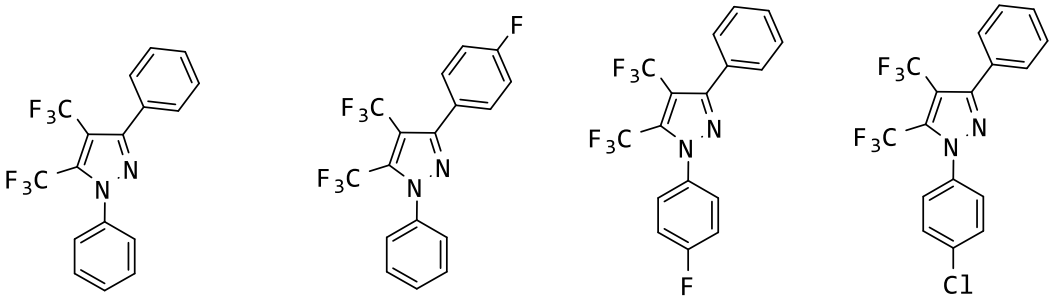
MFSI used normally to acquired trifluoro methylated and difluoro alkylated compounds. Over a decade, a substantial amount of research has been performed to use MFSI as a difluorocarbene precursor and radical difluoro alkylating agent in presence of visible light.



43 **44 (a-h)**



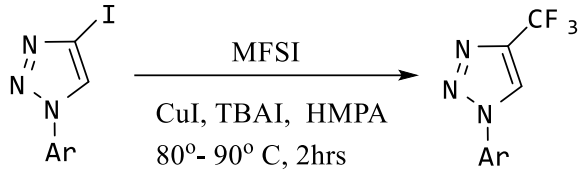
44a, 55% **44b,** 75% **44c** 58% **44d**



44e, 56 % **44f,** 79% **44g,** 77% **44h,** 71%

Scheme 7.17: Trifluoromethylation of 1-aryl-3-alkyl(aryl)-5-trifluoromethyl-4-iodo-1*H*-pyrazoles

Panja et al[94-98] reported the common method for trifluoromethylation of 1-aryl-4-iodo-1*H*-1, 2, 3-triazole **45** which were carried out in TBAI (Tetrabutylammonium iodide), CuI and MFSI, stirred at 80-90°C for 2 hrs. to obtain 1-aryl-4-(trifluoromethyl)-1*H*-1, 2, 3- triazole **46** in moderate yield. (Scheme 7.18). The reaction was not dependent on the electron density of substituent in aryl ring and it was chemoselective when carried out with bromo and chloro derivatives. Consequently, this is a useful method for synthesis of many 1-aryl-4-trifluoromethyltriazoles[99-101] from the respective iodo-precursor. TBAI act as useful reagent as it is solubilizing the Cu and make it available for the reaction.



45 **46**

Ar = 4-Cl-C_6H_4, 4-Br-C_6H_4, 3-Cl-C_6H_{44}-F-C_6H_4, 4-CH_3-C_6H_4, C_6H_5, 3,5-$(CF_3)_2$-C_6H_3
4-$COCH_3$-C_6H_4, 4-$CO_2CH_2CH_3$-C_6H_4, 4-CN-C_6H_4, 4-OCF_3-C_6H_4

Scheme 7.18: Trifluoromethylation of 1- aryl 4-iodo-1, 2, 3-triazoles

7. 3 Conclusion:

Since MFSI was discovered in 1989 as a trifluoromethlating reagent, it has found wide application for the trifluoromethylation of aromatic, herteroaromatic and alkenic compounds. A huge number of CF_3 containing biologically important and structurally diverse molecules have been synthesized by using this excellent reagent. Instead, it shows significant advantages over other trifluoromethlating reagent like CF_3CO_2Na and Ruppert Prakash reagent ($TMSCF_3$). Ruppert Prakash reagent is widely used as a trifluromethlating reagent but it is very expensive. MFSI reagent is commercially available, pretty cheaper and persuadable for trifluoromethylation of halogenated compounds. Scientists are doing more research on this reagent in organic synthesis. However, it has been somewhat underutilised by chemical community. We demand for extra attention to this crucial reagent. This reagent will continue to find more uses in the field of life sciences and material science.

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List of Abbreviations:

CF_3 - Trifluoromethyl

CF_3SiMe_3 - Ruppert-Prakash reagent

CF_3SO_2Cl - Trifluoromethane sulfonyl

$PhSOCF_3$ - Trifluoromethyl sulfoxide

$PhSO_2CF_3$ - Trifluoromethyl sulfone

MFSI - Methyl fluorosulfonyldifluoroacetate

CuI - Copper iodide

KI - Potassium iodide

DMF - Dimethylformamide

HMPA - Hexamethylphosphoramide

NaOH - Sodium Hydroxide

NIS - Nickel sulfide

$[Pb(dba)_2]$ - Bis(dibenzylideneacetone) Palladium

CF_3CO_2H - Trifluoroacetic acid

$Co(OAc)_2$ - Cobalt(II) acetate

NBS - N- Bromosuccinimide

MeCN - Methyl cyanide

n-BuLi - n Butyllithium

CF_3CO_2Na - Sodium trifluoroacetate