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$FeCl_3$–SiO_2 as a reusable heterogeneous catalyst for the synthesis of 5-substituted 1*H*-tetrazoles via [2+3] cycloaddition of nitriles and sodium azide

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ABSTRACT

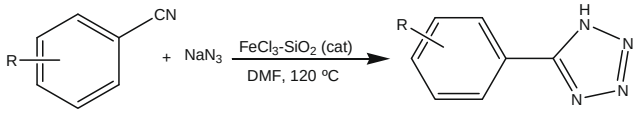
An efficient method for the preparation of 5-substituted 1*H*-tetrazole derivatives is reported using $FeCl_3$–SiO_2 as an effective heterogeneous catalyst. This method has the advantages of high yields, simple methodology, and easy work-up. The catalyst can be recovered by simple filtration and reused delivering good yields.

The growth of tetrazole chemistry over the last 25 years has been significant, mainly as a result of the roles played by tetrazoles in coordination chemistry as ligands, in medicinal chemistry as stable surrogates for carboxylic acids and in materials applications, including explosives, rocket propellants, and agriculture.[1–9] Tetrazoles can be used as isosteric replacements for carboxylic acids in drug design.[2] An advantage of tetrazolic acids over carboxylic acids is that they are resistant to many biological metabolic degradation pathways.[3] Another important application of tetrazoles is in the preparation of imidoylazides.[10] The conventional method of synthesizing tetrazoles is by addition of azide ions to organic nitriles or cyanamides.[11,12] Earlier reported methods for the synthesis of 5-substituted tetrazoles suffer from drawbacks such as the use of strong Lewis acids, or expensive and toxic metals, and the in situ-generated hydrazoic acid which is highly toxic and explosive.[13,14] Recently, Sharpless and co-workers reported a relatively simple, convenient, and safe procedure for the synthesis of tetrazoles by the addition of sodium azide to nitriles using stoichiometric amounts or 50 mol % of Zn(II) salts.[15] However, zinc(II) chloride or bromide being homogeneous Lewis acids it could not be recycled from the reaction mixture.

Several syntheses of 5-substituted tetrazoles have been reported through the [2+3] cycloaddition of nitriles using NaN_3 or $TMSN_3$ in the presence of catalysts such as $AlCl_3$,[16] $BF_3{\cdot}OEt_2$,[17] TBAF,[18] $Pd(PPh_3)_4$,[19] Zn/Al hydrotalcite,[20] ZnO,[21] and Cu_2O.[22]

An important objective of chemistry is to adapt classical processes so that pollution effects are kept to a minimum, with both reduction in energy and consumption of raw materials. Solid acid catalysts play a prominent role in organic synthesis under heterogeneous conditions. In general, solid acid catalysts are mainly based on clay[23] or silica.[24–27] In terms of convenience, silica-based catalysts are inexpensive, easy to prepare, and are insoluble in all organic solvents. Hence they can be recovered and recycled from reactions. Among various silica-based heterogeneous catalysts, $FeCl_3$–SiO_2 has advantages of low cost, ease of preparation and can be recycled.[25,26]

In continuation of our recent work on applications of heterogeneous reagents for the development of synthetic methodologies,[27] we report a new protocol for the preparation of 5-substituted 1*H*-tetrazoles from a wide variety of nitriles using $FeCl_3$–SiO_2 as a solid acid catalyst (Scheme 1). Silica-supported ferric chloride was prepared from the reaction of silica gel with anhydrous ferric chloride.[26i]



Scheme 1.

