A Facile and Efficient Route for Synthesis of 5-Aryl-Thio-1H-Tetrazole Derivatives from Thiocyanates under Sulfamic Acid Promoter

N.Sivakumar[a] & S.Ananthalakshmi [b] & J.Sembian Ruso [c]

[a] Asst Professor ,PG and Research Department of Chemistry, M.R.Govt.Arts College, Mannargudi, TN,India

[b] Associate Professor, PG and Research Department of Chemistry, Urumu Dhanalakshmi College,Kattur,Triuchy-19,TN,India

[c] Shimoga Health Care, Nadikudi, Guntur –DT, Andhrapadesh, India-522414

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ABSTRACT: *A two-step protocol has been developed for the synthesis of selective 5-Aryl-Thio-1 H-Tetrazole derivatives. This procedure describes the employment of aralkyl halides with KSCN to derive tetrazole derivative for the maximum yield. The obtained aralkyl thiocyanate is treated with sodium azide in DMF, catalysed by NH_2SO_3H as an environmentally benign, economically cheap and commercially available Lewis acid catalyst. The synthesized derivatives were characterized by ^1H- NMR, ^{13}C-NMR, and IR and GC-MS spectroscopic techniques.*

Key Words: *Aryl halide, aryl thiocyanate, sulfamic acid, tetrazole*

Introduction

The tetrazole is one such five membered heterocyclic compound which contains four nitrogen atoms in the ring. Though they have not been found in nature, but these derivatives of tetrazoles exhibit considerable attention in various applications including antihypertensive[1], antitubercular[2], anti bacterial[3], anticancer activities[4], act as corrosion inhibitors [5], anti microbial activities [6], anti-inflammetry[7], antileishmanial activities[8] etc. However, the innovative ideas are still implemented in day to day research activity to synthesis terazole derivatives have attributed to their broad scope of applicability found in recent years. Conventionally, 5-Substituted tetrazoles are usually prepared by 3+2 cycloaddition reaction from nitriles and various azides using Bronsted or Lewis acids catalyst such as I_2, NH_4Cl, $AlCl_3$, $FeCl_3$, $ZnCl_2$ [9-12] and $ZnBr_2$[13].

Thiocyanates are ingenious chemical partner which have been significantly used for constructing C-S bonds in various derivatives. Moreover, the amicable importances of thiocyanates have been reported as insecticides[14] as well as antifungal activities[15] so far.

Remarkably, these compounds have also been isolated from cruciferous vegetables which possess potential anticancer activity[16]. Synthetically, several methods were offered for the preparation of aryl and alkyl thiocyanates which incorporates the displacement of leaving group with thiocyanate ion[17]. Despite, the thiocyanates can also be obtained from alcohols[18], silyl ethers[19] thiols[20] and arylboronic acid etc [20]. Owing to their wide utility, they play a vital role in the preparation of heterocyclic with sulphur as one of the heteroatom. Due to the insertion of the sulphur atom in the heterocyclic derivatives, the physical, chemical and biological properties have tremendously been increased to considerable extent. These impacts have been reported very recently in the derivative of 5-sulfenyl tetrazoles. Evidently latamoxef [22] are found have potential bioactive molecule in pharmaceutical chemistry.

In addition, the synthesis of sulphur linked tetrazoles using various Lewis acids have generally been explored in several articles. But no protocols have been found to synthesize these derivatives by means of amidosulfamic acid as a Bronsted-Lewis. As a result, in our continuation, herein we report a facile and efficient route for the synthesis of aryl-sulfur tetrazole derivatives with help of such easily available amidosulfamic acid (NH_2SO_3H) as a catalyst.

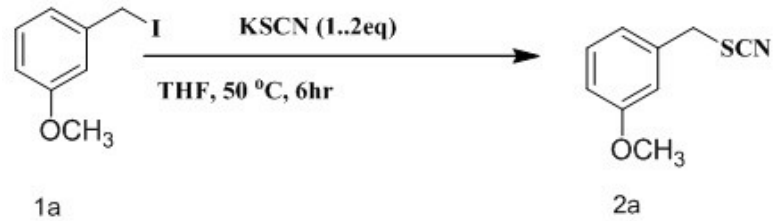
Experimental Section

All the synthesized derivatives of ^1H and ^{13}C NMR data were recorded on a Bruker advanced DPX 400 MHz instrument spectrometer using TMS as the internal standard in $CDCl_3$. IR spectra were recorded on a BOMEM MB –FT-IR spectrometer. Mass spectra were recorded on GC-MS and LC-MS .The purity determination of the products and reaction monitoring were accomplished by TLC using 230-400 mesh silica gel.

