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A versatile and an efficient synthesis of 5-substituted-1*H*-tetrazoles

MADHUSUDANA REDDY MUTHUKUR BHOJE GOWD
and MOHAMED AFZAL PASHA*

Department of Studies in Chemistry, Central College Campus, Bangalore University, Bangalore 560 001, India
e-mail: m_af_pasha@ymail.com

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Abstract. A simple, efficient and a versatile method for the synthesis of 5-substituted-1*H*-tetrazoles by a [3+2]-cycloaddition reaction of arylnitriles with sodium azide in DMF using $ZrOCl_2 \cdot 8\ H_2O$ as catalyst has been developed. The reactions work well at 100°C and give the desired products in excellent yield. The examples studied include arylnitriles having electron donating as well as electron releasing groups on the arene nucleus.

Keywords. Tetrazoles; $ZrOCl_2 \cdot 8\ H_2O$; DMF; arylnitriles; sodium azide.

1. Introduction

Tetrazoles are a class of heterocycles that have received attention due to their wide range of applications.[1] In general, this nitrogen-rich ring system is used in propellants,[2] explosives,[3] and in pharmaceuticals.[4] In addition, tetrazoles are important synthons in synthetic organic chemistry,[5] and also used as precursors of carbenes in flash vacuum pyrolysis.[6] Various tetrazole-based compounds have also shown good coordination properties and are able to form stable complexes with several metal ions.[7] Furthermore, the tetrazole ring has strong electronwithdrawing property and tetrazolyl halides have been successfully used in organic synthesis as derivatising agents for the chemical modification of alcohols.[8]

One of the well-known methods of synthesis of 5-substituted-1*H*-tetrazoles is by a [3+2]-cycloaddition between hydrazoic acid and cyanides.[9] While hydrazoic acid is highly poisonous, explosive and low boiling liquid (~37°C); trialkyltin azide (used in the synthesis of tetrazoles) is also volatile and toxic reagent, and is not readily available.[10] Recently, methods using trimethylsilyl azide (TMS-N_3) are reported by Yamamoto *et al.*, for the synthesis of 5-substituted-tetrazoles;[11a] and 2-allylated-5-substituted-tetrazoles.[11b,c] Trimethylsilyl azide is also volatile and toxic reagent. More recently, CuO,[11d] triethylammonium chloride in nitrobenzene,[11e] $ZnCl_2$ and Tungstates[11f] have been reported for the promotion of this reaction.

In order to overcome the limitations, syntheses have been designed either to control the hydrazoic acid formation[12] or to use a large excess of azide ions in the presence of metal catalysts[13] or strong Lewis acids.[14] Overall, these procedures are less desirable due to the disadvantages of long reaction durations, low yield of products. The use of sodium azide as substrate in place of the hydrazoic acid or TMS-N_3 would be practically convenient. Zirconium compounds on the other hand, are reported as excellent catalysts for various organic reactions.[15] Among the various zirconium compounds, zirconyl chloride is most effective, relatively non-toxic,[16] inexpensive and non-sensitive to air. A wide range of applications of zirconyl chloride as a catalyst in organic synthesis are reported. Some of them include oxidation,[17a] acylation,[17b] esterification,[17c–e] nitration,[17f] Michael addition,[17g] Mannich-type reactions,[17h] Biginelli reaction,[17i] synthesis of 2-aliphatic aryloxazolines,[17j] synthesis of benzimidazoles,[17k] synthesis of benzothiazoles,[17l] and synthesis of *bis*-oxazolines.[17m] Recently, zirconyl chloride has been proved to be highly effective catalyst for the synthesis of β-acetamido ketones,[18a] enaminones and enamino esters,[18b] α-aminophospho-

*For correspondence

nates,[18c] homoallylic alcohols or amines[18d] and 1,8-dioxo-octahydroxanthenes.[18e]

In continuation of our work on the synthesis of biologically important compounds using simple, efficient, non-toxic and readily available catalysts,[19] we report herein the synthesis of 5-substituted-1*H*-tetrazoles by a [3+2]-cycloaddition reaction of arylnitriles with sodium azide in DMF using $ZrOCl_2 \cdot 8\ H_2O$ as a catalyst (scheme 1).

