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Facile and mild synthesis of 1-substituted-1*H*-1,2,3,4-tetrazoles catalyzed by methanesulfonic acid under solvent-free conditions

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ABSTRACT

Methanesulfonic acid (MSA) was found to be an efficient catalyst for the synthesis of 1-substituted-1*H*-1,2,3,4-tetrazoles. A series of 1-substituted tetrazole compounds were synthesized from the reaction of various primary amines, sodium azide and triethyl orthoformate in the presence of catalytic amounts of MSA at room temperature. In this protocol, some of the tetrazole derivatives were synthesized in good to excellent yields and convenient reaction times. This method has the advantages of simple methodology and easy work-up.

Keywords*: 1H-Tetrazoles, Methanesulfonic acid, Solvent-free, Room temperature, Primary amines.*

1. Introduction

Tetrazoles are an increasingly-popular functionality with wide ranging applications and have been used in a variety of synthetic and medicinal chemistry applications [1-3]. Due to the role played by these heterocyclic compounds in medicinal chemistry [4] as HIV inhibitors [5] and sartane drug family (Fig. 1) [6, 7], coordination chemistry as ligand [8, 9] and in material science applications as polymers [10] and explosive agents [11], the interest in tetrazole chemistry has been rapidly increasing. Although, many 5-substituted tetrazoles are known, there is still a dearth of efficient processes for the synthesis of 1-substituted tetrazoles. The general and conventional method for the synthesis of 1-substituted 1*H*-1,2,3,4-tetrazoles is via cyclization reaction of amine moieties orthocarboxylic acid esters and hydrazoic acid salt in the presence of a catalyst [9, 12, 13]. Acetic acid [9], trifluoroacetic acid [14], acidic ionic liquid [15], zeolites [16], ytterbium triflate [3], silica sulfuric acid [17] and indium triflate [18] are common catalysts that were used in this transformation. Unfortunately, these methods suffered from some drawbacks such as using of extra brønsted acid that caused liberation of hydrazoic acid from the reaction media, expensive and toxic metal catalysts, harsh reaction conditions, difficult work-up, refluxing for long time and use of highly-polar organic solvents.

In this research, we wish to report a more efficient and convenient method toward synthesis of 1-substituted 1*H*-1,2,3,4-tetrazoles via three-component cyclization reaction of primary amine derivatives, triethyl orthoformate and sodium azide in the presence of methanesulfonic acid (MSA) as a new catalyst under solvent-free conditions at room temperature.

2. Experimental

2.1. General

All reagents were commercially available and used without any purification. All the solvents were purchased from Merck chemical Company (reagent grades) and were used as received unless otherwise specified. FT-IR spectra were recorded as KBr pellets on a Nicolet FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker DRX-400 spectrometer with tetramethylsilane as internal reference.

2.2. General Procedures for preparation of 1-substituted-1H-1,2,3,4-tetrazoles

A mixture of 2 mmol selected amine, 2.4 mmol triethyl orthoformate (0.4 ml) and 2 mmol sodium azide

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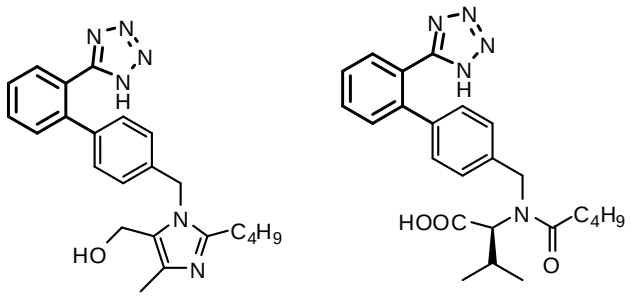


Fig. 1. Two types of sartane drug family.

(0.13 g) was added to 0.4 mmol methanesulfonic acid (0.04 ml, 20 mol %). The mixture was stirred for modified time and the progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was diluted by 1:1 H_2O/EtOAc (10 ml), stirred at ambient temperature (20 min) and the organic phase of the solution was separated by separating funnel, dried over sodium sulfate, and the solvent was distilled off under reduced pressure. To reach further purification, recrystallization of the product was performed at 3:1 EtOAc:MeOH to yield the desired 1-substituted 1*H*-1,2,3,4-tetrazole. Due to the toxicity, reactivity and energetic azide materials, safety precautions were taken.

Selected spectral data

1-Phenyl-1H-1,2,3,4-tetrazole (**4a**): yellow solid; m.p.=63-65 °C (Lit. [3, 18, 19]: 65-67 °C); FT-IR (KBr)/ ν (cm^{-1}) 3051 (C-H, sp^2 stretch Ar), 1677 (C=N), 1588, 1488 (C=C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.07-7.34 (m, 5H, Ar), 8.20 (s, 1H tetrazole).

