Solvent-free synthesis of 1-aryl-1*H*-1,2,3,4-tetrazoles using $FeCl_3$–SiO_2 catalysis under conventional and ultrasound irradiation conditions

Davood Habibi*, Samaneh Mostafaee and Leila Mehrabi

Department of Organic Chemistry, Bu-Ali Sina University, Hamedan, Iran

1-Aryl-1*H*-1,2,3,4-tetrazoles were synthesised by the solvent-free reactions of aryl amines, sodium azide and triethyl orthoformate using $FeCl_3$–SiO_2 as an effective heterogeneous catalyst under conventional and ultrasound irradiation conditions. This method has the advantages of high yields, simple methodology and easy work-up. The catalyst can be recovered by simple filtration and reused delivering good yields.

Keywords: 1-aryl-1*H*-1,2,3,4-tetrazoles, triethyl orthoformate, aryl amine, sodium azide, $FeCl_3$–SiO_2, heterogeneous catalyst

The preparation of substituted tetrazoles has been the subject of thorough investigation, over the last few decades.[1] Tetrazoles have a wide range of applications in pharmaceutical, material and coordination chemistry.[2–4] However, the use of these compounds is limited by their availability.

The common methods[5–7] of preparing tetrazoles suffer from disadvantages such as low yield, long reaction times, harsh reaction conditions, tedious work-up and from the presence of hydrazoic acid which is highly toxic and explosive.

In recent years heterogeneous catalysts have become important in organic syntheses because of economic and environmental considerations. Among various silica-based heterogeneous catalysts, $FeCl_3$–SiO_2 has advantages of low cost, ease of preparation and recyclability.[8–10]

A large number of organic reactions can be carried out in a higher yield, shorter reaction time and milder conditions under ultrasonication. Compared with traditional methods, this method is more convenient and can be easily controlled.[11,12]

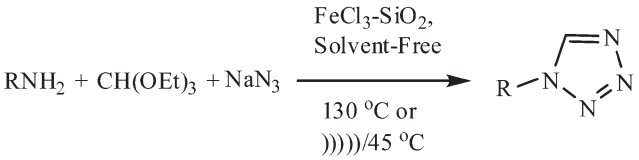
In continuation of our work on the synthesis of heterocycles and application of the heterogeneous reagents,[13–18] we report a new protocol for preparation of 1-aryl tetrazoles from the reaction of wide variety of primary amines, sodium azide and triethyl orthoformate using $FeCl_3$–SiO_2 as a solid acid catalyst under conventional conditions and ultrasound irradiation (Scheme 1).

Results and discussion

First, we optimised the required amount of the catalyst in the reaction between aniline, sodium azide and triethyl orthoformate (Table 1). The optimum amount of $FeCl_3$–SiO_2 was found to be 0.02 g in the presence of amine (2 mM), sodium azide (2 mM) and triethyl orthoformate (2.4 mM).

Next we examined a variety of amines possessing a wide range of functional groups to establish the scope of the $FeCl_3$–SiO_2 promoted reaction to form the 1-substituted tetrazoles. The results are summarised in Table 2.

Recovery and catalyst reusability are important issues in the cyclisation reactions. Easy catalyst separation and recycling in successive batch operations can greatly increase the efficiency of the reaction. $FeCl_3$–SiO_2 as an inexpensive and non-hazardous solid acid catalyst can easily be handled and removed from the reaction mixtures by simple filtration. The recovered catalyst was reused three times without any loss of activity (Table 2, entry 1). No deterioration of the catalyst was observed, confirming the high stability of the applied catalytic system under the reaction conditions.



Scheme 1 Synthesis of the 1-aryl-1H-1,2,3,4-tetrazoles under conventional and ultrasound irradiation.

