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

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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 NH₄SO₃H as an environmentally benign, economically cheap and commercially available Lewis acid catalyst. The synthesized derivatives were characterized by 1H- NMR, 13C-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 tetrozoles exhibit considerable attention in various applications including antihypertensive1, antitubercular2, anti bacterial3, anticancer activities4, act as corrosion inhibitors 5 anti microbial activities 6, anti-inflammatory7, antileishmanial activities8 etc. However, the innovative ideas are still implemented in day to day research activity to synthesis ter azole derivatives have attributed to their broad wide scope of applicability found in recent years. Conventionally, 5-Substituted tetrozoles are usually prepared by 3+2 cycloaddition reaction from nitriles and various azides using Bronsted or Lewis acids catalyst such as I₂, NH₄Cl, AlCl₃, FeCl₃, ZnCl₂ 9-12 and ZnBr₂13.

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 insecticides14 as well as antifungal activities15 so far. Remarkably, these compounds have also been isolated from cruciferous vegetables which possess potential anticancer activity16. Synthetically, several methods were offered for the preparation of aryl and alky1 thiocyanates which incorporates the displacement of leaving group with thiocyanate ion17. Despite, the thiocyanates can also be obtained from alcohols18, silyl ethers19 thiols20 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 (NH₂SO₃H) as a catalyst.

Experimental Section
All the synthesized derivatives of 1H and 13C NMR data were recorded on a Bruker advanced DPX 400 MHz instrument spectrometer using TMS as the internal standard in CDCl₃. 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 (1.0 mmol) and KSCN (1.2 mmol) in THF were placed in a round bottomed flask and the reaction was stirred at 50 °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), NaN₃ (1.2 equiv) and NH₂SO₃H (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 (Na₂SO₄) and concentrated under reduced pressure. The obtained residue was purified by column chromatography (hexane/EtOAc 90:10).

**Results and Discussion**

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

At first, a trial reaction was run with 3-methoxy benzyl iodide (1a) and potassium thiocyanate 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.

**Scheme 2** 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 (0.1 eq) and NaN₃ (1.2 eq) in DMF gave 3a in excellent yield whereas other solvents did not give the same results as well (Table 1).

**Table 1. Optimization for Tetrazole Derivative from aralkyl thiocyanates**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvents</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toluene</td>
<td>Very low</td>
</tr>
<tr>
<td>2</td>
<td>Ethanol</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>t-BuOH</td>
<td>14</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>Very low</td>
</tr>
<tr>
<td>5</td>
<td>DMF</td>
<td>80</td>
</tr>
</tbody>
</table>

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.

**Table 2. Synthesis of Tetrazole Derivatives 3b-3j**
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 CDCl₃) δ (ppm): 3.92-3.83 (m, 3H), 4.31 (s, 2H), 6.86-
7.27 (m, 4H). 13C NMR (75 MHZ CDCl3) δ: 54.7, 55.5, 112.0, 113.8, 120.4, 129.0, 136.0, 159.9, 192.1; LCMS: 226 (m+1).

5-[(3-nitrobenzyl)thio]-1H-tetrazole (3b): yield 88 %; IR spectrum (KBr,ν,cm⁻¹): 3435,1531,1351,1265,1097,804. 1H NMR (300 MHZ CDCl3) δ: 4.51 (s, 2H), 7.56-7.68 (m, 2H), 8.20-5.21 (m, 2H). 13CNMR (75 MHZ CDCl3) δ: 53.5, 124.1, 125.3, 130.3, 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. 1H NMR (300 MHZ CDCl3) δ (ppm): 4.31 (s, 2H), 7.33-7.37 (m, 4H). 13C NMR (75 MHZ CDCl3) 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. 1H NMR (300 MHZ CDCl3) δ (ppm): 1.35(s, 9H), 4.31(s, 2H), 7.39-7.83 (m, 4H). 13C NMR (75 MHZ CDCl3) 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. 1H NMR (300 MHZ CDCl3) δ(ppm): 3.99 (s, 3H), 4.41 (s, 2H),7.00 (s, 1H), 8.39– 8.27 (m,2H). 13C NMR (75 MHZ CDCl3) 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 thiocyanate (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.

References