An Efficient and One Spot Synthesis of Silica Supported Synthesis of Fluorinated 1,3,4-Thiadiazole Derivative Under Microwave Irradiation

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Abstract :

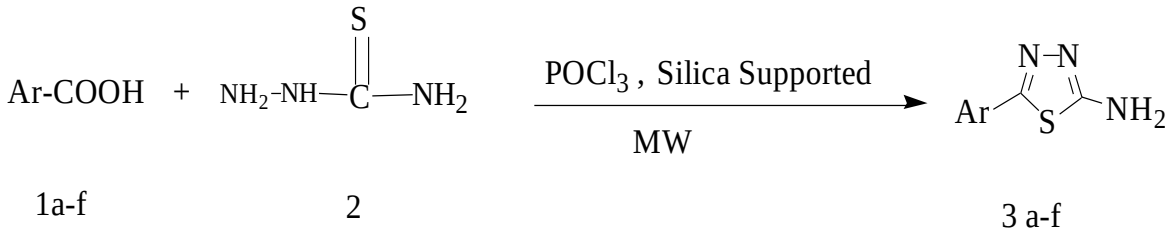
An efficient and one pot reaction of fluorinated 1,3,4-Thiadiazole derivatives was synthesis by fluorinated aromatic carboxylic with thiosemicabazide in the presence of phosphorus oxychloride as a catalyst under Microwave irradiation with silica supported. The synthesis compound was characterized by ^{1}H NMR, IR, and mass spectroscopic techniques. The present approach offers the advantages such as short reaction time, simplicity of the workup procedure, low cost and mild reaction condition.

Keywords:1,3,4-Thiadazole, thiosemicarbazide, Silica supported, Microwave irradiation

Introduction :

Heterocyclic compounds containing five member rings with nitrogen and sulfur commonly are building blocks, with a possessing large number of interesting biological activities. 1,3,4-thiadiazoles derivatives are five-member with exciting isomeric form of thiadiazoles [1,2]. The important of 1,3,4-thiadiazole is due to its Central Nervous System (CNS) disorders diagnostic ability due the lipo-solubility of sulfur atom. Compounds containing a 1,3,4-thiadiazole template have received significant attention in chemical, medicinal and pharmaceutical research as this structural scaffold is found in a variety of drugs. 1,3,4-thiadiazole and its derivatives are showing immense importance in medicinal chemistry research due to biological activity as well as producing useful intermediates in several organic preparations [3-7]. 1,3,4-Thiadiazoles are heterocyclic scaffolds incorporated in many compounds presenting various pharmacological activities such as antibacterial [8-9], anticonvulsant [10], anti-inflammatory [11-13], antimicrobial [14-17] , antiproliferative [18-20], antioxidant [21], antitubercular [22], antitumor [23], anticancer [24-25], antiviral [26]. Similarly, the diagnostic section exhibits a complete investigation of the isomeric form and the anticancer activity of biocaster 1,3,4-thiadiazoles due to therapeutic potential [27-30]. Also fluorinated 1, 3, 4-thiadiazole exhibits more potent antitumor inhibitory activity than doxorubicin [31]. 1,3,4-thiadiazole is central part in several marketed drugs such as acetazolamide, a carbonic anhydrase inhibitor used in treatment of glaucoma or sulfamethizole an antibacterial agent.

Scheme



1a-f 2 3 a-f

Materials and Methods:

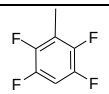
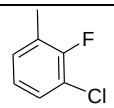
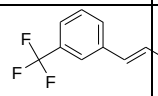
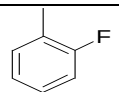
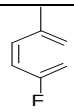
General: All the chemical and reagents used were of analytical grade from Aldrich and used without further purification. and the completion of reaction and purity of the synthesized compounds were checked by TLC (0.5 mm thickness) using silica gel-G coated Aluminum plates (Merck).Melting points of the compounds were determined in open capillary tube by digital melting point apparatus and were uncorrected.

Synthesis of Fluorinated 1,3,4-thiadiazol-2-amine 3 (a-f) under microwave irradiation.

The mixture of fluoro substituted aromatic carboxylic acid (0.01mole), thiosemicarbazide (0.01mole), Silica oxide and 5 ml of phosphorus oxychloride were added. The mixture was irradiated under microwave irradiation at 120 ^{0}C for 15 min. The completion of the reaction was monitored by TLC. After completion of the reaction the RBF was removed from the oven. The reaction mixture was poured on to crushed ice drop wise with continuous stirring, neutralized by saturated KOH. Then filter, dried and re-crystallized from ethanol.