* Correspondent. E-mail: davood.habibi@gmail.com

To show the advantages of the present work in comparison with the results reported in the literature, we compared $FeCl_3$–SiO_2 with AcOH,[6] ionic liquid[19] and $Yb(OTf)_3$[7] in the synthesis of the 1-substituted tetrazoles (Table 3). As shown, $FeCl_3$–SiO_2 is a better catalyst with respect to the reaction times and yields of the products. In comparison with $Yb(OTf)_3$ and AcOH, it uses only 20 mol % of the catalyst with a shorter reaction time and improved yield and in contrast with the ionic liquids, this method does not require purification by column chromatography.

To determine the specific effect of ultrasonic irradiation, all reactions were carried out under the new condition and the results showed that the new procedure gave better yields with shorter reaction times (Table 2). This observation is probably consistent with the basic concept of the green chemistry.[20] To the best of our knowledge, this new procedure provides the first example of an efficient ultrasound promoted one-pot three-component approach to the synthesis of 1-substituted aryl tetrazoles.

Conclusions

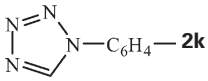
In conclusion, we have developed a novel and highly efficient method for the solvent-free synthesis of 1-aryl tetrazoles by the treatment of primary aryl amines with ethyl orthoformate and sodium azide in the presence of $FeCl_3$–SiO_2 as catalyst under conventional conditions and ultrasound irradiation. The significant advantages of this method are high yields, elimination of dangerous and harmful hydrazoic acid, a simple work-up procedure and easy preparation and handling of the catalyst. The catalyst can be recovered by filtration and reused.

Table 1 Preparation of 1-phenyl-1*H*-1,2,3,4-tetrazole (**2a**) using various amounts of $FeCl_3$–SiO_2 under solvent-free conditions at 130 °C[a]

Entry	$FeCl_3$–SiO_2/g	Temperature/°C	Yield/%[b]
1	0.008	130	72
2	0.01	130	85
3	0.015	130	91
4	**0.02**	**130**	**95**
5	0.02	120	80
6	0.02	110	63
7	0.02	100	45
8	0.02	90	34
9	0.00	130	0.0[c]

[a] Reaction conditions: amine (2 mmol), NaN_3 (2 mmol), orthoformate (2.4 mmol), reaction time (2.30 h).
[b] Isolated yield.
[c] In the absence of catalyst at 130 °C, no reaction was observed even after 2.30 h.

Table 2 Preparation of the 1-substituted tetrazoles (**2a–k**) by reaction of different amines (**1a–k**) with sodium azide and triethyl orthoformate in the presence of $FeCl_3$–SiO_2 under conventional conditions[b] or ultrasound irradiation[c]

Entry	R in R–NH_2	R in 1-substituted 1*H*-1,2,3,4-tetrazoles	Time/h	Yield/%[a]	Ref.
1	C_6H_5-**1a**	C_6H_5-**2a**	2.30[b]	95[b], 92[d]	7, 19
			2.0[c]	96[c]	
2	3-$H_3CC_6H_4$-**1b**	3-$H_3CC_6H_4$-**2b**	2.45[b]	90[b]	7
			1.45[c]	92[c]	
3	4-$H_3CC_6H_4$-**1c**	4-$H_3CC_6H_4$-**2c**	2.15[b]	85[b]	7, 19
			1.45[c]	92[c]	
4	2-$H_3CC_6H_4$-**1d**	2-$H_3CC_6H_4$-**2d**	3.0[b]	75[b]	19
			2.30[c]	79[c]	
5	4-ClC_6H_4-**1e**	4-ClC_6H_4-**2e**	2.45[b]	93[b]	7, 19
			1.30[c]	95[c]	
6	2-ClC_6H_4-**1f**	2-ClC_6H_4-**2f**	3.0[b]	79[b]	7
			2.15[c]	83[c]	
7	4-BrC_6H_4-**1g**	4-BrC_6H_4-**2g**	2.45[b]	85[b]	23
			2.00[c]	89[c]	
8	3-$F_3CC_6H_4$-**1h**	3-$F_3CC_6H_4$-**2h**	2.30[b]	84[b]	23
			1.45[c]	89[c]	
9	4-$H_3CCOC_6H_4$-**1i**	4-$H_3CCOC_6H_4$-**2i**	2.45[b]	87[b]	19
			1.45[c]	89[c]	
10	2,4-$(H_3C)_2C_6H_3$-**1j**	2,4-$(H_3C)_2C_6H_3$-**2j**	2.30[b]	76[b]	23
			2.00[c]	82[c]	
			3.30[b]	71[b]	
11	2-$H_2NC_6H_4$-**1k**	 **2k**	3.00[c]	74[c]	23