2. Experimental

2.1 *Materials*

All solvents and reagents were commercial and used without further purification unless otherwise stated. Nitrile (**1h**, table 1) was prepared from corresponding aldehyde as reported in the literature.[20]

2.2 *Apparatus*

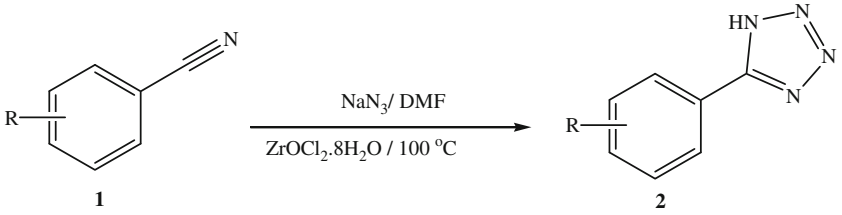
Melting points were determined on a Raaga, Chennai, India melting point apparatus. Nuclear magnetic resonance spectra were obtained on a Bruker AMX spectrophotometer in DMSO-d_6 at 400 MHz instrument. Chemical shifts are obtained in parts per million (δ) and are measured using tetramethylsilane (TMS) as reference. GC-MS spectra were obtained on a Shimadzu GC-MS QP 5050A (equipped with a 30 meter length and 0·32 mm of diameter BP-5 column with the column temperature 80–15–250°C). IR spectra were recorded on a Shimadzu FT-IR-8400s Spectrophotometer using KBr pellets and are reported as wave numbers (ν cm^{-1}).

2.3 *General procedure for preparation of 5-(4'-methoxyphenyl)tetrazole* **(2e)**

$ZrOCl_2 \cdot 8H_2O$ (10 mol%) is added to a mixture of 4-methoxybenzonitrile (0·266 g, 2 mmol), sodium azide (0·195 g, 3 mmol) in DMF (5 mL) and stirred at 100°C for 6 h. After completion of the reaction (TLC), the catalyst was separated by filtration, washed with ethyl acetate and the filtrate was taken into ethyl acetate (30 mL) and 5N HCl (20 mL) was then added and stirred vigorously. The organic layer was separated, and the aqueous layer was washed with ethyl acetate (20 mL), and the combined extract was washed with water, dried over anhydrous Na_2SO_4 and concentrated to get the crude crystalline 5-(4'-methoxyphenyl)-1*H*-tetrazole. Column chromatography was performed using silica gel (100–200 mesh) to afford pure product as white solid (0·316 g, 90%), mp = 230–232°C. IR (KBr, ν cm^{-1}) 3200–3300 (br), 1298, 1184, 1035, 750; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3·82 (3 H, s), 7·13 (2 H, d, J = 9·0 Hz), 7·95 (2 H, d, J = 9·0 Hz); GC-MS: m/z 175·1.

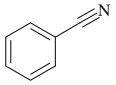
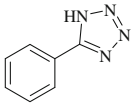
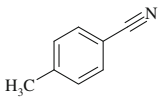
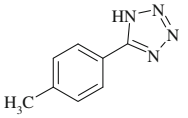
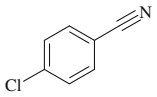
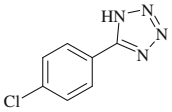
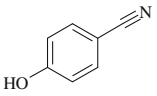
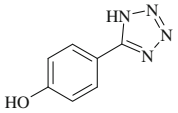
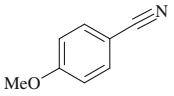
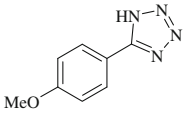
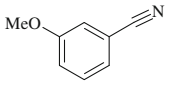
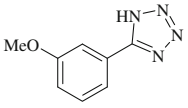
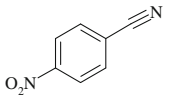
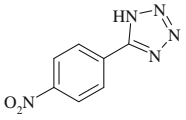
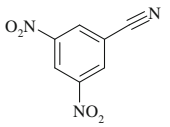
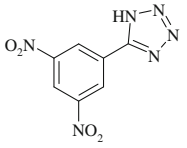
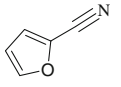
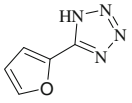
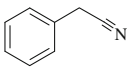
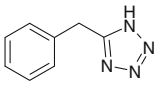
3. Results and discussion

