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Research Article

A ONE POT SYNTHESIS OF TETRAZOLE DERIVATIVES FROM ALDEHYDES AND SULFAMIC ACID WITH SODIUM AZIDE

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ABSTRACT

A Simple and an efficient one pot protocol for the synthesis of tetrazole derivatives from aldehydes and sulfamic acid is described. This protocol is found to have a better tolerability for various functional group of aromatic motif. Moreover, it involves remarkable and environmentally with cheap reagents and without the assistance of any catalyst for affording good to excellent yield of the product.

Keywords: Aldehyde, Sulfamic acid, Tetrazole

1. INTRODUCTION

In the recent years, the significant impacts on the synthesis of tetrazole derivatives have been put forwarded due to their wide variety of applications in the field of medicinal chemistry as well as in material science etc. The major exploration of these compounds in medicinal chemistry have been found as antifungal [1], antiviral [2], antimicrobial [3-6], antibacterial [7], anti inflammatory [8], antitubercular [9] and antihypertensive activities [10] and also as anticancer agent [11] so far. In general, the preparation of tetrazole derivatives are incorporated with the treatment of corresponding aldehydes or nitriles with azides in the presence of a Lewis acid such as $ZnCl_2$, $AlCl_3$, $MoCl_3$, $FeCl_3$-SiO_2, ZnO, Cu_2O, $ZnBr_2$-SiO_2 etc. [12-17]. In addition to that the synthesis of tetrazoles derivatives involving with toxic metals, Schiff bases and expensive chemicals, upon drastic conditions are also reported [18]. However, the one pot protocols are of particular interest is owing to their short reaction time, get rid of unwanted chemicals, presumably avoiding the intermediate and minimising the cost [19-20]. Conversely, considering the setbacks, the synthesis using inexpensive and easily available materials are extremely to be a valuable and challenging task in organic synthesis. Sulfamic acid is one such Bronsted-and Lewis acid which has not only been used in organic transformation but also for nano material synthesis and denitrification of simulated nitrate-rich wastewater [21]. Interestingly the promising progressive reactions of organic synthesis using sulfamic acid have been reported in recent days due to its versatility, environmental benign, cheap and easy availability. However, it has been depicted as a heterogeneous catalyst in most of the organic reactions including the synthesis of quinoline, triazolopyridine, imidazole and pyrimidine derivatives [22].

Though the handful reports are available in the literature to derive tetrazole, relatively few protocols are found to disclose the utility of sulfamic acid in tetrazole synthesis. In this connection, our attention is to develop a method to synthesize tetrazole derivatives from aldehyde and sulfamic acid which are employing as a reagent. In our protocol, it is successfully executed for the various functional groups bearing aromatic and hetero aromatic aldehydes.

2. EXPERIMENTAL SECTION

All reagents were purchased from commercial suppliers and were used without purification. Melting points were determined in Buchi B-545 melting point apparatus and were uncorrected. All the tetrazole derivatives synthesized were purified by flash column Chromatography using 230-400 mesh silica gel. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Advanced 400 & 300 NMR MHz spectrometers in $CDCl_3$ solution using TMS as an internal reference and ^{13}C NMR spectra were recorded on 100 & 75 MHz. Mass spectra were recorded on GC-MS and LC-MS.

2.1. Typical procedure for Tetrazole derivatives

A mixture of benzaldehyde (1 mmol) and sulfamic acid (2 mmol) in DMF (5mL) was heated at 90˚C for 1 hr and, cooled to 40˚C and slowly charged sodium azide (2 mmol). The reaction mixture was further heated at 90 °C for 8hrs. After complete conversion, as indicated by TLC, the reaction mixture was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel to give the product. Pale yellow solid; Yield 75%.

2.2. Analytical data for selected compounds

5-(3-Methoxyphenyl-*H*-tetrazole (2b): yield 80%; mp 112-115 °C. ^{1}H NMR (300 MHZ $CDCl_3$) δ: 3.87 (s, 3H), 7.16-7.22 (m, 1H), 7.40-7.42 (m, 1H), 7.44-7.48 (m, 2H). ^{13}C NMR (75 MHZ $CDCl_3$): δ 55.3, 112.1,121.4, 123.5,130.0, 137.7, 160.1, 192.2; LCMS: 177 (m+1).

5-(3, 4, 5-Trimethoxyphenyl)-1-*H*-tetrazole (2c): yield 72%; mp 125-128 °C. ^{1}H NMR (300 MHZ $CDCl_3$) δ: 3.76 (s, 3H), 3.86 (s, 6H), 7.26 (s, 2H). ^{13}C NMR (75 MHZ $CDCl_3$): δ 56.4, 60.6, 107.1, 132.1, 143.2, 153.7, 192.2; LCMS: 237 (m+1).