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Table 1
Preparation of 5-phenyltetrazole using varying amounts of $FeCl_3$–SiO_2 under thermal conditions at 120 °C[a]

Entry	$FeCl_3$–SiO_2 (g)	Solvent	Yield[b] (%)
1	0.15	DMF	81
2	0.11	DMF	80
3	0.10	DMF	80
4	0.09	H_2O	6
5	0.09	DMSO	79
6	0.09	DMF	80
7	0.07	DMF	76
8	0	DMF	0[c]

[a] Reaction conditions: nitrile (2 mmol), NaN_3 (3 mmol), $FeCl_3$–SiO_2 (0.09 g), DMF (6 mL), reaction time (12 h) at 120 °C.
[b] Isolated yield.
[c] In the absence of catalyst at 120 °C, no reaction occurred after 12 h.

First, we optimized the amount of $FeCl_3$–SiO_2 catalyst required in the reaction between benzonitrile and sodium azide (Table 1). Water was not a suitable solvent for this reaction. Not many organic solvents are stable at the high temperatures necessary for cycloaddition reactions (sometimes as high as 130 °C), and for this reason DMF is most commonly used for this purpose.[2,8,17,20,28] The optimum amount of $FeCl_3$–SiO_2 was found to be 0.09 g in the presence of nitrile (2 mmol) and sodium azide (3 mmol) in DMF (6 mL). We next examined a variety of structurally divergent benzonitriles possessing a wide range of functional groups to understand the scope and generality of the $FeCl_3$–SiO_2-promoted [2+3] cycloaddition reaction to form 5-substituted 1*H*-tetrazoles and the results are summarized in Table 2. The nature of the substituent on the benzonitrile did not affect the reaction time (Table 2, entries 1–7). Interestingly 1,4-dicyanobenzene (Table 2, entry 8) afforded the mono-addition product, whereas in the reaction between sodium azide and 1,4-dicyanobenzene in the presence of Zn(II) salts the double addition product was reported.[15] Reaction of the heteroaromatic nitrile, 3-pyridinecarbonitrile was complete at 120 °C after 5 h and gave the corresponding tetrazole in an excellent yield.

The $FeCl_3$–SiO_2 catalyst was recovered from the reaction mixture by simple filtration and was purified by washing the solid residue with water and ethanol followed by drying in an oven at 100 °C for 40 min. From each experiment, more than 98% of the $FeCl_3$–SiO_2 catalyst was recovered. The recovered catalyst was reused three times without any loss of activity (Table 2, entry 1).

Table 2
Preparation of 5-substituted 1*H*-tetrazoles in the presence of $FeCl_3$–SiO_2 by reaction between sodium azide and nitriles at 120 °C

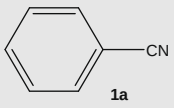
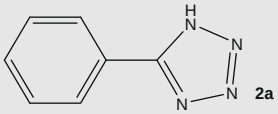
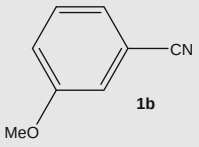
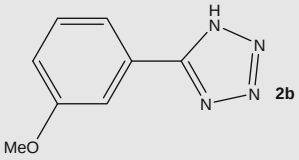
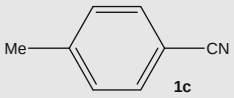
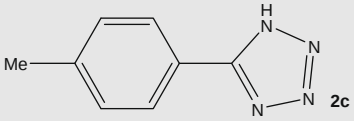
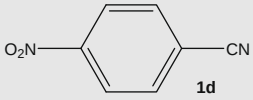
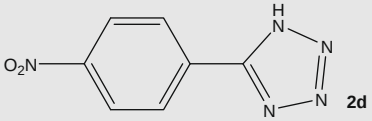
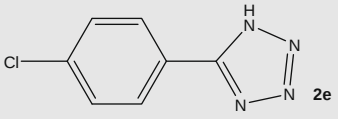
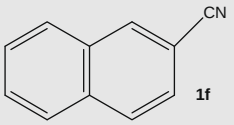
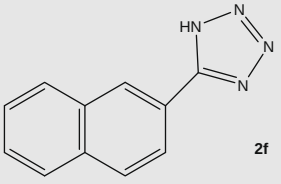
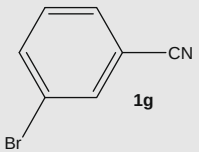
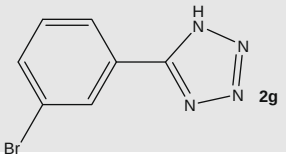
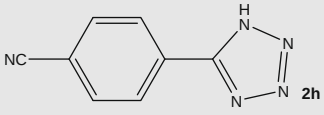
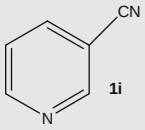
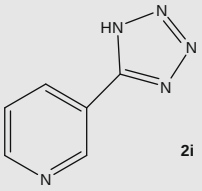
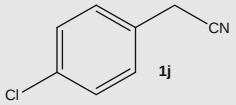
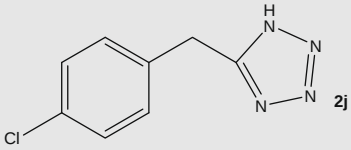
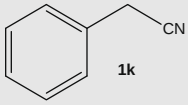
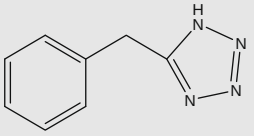
Entry	Substrate	Product	Time (h)	Yield[a] (%)	Ref.
1	 1a	 2a	12	79, 76[b]	11c,15a,18,20,21
2	 1b	 2b	12	78	18
3	 1c	 2c	12	78	11c,22
4	 1d	 2d	12	81	15a,18,22
5	 1e	 2e	12	77	20,21
6	 1f	 2f	12	82	15a,22
7	 1g	 2g	12	79	14