In search of an effective catalyst and to optimize the experimental conditions, the reaction of 4-methoxybenzonitrile and sodium azide was considered as the model reaction, and various zirconium compounds were tested as catalysts. The best results were obtained by using 10 mol % of $ZrOCl_2 \cdot 8H_2O$ (table 2, entry **e**) in DMF as a solvent at 100°C after 6 h to get the respective product in 90% yield. Under similar conditions, other zirconium compounds such as ZrO_2, $ZrCl_4$ and $ZrO(ClO_4)_2 \cdot 6H_2O$ gave lower yields of tetrazole even after 10 h (table 2, entries **a–c**). Other metal catalysts such as $CuCl_2$, $FeCl_3$, $NiCl_2$ or $CoCl_2$ were also less effective in the promotion of this reaction (table 2, entries **f–i**). The effect of solvent on the formation of tetrazoles was also studied. Use of other solvents (other than DMF) such as DCM, MeCN and MeOH at reflux required longer time (20 h) to give the desired product in 30%, 61% and 45% yield respectively. The necessity to use the catalyst was realized by the observation that no product was detected when the reaction was carried out in the absence of any catalyst either at room temperature or at 100°C under neat conditions (table 2, entry **d**).



Scheme 1. Synthesis of 1*H*-tetrazoles from nitriles and catalytic $ZrOCl_2 \cdot 8H_2O$.

Table 1. Synthesis of tetrazoles from aromatic nitriles with sodium azide.

Entry	Nitrile(**1**)	Tetrazole(**2**)[a]	Time(h)	Yield(%)[b]
a			6	95
b			6·5	93
c			6	90
d			6	88
e			6	90
f			5	88
g			5·5	92
h			5	91
i			5	93
j			9	87

[a] All reactions were performed using a nitrile (2 mmol), sodium azide (3 mmol) and $ZrOCl_2 \cdot 8H_2O$ (10 mol%).
[b] Isolated yield; and All the compounds are known and physical properties agree with literature values [refs. 9–11].

Table 2. Effect of catalyst on the formation of 5-(4'-methoxyphenyl)-1*H*-tetrazole.

Entry	Catalyst[a]	Time(h)/Temp (°C)	Yield, **2e** (%)[b]
a	ZrO_2	10/100	43
b	$ZrCl_4$	10/100	52
c	$ZrO(ClO_4)_2 \cdot 6H_2O$	10/100	63
d	No Catalyst	20/rt	no product/ (10)[c]
e	$ZrOCl_2 \cdot 8H_2O$	6/100	90
f	$CuCl_2$	10/100	58
g	$FeCl_3$	10/100	66
h	$NiCl_2$	10/100	59
i	$CoCl_2$	10/100	44

[a] All reactions were performed using an 4-methoxybenzonitrile (2 mmol), sodium azide (3 mmol) and 10 mol% of catalyst in DMF (5 ml)

[b] yields are based on GC-MS analysis

[c] Reaction at 100°C without solvent and catalyst

To establish generality, the catalyst has been applied successfully for various arylnitriles with sodium azide and the results are presented in table 1. From table 1 it is clear that, excellent results were obtained with aryl, heteroaryl, arylmethyl nitriles. It can also be seen from this Table that, the reaction is compatible with various functional groups such as −Cl, $-OCH_3$, $-NO_2$ and −OH that do not interfere with the catalyst. However, benzylnitrile required longer reaction time when compared to other aldehydes (table 1, entry **2j**).

4. Conclusion

We have reported an efficient method of the synthesis of 5-substituted-1*H*-tetrazoles from various nitriles with sodium azide in the presence of catalytic amount of $ZrOCl_2 \cdot 8H_2O$. This method is applicable to a range of nitriles including aromatic, arylmethyl and heterocyclic nitriles. It has also been shown that, the yields are high and reactions completion time is within 5–9 h. The catalyst used is readily available and is environment friendly.

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