5-(4-Methoxyphenyl)-1-*H*-tetrazole (2d): yield 78%; mp 114-116 °C. ^{1}H NMR (300 MHZ $CDCl_3$) δ: 3.87 (s, 3H), 6.72-6.75 (d, 2, *J* = 9 Hz), 7.85-7.88 (d, 2, *J* = 9 Hz), 7.44-7.48 (m, 2H). ^{13}C NMR (75 MHZ $CDCl_3$): δ 56.1, 115.0, 132.2, 152.5, 164.6, 191.7; LCMS: 177 (m+1).

5-(4-Benzyloxy) phenyl)-1*H*-tetrazole (2f): yield 75%; mp 140-142 °C. ^{1}H NMR (300 MHZ $CDCl_3$) δ: 5.2 (s, 2H), 6.94-6.91 (m, 2H), 7.23-7.37 m, 5H), 7.90 (d, 2H). ^{13}C NMR (75 MHZ $CDCl_3$): δ 70.1, 128.5, 128.8, 128.9, 132.2, 132.5, 136.7, 163.7, 191.8; LCMS: 253 (m+1).

5 –Bromo-(2-tetrazole-5-yl) pyridine (2g): yield 78%; mp 110-112C. ^{1}H NMR (300 MHZ $CDCl_3$) δ: 8.02 (m, 2H), 8.76 (s, IH). ^{13}C NMR (75 MHZ $CDCl_3$): δ 124.2, 128.7, 130.8, 139.0, 1421.9, 162.5; LCMS: 225 (m+1).

5-(3, 5-dichlorophenyl)-1H-tetrazole (2h): yield 78%.^{1}H NMR (300 MHz $CDCl_3$) δ: 7.67 (s, J= 7.8 1H), 8.21 (d, 2H). ^{13}C NMR (75 MHz DMSO): δ 116.99, 126.25, 130.18, 132.06, 151; LCMS: 215 (m+1).

5-(4-(trifluoromethyl)phenyl)-1H-tetrazole (2i) : yield 76%.^{1}H NMR (300 MHz $CDCl_3$) δ: 7.39 (d, J= 8.1 2H), 8.065 (d, J= 4.8 2H). ^{13}C NMR (75 MHz $CDCl_3$): δ 113.65, 120.42, 123.61, 129.90, 138.87, 159.94; LCMS: 214 (m+1).

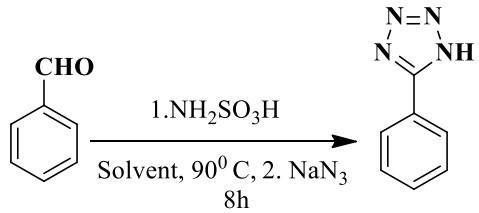
5-(3-bromophenyl)-1H-tetrazole (2j): yield 80%.^{1}H NMR (300 MHZ $CDCl_3$) δ: 7.559 (s, J= 6.9 1H), 7.92 (s, J= 6.9 1H), 8.14 (s, 1H), 8.867(s, 1H). ^{13}C NMR (75 MHz $CDCl_3$): δ 122.30, 123.18, 124.95, 128.65, 134.81, 153, 154.60; LCMS: 225 (m+1).

3-(1H-tetrazole-5-yl) -1H-indole (2k): yield 81%.^{1}H NMR (300 MHz DMSO) δ: 7.25 (s, J= 6.0 1H), 7.50 (s, 1H), 7.52 (s, 1H), 8.07(s, 1H) 8.27 (s, J= 6.0 1H), 9.92 (s, 1H). ^{13}C NMR (75 MHz DMSO): δ 112.8 118.6, 121.2, 122.6, 123.95, 124.5, 137.5, 138.96, 162; LCMS: 186 (m+1).

3. RESULTS AND DISCUSSION

To prove the viability of the reaction, the model substrate **1a** is treated with sulfamic acid and sodium azide under various conditions as shown in the Table 1.

Table1. Optimization for Tetrazole using Benzaldehyde and sulfamic acid in various solvents



Entry	Solvents	Reagent	Yield (%)
1	Toluene	NH_2SO_3H	NA
2	Methanol	NH_2SO_3H	NA
3	Ethanol	NH_2SO_3H	10
4	*t*-BuOH	NH_2SO_3H	14
4	THF	NH_2SO_3H	NA
5	DMA	NH_2SO_3H	NA
6	DMSO	NH_2SO_3H	35
7	DMF	NH_2SO_3H	75

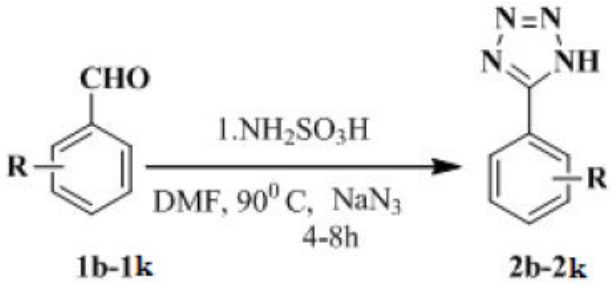
Reaction was performed using benzaldehyde (1 mmol) in Solvent (5 mL), 2 eq. of Sulfamic acid and 2 eq. of Sodium azide.