[a] Yield refers to the pure isolated product.
[b] Under thermal conditions at 130 °C.
[c] Under ultrasound irradiation conditions at 45 °C.
[d] Yield after the third cycle.

Table 3 Comparison of $FeCl_3$–SiO_2 with AcOH, ionic liquid and $Yb(OTf)_3$ in synthesis of 1-phenyl-1*H*-1,2,3,4-tetrazole (**2a**)

Entry	Catalyst	Amine:orthoformate:sodium azide:catalyst mol %, reaction conditions	Time	Yield/%
1	AcOH	1:3:1.1:70 %, AcOH, reflux, recrystallisation	2.5 h	85
2	$Yb(OTf)_3$	1:1.2:1:20 %, $CH_3OC_2H_4OH$, 100 °C, recrystallisation	6 h	85
3	Ionic liquid	1:1.2:1:30 %, Ionic liquid, 100 °C, column chromatography	25 min	89
4	$FeCl_3$–SiO_2	2:2.4:2:20 %, Solvent-free, 130 °C, recrystallisation	90 min	95

Experimental

All reagents were purchased from the Merck and Aldrich chemical companies and used without further purification. Products were characterised by spectroscopy data (FT-IR, ^{1}H NMR and ^{13}C NMR spectra), elemental analysis (CHN) and melting points. The NMR spectra were recorded in DMSO and $CDCl_3$. ^{1}H NMR spectra were recorded on a Bruker Avance DRX 90 MHz instrument. The chemical shifts (δ) are reported in ppm relative to the TMS as internal standard and *J* values are given in Hz. ^{13}C NMR spectra were recorded at 22.5 Hz. FT-IR (KBr) spectra were recorded on a Perkin-Elmer 781 spectrophotometer. Ultrasonication was performed in a PARSONIC 2600s ultrasound cleaner with a frequency of 28 kHz and an output power of 50 W (Builtin heating, 20–70 °C thermostatically adjustable). Melting points were taken in open capillary tubes with a BUCHI 510 melting point apparatus and were uncorrected. The elemental analysis was performed using Heraeus CHN–O-Rapid analyser. TLC was performed on silica gel polygram SIL G/UV 254 plates.

Preparation of $FeCl_3$–SiO_2 catalyst[21]

Silica gel (10 g, 70–230 mesh) was added to a solution of ferric chloride hexahydrate (1.2 g) in acetone (16 mL), at room temperature. The solvent was evaporated under reduced pressure and the resulting yellow powder was kept under nitrogen at room temperature for further reactions.

Synthesis of the 1-aryl-1H-1,2,3,4-tetrazoles; typical procedure

$FeCl_3$–SiO_2 (0.02 g) was added to a mixture of amine (2 mM), NaN_3 (2 mM), triethyl orthoformate (2.4 mM) and stirred at 130 °C or sonicated in an ultrasonic cleaner water bath at 45 °C for the appropriate time (Table 2). After completion (as monitored by TLC), the reaction mixture was diluted with cold water (5 mL) and extracted with ethyl acetate (3×10 mL). The catalyst was removed by filtration and the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. After concentration, the product was crystallised from EtOAc–hexane to afford the pure product.

The products were characterised by spectroscopic methods, elemental analysis (CHN) and melting points and the physical data of known compounds were found to be identical with those reported in the literature.[7] ^{13}C NMR spectra displayed signals about δ = 147–157 ppm for C5 of tetrazole ring.[19]

1-Phenyl-1H-1,2,3,4-tetrazole (**2a**, *Table 2, entry 1*): M.p. 65–66 °C (lit: 64–65 °C)[7]; ^{1}H NMR (90 MHz, $CDCl_3$): δ = 7.39–6.99 (m, 4H), 8.21 (s, 1H).