Typical procedure for the synthesis of the thiocyanates: A magnetically stirred mixture of the aryl halides (1.0mmol) and KSCN (1.2mmol) in THF were placed in a round bottomed flask and the reaction was stirred at 50 ^{0}C until complete consumption of the starting material (TLC). After the completion, the mixture was cooled to RT and extracted with ether. The combined organic layers were dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by chromatography (hexane/EtOAc 90:10)

Typical procedure for the synthesis of the 5-sulfenyl tetrazoles: To a mixture of the thiocyanate (1.0 equiv), NaN_3 (1.2equiv) and NH_2SO_3H (0.1 equiv) in DMF were heated at 120 ˚C until for 6 hrs. After complete conversion, as indicated by TLC, the organic layers were dried (Na_2SO_4) and concentrated under reduced pressure .The obtained residue was purified by column chromatography (hexane/EtOAc 90:10).

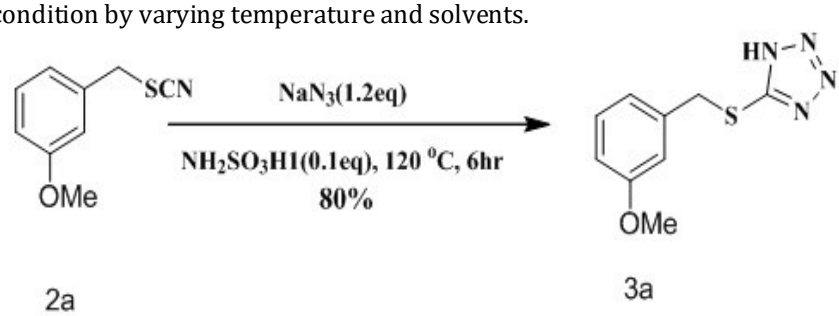
Results and Discussion



1a 2a

Scheme1 Optimisation for aralkylthiocyanate **2a** from aralkyl iodide **1a**

At first, a trial reaction was run with 3- methoxy benzyl iodide (**1a**) and potassium thiocyante in toluene at room temperature for 24 hr to derive **2a** (**Scheme 1**). In order to increase the yield, the reaction was carried out in different condition by varying temperature and solvents.



2a 3a

Scheme2 Optimisation of Tetrazole Derivative **3a** from **2a**

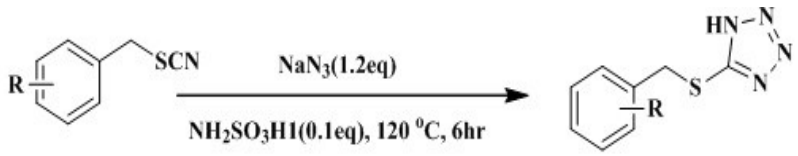
After the quick screening, the reaction found working well in THF at 50 °C, albeit the yield improvement was also observed in good extent. To achieve the compound **3a**, the intermediate **2a** was treated with sodium azide and amidosulfamic acid under various solvents like toluene, ethanol, THF and etc. After the several attempt, the amidosulfamic acid (0.1eq) and NaN_3 (1.2 eq) in DMF gave **3a** in excellent yield whereas other solvents did not give the same results as well **(Table1)**.

Table1. Optimization for Tetrazole Derivative from aralkyl thiocyanates

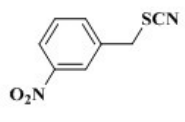
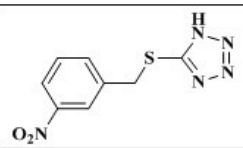
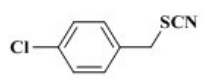
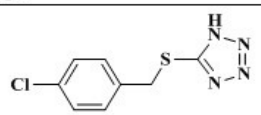
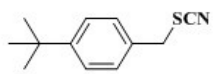
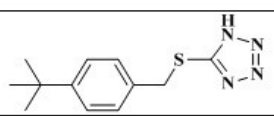
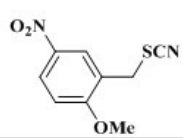
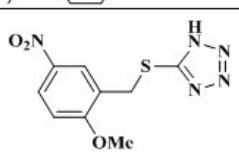
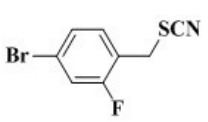
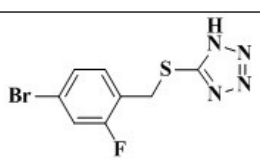
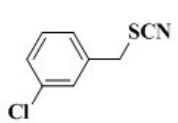
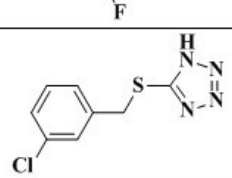
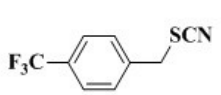
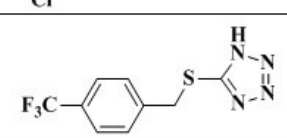
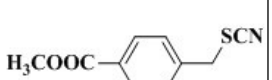
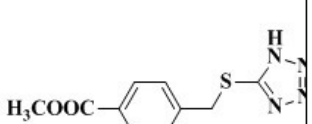
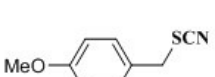
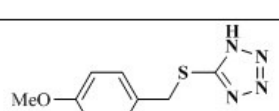
Entry	Solvents	Yield (%)
1	Toluene	Very low
2	Ethanol	10
3	*t* -BuOH	14
4	THF	Very low
5	DMF	80