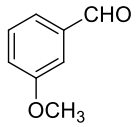
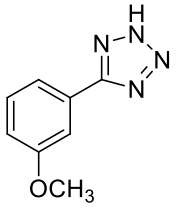
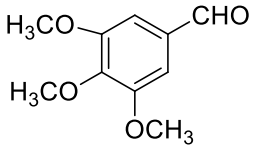
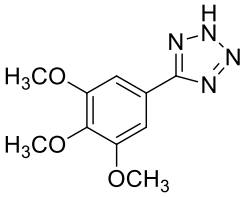
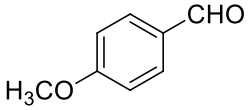
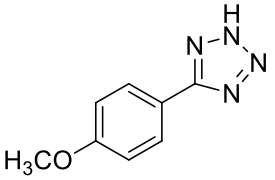
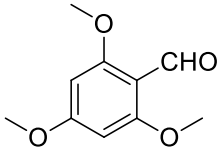
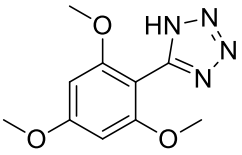
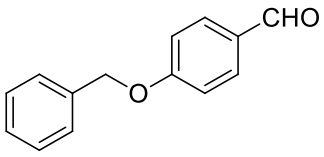
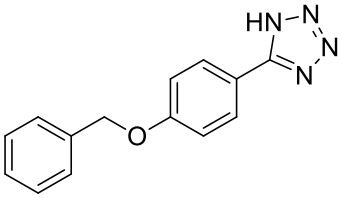
At first, the **Ia is** treated at room temperature in toluene for 3 hr, latter sodium azide is added and heated at 90 °C for 8 hrs, which results no formation of the product. Similarly the same result has obtained even at refluxing temperature. This attempt as kept on continued by using polar protic solvents such as MeOH, EtOH and t-buOH

and polar aprotic solvent such THF, DMA, DMSO and aprotic solvent but the afforded yield is very low (Table 1). After a quick screening, it is found that the reaction is working well in DMF and the isolated yield is good **2a** (75%).

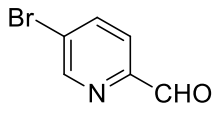
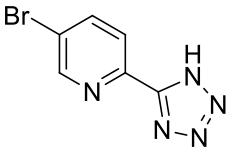
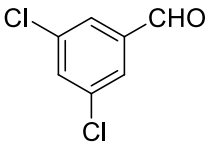
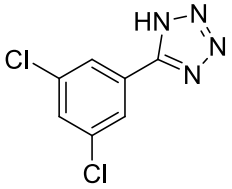
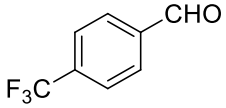
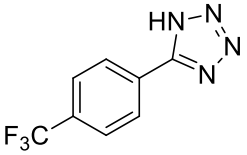
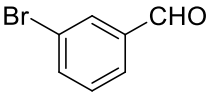
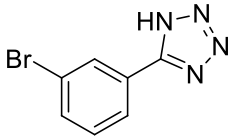
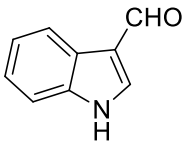
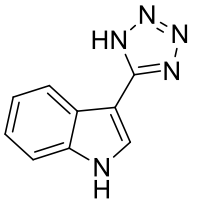
In order to check the scope and applicability of the protocols, the aldehydes bearing various functional DMF. Albeit the reaction proceeded smoothly in polar groups are subjected, where the electron donating groups such as methoxy, benzyloxy aldehydes (**2b-2e and 2f**) furnished excellent yield (**Table 2**). The bromo, chloro and fluoro aldehydes (**2h-2j**) smoothly delivered the required tetrazole in good yield. Besides, the indole and pyridine aldehyde also give good yields (**2g and 2k).**

Table 2: Synthesis of compounds 2b-k



Entry	Substrate	Product	Time (Hrs)	Yield (%)
2b			**5**	80
2c			**6**	72
2d			**4**	78
2e			**7**	81
2f			**7**	75

Continued…

2g			**6**	78
2h			**4**	78
2i			**8**	76
2j			**7**	80
2k			**8**	81

4. CONCLUSION

At the outset, a simple and catalyst free synthesis of tetrazole derivatives by employing the reaction of aldehydes and sulfamic acid with sodium azide is demonstrated. The one-pot protocol is well performed to obtain the tetrazole derivatives using cheaply available and environment benign sulfamic acid as a reagent. The yield obtained is good to excellent.

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