1-(3-Methylphenyl)-1H-1,2,3,4-tetrazole (**2b**, *Table 2, entry 2*): M.p. 53–55 °C (lit: 53–54 °C)[7]; ^{1}H NMR (90 MHz, $CDCl_3$): δ = 2.30 (s, 3H), 6.82–7.19 (m, 4H), 8.19 (s, 1H).

1-(4-Methylphenyl)-1H-1,2,3,4-tetrazole (**2c**, *Table 2, entry 3*): M.p. 94–95 °C (lit: 93–94 °C)[7]; ^{1}H NMR (90 MHz, $CDCl_3$): δ = 2.30 (s, 3H), 6.92–7.27 (m, 4H), 8.16 (s, 1H).

1-(2-Methylphenyl)-1H-1,2,3,4-tetrazole (**2d**, *Table 2, entry 4*): M.p. 153–155 °C (lit: 153–155 °C)[22]; ^{1}H NMR (90 MHz, $CDCl_3$): δ = 3.38 (s, 3H), 6.88–7.17 (m, 4H), 7.87 (s, 1H).

1-(4-Chlorophenyl)-1H-1,2,3,4-tetrazole (**2e**, *Table 2, entry 5*): M.p. 156–158 °C (lit: 157–158 °C)[7]; ^{1}H NMR (90 MHz, $CDCl_3$): δ = 6.96 (d, *J* = 6.8 Hz, 2H), 7.28 (d, *J* = 6.7 Hz, 2H), 8.09 (s, 1H).

1-(2-Chlorophenyl)-1H-1,2,3,4-tetrazole (**2f**, *Table 2, entry 6*): M.p. 127–131 °C (lit: 127–131 °C)[22]; ^{1}H NMR (90 MHz, $CDCl_3$): δ = 7.10–7.44 (m, 4H), 8.07 (s, 1H).

1-(4-Bromophenyl)-1H-1,2,3,4-tetrazole (**2g**, *Table 2, entry 7*): M.p. 183–185 °C (lit: 183–185 °C)[22]; ^{1}H NMR (90 MHz, $CDCl_3$): δ = 6.90 (d, *J* = 8.7 Hz, 2H), 7.40 (d, *J* = 7.7 Hz, 2H), 8.07 (s, 1H).

1-(3-Trifluoromethylphenyl)-1H-1,2,3,4-tetrazole (**2h**, *Table 2, entry 8*): M.p. 125–127 °C (lit: 125–127 °C)[22]; ^{1}H NMR (90 MHz, DMSO–d_6): δ = 7.60–7.20 (m, 4H), 8.19 (s, 1H).

1-(4-Acetylphenyl)-1H-1,2,3,4-tetrazole (**2i**, *Table 2, entry 9*): M.p. 147–154 °C (lit: 147–154 °C)[22]; ^{1}H NMR (90 MHz, $CDCl_3$): δ = 2.59 (s, 3H), 7.09–8.00 (m, 4H), 8.29 (s, 1H).

1-(2,4-Dimethylphenyl)-1H-1,2,3,4-tetrazole (**2j**, *Table 2, entry 10*): M.p. 133–135 °C (lit: 133–135 °C)[22]; ^{1}H NMR (90 MHz, DMSO-d_6): δ = 3.33 (s, 1H), 6.95 (s, 3H), 7.81 (s, 1H).

1,1′-(1,2-Phenylene)bis(1H-1,2,3,4-tetrazole) (**2k**, *Table 2, entry 11*): M.p. 167–169 °C (lit: 167–169 °C)[22]; ^{1}H NMR (90 MHz, DMSO–d_6): δ = 7.12–7.69 (m, 4H), 8.30 (s, 1H).

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