Having the optimised condition in our hand, to check the scope of the substrate tolerability, the various benzyl thiocyanate **(2b-2j)** bearing electron withdrawing and electron donating substituent were subjected to this condition to obtain the tetrazole derivatives of **3b-3j** as in the **Table 2**. The electron donating group such as methoxy and tert-butyl containing aralkyl iodide **(3j, 3d)** afforded the compounds in moderate yield whereas the electron withdrawing **(3b)**surrogated substance furnished good yield, albeit the halo substrates of **(3f-3h)** are also under went smoothly to provide in reasonable yield.

Table2. Synthesis of Tetrazole Derivatives 3b**-3j**.



2b-2j 3b-3j

Entry	Substrate	Product	Yield (%)
3b			88
3c			81
3d			78
3e			77
3f			82
3g			78
3h			77
3i			79
3j			78

Analytical Data for Selected Compounds

5-[(3-methoxybenzyl)thio]-1H-tetrazole (3a): yield 78%; IR spectrum (KBr,ν,cm^{-1}): 3438,1635,1402,1095,1025,676. ^1H NMR (300 MHZ $CDCl_3$) δ (ppm): 3.92-3.83 (m, 3H), 4.31(s, 2H), 6.86-

7.27 (m, 4H). ^{13}C NMR (75MHZ CDCl3) δ: 54.7, 55.5, 112.0, 113.8, 120.4, 129.0, 136.8, 159.9, 192.1; LCMS: 222 (m+1).

5-[(3-nitrobenzyl)thio]-1H-tetrazole (3b): yield 88 %; IR spectrum (KBr,ν,cm^{-1}): 3435,1531,1351,1265,1097,804. ^{1}H NMR (300 MHZ $CDCl_3$) δ: 4.51(s, 2H), 7.56-7.68(m, 2H), 8.20-5.21(m, 2H).^{13}CNMR (75MHZ,CDCl3) δ: 55.3,121.4,123.5,129.3,130.0,137.7,160.1,162.7;LCMS:237(m+1).

5-[(4-chlorobenzyl)thio]-1H-tetrazole (3c) : yield 81%; IR spectrum (KBr,ν,cm^{-1}): 3407,1647,1412, 1212,1094,1076,783.^{1}H NMR (300 MHZ CDCl3) δ (ppm): 4.31 (s, 2H), 7.33-7.37(m, 4H). ^{13}C NMR (75MHZ $CDCl_3$) δ: 52.9, 127.9, 128.4, 132.8, 133.1, 162.1 LCMS: 226 (m+1).

5-[(4-tert-butyl) benzyl)thio]-1H-tetrazole (3d)): yield 78%; IR spectrum (KBr,ν,cm^{-1}): 3438,1640,1403,1164,1097,1025,614. ^{1}H NMR (300 MHZ CDCl3) δ (ppm):1.35(s, 9H), 4.31(s, 2H), 7.39-7.83 (m, 4H). ^{13}C NMR (75MHZ $CDCl_3$) δ: 29.7, 31.3, 34.6, 126.0, 128.0, 129.7, 132.4, 151.3. LCMS: 236 (m+1).

5-[(2-methoxy-5-nitrobenzyl)thio]-1H-tetrazole (3e) yield 77%; IR spectrum (KBr,ν,cm^{-1}): 3436,1594,1518,1272, 1092,1022, 751. ^{1}H NMR (300 MHZ CDCl3) δ(ppm): 3.99 (s, 3H), 4.41(s, 2H),7.00 (s, 1H), 8.39– 8.27 (m,2H). ^{13}C NMR (75MHZ $CDCl_3$) δ: 29.7, 56.3, 110.2, 125.2, 125.3, 125.9, 141.2, 162.0. LCMS: 267 (m+1).

Conclusion

At the outset, a series of new 5-aryl-thio-1H-tetrazole derivatives were synthesised using aralkyl thiocyante (**2a-2j**) as the intermediate substance for this conversion. Successfully this protocol is applied for the synthesis of thio-tetrazole derivatives bearing various functional groups in the phenyl ring. However, the economically cheap and commercially available amidosulfamic acid is used as Lewis-Bronsted acid catalyst to afford the corresponding compounds (**3a-3j**) in good to excellent yield.

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