Results and Discussion

Table .1. Physical data of synthesized compounds 3(a-f) under microwave irradiation

Entry	Compound	Ar	Reaction Time (min)	Yield (%)	M.P.(^{0}C)
1	3a		15	91	**222**
2	3b		15	90	**216**
3	3c		15	88	**236**
4	3d		15	90	**155**
5	3e		15	90	165
6	3f		15	88	236

An efficient, simple and one pot procedure is reported for the synthesis of fluorinated 1,3,4-Thiadiazole derivative with silica-support in the presence of phosphorus oxychloride microwave radiation technique. 1,3,4-

Thiadiazole derivative are synthesized by fluorinated aromatic carboxylic acid under above of mention condition. The formation of substituted 1,3,4-Thiadiazole derivative were confirmed by recording their IR, ^{1}H NMR, and mass spectral data. The compound 5-(2,3,5,6-tetrafluorophenyl)-1,3,4-thiadiazol-2-amine **(3a)** does not shows absorption band at 1700 (carbonyl stretching) broad band at 815 (C-S-C) is present. It shows absorption band at 1095, 1417, 1603cm^{-1}is for to C-F, C=C, C=N, stretching respectively.^{1}H NMR of compound **3a** showed broad singlet in the region of δ:8.02 which is due to de-shielded caused by the four fluorine proton, the singlet at 8.02 for the NH_2 of thiadiazole. The mass spectrum of **3a** showed a molecular ion peak at m/z 250 which is in agreement with the molecular formula $C_8H_3F_4N_3S$. The IR absorption band around 815 cm^{-1} could be attributed to the –C–S–C functional group. IR spectrum of **3b** showed absorption bands at 3369, 1443, 1596, 1054 cm^{-1} indicating the presence of NH_2, C=C, C=N, C-F groups respectively. ^{1}HNMR spectrum peaks due to NH_2 protons appeared at δ:7.46. Peaks for three aromatic proton appeared between 7.20-8.12. Further, LC mass spectrum showed molecular ion peak at m/z 214 which is in conforming the Molecular Structure of **3b.**

Conclusions

In conclusion, we have reported an efficient and one pot method for the synthesis of fluorinated 1,3,4-Thiadiazole by using fluorinated aromatic acid and thiosemicarbazide in of presence phosphorus oxychloride of under microwave irradiation. This method offers several advantages, including the low of cost, high yields, clean reactions, and short reaction time for the synthesis of one pot synthesis of 1,3,4-thiadiazole. These derivatives have been given a key to more modifications in pharmacophore replacements.

Data Availability

5-(2,4-Difluoro-phenyl)-[1,3,4]thiadiazol-2-ylamine (3a)

Yield 85 % m.p.216°C; IR spectrum, ν, cm^{-1}: 682(C-S-C stretching), 3369 (NH_2 stretching.) ; 1443(C=C Ar stretching), 1596 (C=N stretching),1054 (C-F stretching),; ^{1}H NMR spectrum, δ, ppm :: 7.20 (s, 1H), 7.41(d, J=8.96, 1H), 7.46(s, 2H), 8.12(d, J=8.96, 1H), (MS: *m/z*: 214 (M+H)$^+$.

5-(3-Chloro-2-fluoro-phenyl)-[1,3,4]thiadiazol-2-ylamine (3b)

Yield 84 %, m.p.151°C; IR spectrumcm^{-1}: 703 (C-S-C stretching), 3385 (**N**H_2stretching.); 1487(C=C Ar stretching), 1607 (C=N stretching),1009 (C-F stretching),; ^{1}H NMR spectrum, δ, ppm : 7.40 (dd, J=7.96, 8.4, 1H) , 7.52(1H, d, J=7.96, 1H), 8.00(s,2H), 8.16(d, J=8.4, 1H). (MS: *m/z*: 230 (M+H)

5-(2,3,5,6-Tetrafluoro-phenyl)-[1,3,4]thiadiazol-2-ylamine (3c)

Yield 82 %, m.p. 222 °C; IR spectrum, ν, cm^{-1}: 793 (C-S-C stretching), 3313 (**N**H_2 stretching.); 1413 (C=C Ar stretching), 1595 (C=N stretching),1030 (C-F stretching) ,; ^{1}H NMR spectrum, δ, ppm ::8.02 (s, 1H), 8.01 (s,1H). (MS: *m/z*: 250 (M+H)$^+$.

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Conflicts of Interest

Authors do not have any conflict of interest with any person, institution or agency

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