1-(4-Methylphenyl)-1H-1,2,3,4-tetrazole (**4b**): Light yellow solid; m.p.=93-94 °C (Lit. [3, 18, 19]: 92-94 ^{o}C); FT-IR (KBr)/ ν (cm^{-1}) 3022 (C-H, sp^2 stretch, Ar), 2918(C-H, sp^3 stretch), 1664 (C=N), 1607, 1506 (C=C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 2.34 (s, 3H), 6.94-6.96 (d, 2H, *J*=8 Hz), 7.11-7.13 (d, 2H, 8 Hz), 8.17 (s, 1H tetrazole); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 20.79, 119.08, 129.63, 130.17, 142.95, 149.77.

1-(4-Boromophenyl)-1H-1,2,3,4-tetrazole (**4c**): White solid; m.p.=183-185 °C (Lit.: CAS No.: 57058-01-2, 182-184 ^{o}C); FT-IR (KBr)/ ν (cm^{-1}) 3151 (C-H, sp^2 stretch, Ar), 1659 (C=N), 1576, 1481 (C=C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 6.92-6.94 (s, 2H), 7.40-7.42 (d, 2H, *J*=8 Hz), 8.09 (s, 1H tetrazole); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm)): 116.43, 120.76, 132.03, 143.99, 149.29.

1-(3-Methylphenyl)-1H-1,2,3,4-tetrazole (4d): White solid; m.p.=55-58 °C (Lit. [3, 19]: 55-57^{o}C); FT-IR (KBr)/ ν (cm^{-1}) 3066 (C-H, sp^2 stretch, Ar), 2920 (C-H, sp^3 stretch), 1680 (C=N), 1598, 1483 (C=C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 2.33 (s, 3H), 6.86 (s, 1H), 6.89- 6.91 (d, 2H, *J*=8 Hz), 7.18-7.22(t, 1H), 8.21 (s, 1H tetrazole); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 21.43, 115.93, 119.97, 124.06, 129.19, 139.26, 145.28, 149.23.

1-(2-Methylphenyl)-1H-1,2,3,4-tetrazole (**4e**): White solid; m.p.=153-155°C (Lit. CID No.= 22762385: 152-155 ^{o}C); FT-IR (KBr)/ ν (cm^{-1}) 3015 (C-H, sp^2 stretch, Ar), 2870 (C-H, sp^3 stretch), 1664(C=N), 1488, 1590 (C=C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 2.33 (s, 3H), 7.02-7.03 (d, 1H), 7.05-7.07 (d, 1H, *J*=8 Hz), 7.18-7.22 (t, 2H, *J*=7 Hz), 8.08 (s, 1H tetrazole); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 17.94, 117.68, 123.43, 127.00, 128.71, 130.72, 144.10, 147.78.

1-[4-(1H-Tetrazol-1-yl)phenyl]ethanone (**4f**): yellow solid; m.p.=148-150°C (Lit. [15]: 147-149^{o}C); FT-IR (KBr)/ ν (cm^{-1}) 3075 (C-H, sp^2 stretch, Ar), 2995 (C-H, sp^3 stretch), 1669 (C=N), 1499, 1585 (C=C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 2.60 (s, 3H), 7.13-7.15 (d, 2H, *J*=8 Hz), 7.95-7.97 (d, 2H, *J*=8 Hz), 8.30 (s, 1H tetrazole).

1-(2,4-Dimethylphenyl)-1H-1,2,3,4-tetrazole (**4g**): White solid; m.p.=133-135°C (Lit. [18]: 130-135^{o}C); FT-IR (KBr)/ ν (cm^{-1}) 3069 (C-H, sp^2 stretch, Ar), 2914 (C-H, sp^3 stretch), 1663 (C=N), 1495, 1607 (C=C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 2.29 (s, 3H), 2.30 (s, 3H), 6.94-6.96 (d, 1H, *J*=8 Hz), 6.98-7.00 (m, 1H), 7.02 (s, 1H), 8.00 (s, 1H tetrazole).

1-(2-Chlorophenyl)-1H-1,2,3,4-tetrazole (**4h**): White solid; m.p.=129-131°C (Lit. [3,18]: 130-132^{o}C); FT-IR (KBr)/ ν (cm^{-1}) 3047 (C-H, sp^2 stretch, Ar), 1664 (C=N), 1470, 1582 (C=C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.03-7.50 (m, 4H), 8.10 (s, 1H tetrazole).