Table 2 (*continued*)

Entry	Substrate	Product	Time (h)	Yield[a] (%)	Ref.
8	 **1h**	 **2h**	20	80	20
9	 **1i**	 **2i**	5	83	18
10	 **1j**	 **2j**	24	65	20,21
11	 **1k**	 **2k**	24	67	11c,18,22

[a] Yield refers to pure isolated product.
[b] Yield after the third cycle.

The products were characterized by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy and from melting points. The disappearance of one strong and sharp absorption band (CN stretching band), and the appearance of an NH stretching band in the IR spectra, were evidence for the formation of 5-substituted 1*H*-tetrazoles.

In conclusion, we have developed a novel and highly efficient method for the synthesis of 5-substituted 1*H*-tetrazoles by treatment of nitriles with sodium azide in the presence of $FeCl_3$–SiO_2 as catalyst. The significant advantages of this methodology 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.

Preparation of $FeCl_3$–SiO_2 catalyst:[26i] To a solution of ferric chloride hexahydrate (1.2 g) in acetone (16 mL) was added silica gel (10 g, 70–230 mesh) at room temperature. The solvent was evaporated under the reduced pressure and the resulting yellow powder kept under nitrogen at room temperature for further reactions.[26i–m]

Preparation of 4-(1H-tetrazol-5-yl)benzonitrile (2 h); typical procedure: $FeCl_3$–SiO_2 (0.09 g) was added to 1,4-dicyanobenzene (2 mmol), sodium azide (0.2 g, 3 mmol), and distilled dimethylformamide (6 mL) and the mixture was stirred at 120 °C for 20 h (Table 2). After completion of the reaction (as indicated by TLC), the catalyst was removed by filtration and the filtrate was treated with ethyl acetate (35 mL) and 4 N HCl (20 mL) and stirred vigorously. The resultant organic layer was separated and the aqueous layer was extracted with ethyl acetate (25 mL). The combined organic layer was washed with water (8 mL) and concentrated to give a crude product. Column chromatography using silica gel gave pure product in 80% yield (entry 8). ^{1}H NMR (DMSO-d_6, 250 MHz): δ 7.76 (d, J = 7.3 Hz, 2H), 8.21 (d, J = 7.3 Hz, 2H), 10.96 (br s, 1H). All the products are known compounds and the spectral data and melting points were identical to those reported in the literature.

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