1-(3-Chlorophenyl)-1H-1,2,3,4-tetrazole (**4i**): White solid; m.p.=137-139°C (Lit. [19]: 137-140^{o}C); FT-IR (KBr)/ ν (cm^{-1}) 3065 (C-H, sp^2 stretch, Ar), 1670 (C=N), 1469, 1589 (C=C). 1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 6.92-6.94 (d, 1H, *J*=8 Hz) 7.07-7.09 (d, 2H, *J*=8 Hz) 7.26-7.27 (m, 1H), 8.14 (s-1H tetrazole); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 117.45, 119.23, 123.73, 130.34, 135.12, 146.14, 149.72.

1-(4-Chlorophenyl)-1H-1,2,3,4-tetrazole (**4j**): White solid; m.p.=153-155 °C (Lit. [3, 15]: 155-156°C); FT-IR (KBr)/ ν (cm^{-1}) 3052 (C-H, sp^2 stretch, Ar), 1661 (C=N), 1485, 1581 (C=C) ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 6.98-7.00 (d, 2H, *J*=8 Hz), 7.27-7.29 (d, 2H, *J*=8 Hz), 8.09 (s, 1H tetrazole); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm)): 120.35, 128.85, 129.47, 143.52, 149.50.

1-(Naphthalene-1-yl)-1H-1,2,3,4-tetrazole (**4k**): White solid; m.p.=181-183°C (Lit. [20]: 180-182°C); FT-IR

(KBr)/ ν (cm^{-1}) 3048 (C-H, sp^2 stretch, Ar), 1658(C=N), 1574, 1432 (C=C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.23-8.27 (m, 7H), 8.36 (s, 1H tetrazole).

1-[2-(1H-Tetrazol-1-yl)phenyl]-1H-1,2,3,4-tetrazole (**4l**): White solid; m.p.=167-169°C; FT-IR (KBr)/ ν (cm^{-1}) 3062 (C-H, sp^2 stretch, Ar), 1619 (C=N) 1458, 1588 (C=C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.30-7.70 (m, 4H), 8.11 (s, 1H tetrazole); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 115.76, 122.37, 138.50, 142.40.

3. Results and Discussion

In order to optimize the reaction conditions, a typical reaction of aniline with triethyl orthoformate and sodium azide was chose. Firstly, the reaction was carried out in the presence of the various amounts of catalyst under solvent free conditions at room temperature. The results of this study are shown in Table **1**. It was found that in the presence of 0.04 ml (20 mol %) of the catalyst, the reaction was completed after 6 minutes to afford the related product in high yield (Table 1, entry 5). When the reaction was performed in the presence of 0.01 ml of MSA (5 mol %), the reaction proceeded but it was not completed; even after 20 minutes, the yields of the desired product was reached only 53 % (Table 1, entry 2). It is notable that in the reaction condition, the substrates were treated with an equimolar amount of sodium azide for the reaction completion. In this condition, any volatile and dangerous hydrazoic acid gas was evaporated and the reaction process was safe.

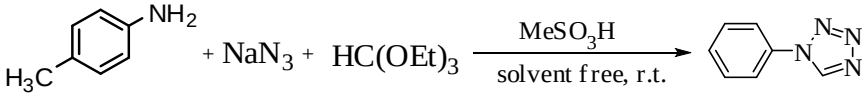
In order to ascertain the limitations of the reaction, a variety of primary aromatic amines were used to investigate the scope and generality of this process (Table 2). The results showed that a wide range of aromatic amine derivatives containing electron-withdrawing as well as electron-donating groups in the cyclization easily underwent conditions with sodium azide and triethyl orthoformate to give corresponding tetrazoles in moderate to excellent isolated yields. The regarding results are summarized in Table **2**.

The results showed that electron-donating (ED) groups on the *para* position of the aniline ring caused to accelerate the reaction rate (Table 2, entry 2).

Accordingly, the ED functional groups in the *ortho* position had steric effect and somewhat decreased the rate of the reaction (Table 2, entries 5 and 7). The *o*-phenylenediamine reacted in the presence of double mol ratio of triethyl orthoformate, sodium azide and 40 mol % of MSA as catalyst in the reaction conditions to give desired product **4l** in good yield (Table 2, entry 12). Electron-withdrawing (EW) groups generally caused to decrease the reaction rate and the isolated product yields of these substrates were somewhat lower than others (Table 2, entries 3, 6, 8-10).

A comparative table was arranged (Table **3**) in order to compare the catalytic activity of MSA with other previously-reported conditions with various catalysts. In this table, five recently methods for the synthesis of 1-substituted-1*H*-tetrazoles were compared. All of the reported procedures were carried out at harsh reaction conditions such as high temperature (entries 3-6), high loading amounts of catalyst (entries 2 and 3) and long

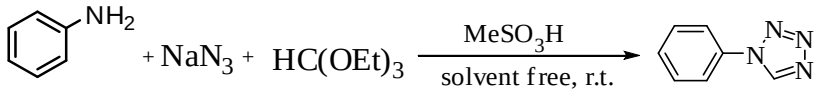
Table 1. Optimization of the various amounts of the catalyst.[a]



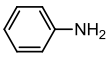
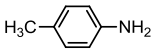
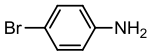
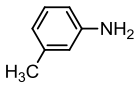
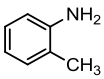
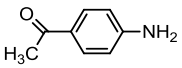
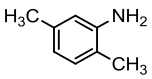
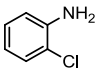
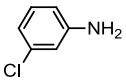
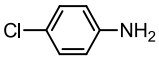
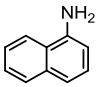
Entry	MSA (ml)	Time (min)	Yield (%)[b]
1	-	50	-
2	0.01 (5 mol %)	20	53
3	0.02 (10 mol %)	12	64
4	0.03 (15 mol %)	8	72
5	0.04 (20 mol %)	6	83
6	0.05 (25 mol %)	6	83

[a]Reaction conditions: 4-methyl aniline 2.0 mmol, triethyl orthoformate 2.4 mmol and sodium azide 2.0 mmol.
[b]Isolated yields.

Table 2. Synthesis of 1-substituted tetrazoles from several primary amines catalyzed by MSA.[a]



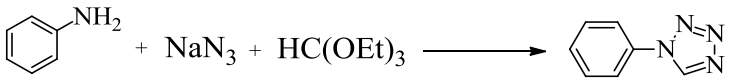
1a-l **4a-l**

Entry	Primary amine	Product	Time (min)	Yield (%)[b]
1		**4a**	10	78
2		**4b**	6	74
3		**4c**	8	79
4		**4d**	12	76
5		**4e**	14	64
6		**4f**	12	72
7		**4g**	14	63
8		**4h**	15	64
9		**4i**	13	65
10		**4j**	12	68
11		**4k**	16	61
12[c]		**4l**	18	56

[a]Reaction conditions: aniline derivatives 2.0 mmol, triethyl orthoformate 2.4 mmol, sodium azide 2.0 mmol, catalyst 0.04 ml (20 mol %).
[b]Isolated yields.
[c]Reaction conditions: *o*-phenylenediamine 2.0 mmol, triethyl orthoformate 5 mmol, sodium azide 4.0 mmol, catalyst 0.08 ml (40 mol %).

reaction times (entries 4-6). Moreover, it seems that using expensive activated metal catalysts (entries 4 and 6) is not a good idea for this reaction. In comparable conditions, the present work is the best among other methods because it was carried out without solvent at ambient temperature and low reaction time in the presence of catalytic amounts of MSA as inexpensive and accessible catalyst.

Table 3. Comparison of various catalysts for the synthesis of 1-substituted-1*H*-tetrazoles.



Entry	Catalyst (mol %)	Solvent	Temp. (°C)	Time	Yield (%)	Ref.
1	MSA (20)	neat	r.t.	10 min	78	Present work
2	[bbim]Br (50)	DMSO	30	20 min	86	[19]
3	$[Hbim]BF_4$ (300)	neat	100	25 min	89	[15]
4	$Yb(OTf)_3$ (20)	2-methoxyethanol	100	6 h	85	[3]
5	Silica sulfuric acid	neat	120	4 h	90	[17]
6	$In(OTf)_3$ (5)	neat	100	2 h	90	[18]

4. Conclusion

In this study, we have developed a simple and efficient catalyst for the synthesis of 1-substituted-1*H*-1,2,3,4-tetrazole compounds. A series of tetrazole compounds were synthesized in good to excellent yields and convenient reaction times. This protocol proceeded via the reaction of various primary amines, sodium azide and triethyl orthoformate catalyzed by methanesulfonic acid at room temperature under solvent-free conditions. The present procedure has some valuable advantages such as; mild reaction conditions, short reaction times, high yields of tetrazoles, simple work-up and no side reactions. Also, availability, cheapness and efficiency of the methanesulfonic acid as catalyst make this procedure a valid contribution to the existing processes in the field of tetrazole synthesis.

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