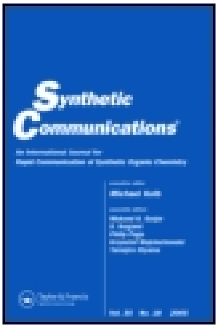

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Cadmium Chloride as an Efficient Catalyst for Neat Synthesis of 5-Substituted 1H-Tetrazoles

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Cadmium Chloride as an Efficient Catalyst for Neat Synthesis of 5-Substituted 1*H*-Tetrazoles

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Abstract: Cadmium chloride ($CdCl_2$) has been found to be an efficient catalyst for a neat [2 + 3]-cycloaddition of NaN_3 with nitriles to afford 5-substituted 1*H*-tetrazoles in good yields. The shorter reaction times, greater yields of the product, and easy workup are the advantages of this methodology.

Keywords: Cadmium chloride as efficient catalyst, good product yields, NaN_3, neat [2 + 3]-cycloaddition, shorter reaction times, 5-substituted 1*H*-tetrazoles

INTRODUCTION

Tetrazole chemistry has been largely associated with a broad spectrum of applications in pharmaceuticals, medicine, biochemistry, agriculture, and photography. Tetrazoles serve as effective ligands for a number of useful biochemical transformations and also as precursors for a wide variety of N-containing heterocycles.[1] Several tetrazoles are pharmaceutical agents, which act as a pharmacophores for the carboxylate group by increasing their utility. Although tetrazoles were discovered more than 100 years ago, a systematic examination of these compounds was initiated only in the latter half of the 20th century. Tetrazole was first prepared by the reaction of anhydrous hydrazoic acid and hydrogen cyanide under pressure. The reagents used in the basic method are highly toxic,

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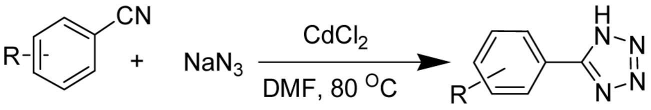
expensive, and water-sensitive. In particular, hydrazoic acid is not only highly toxic but also explosive and volatile. In view of these drawbacks, there has been an upsurge to modify the method of preparation of tetrazoles.[2–12] Su et al.[7] reported a series of 1-substituted 1*H*-1,2,3,4-tetrazoles synthesized in good yields from amines, triethyl orthoformate, and NaN_3 through a catalyzed reaction with $Yb(OTf)_3$. A series of primary alcohols and aldehydes were treated with I_2 in NH_3/H_2O under microwave irradiation to give the intermediate nitriles, which, without isolation, underwent [2 + 3]-cycloaddition with dicyandiamide and NaN_3 to afford the corresponding triazines and tetrazoles in high yields.[8] Katritzky and coworkers[9] suggested a general method for the synthesis of 1,5-disubstituted tetrazoles from imidoylbenzotriazoles under mild reaction conditions and shorter reaction times. A versatile and highly efficient $Zn(OTf)_2$-mediated one-pot synthesis of 1,5-disubstituted tetrazoles derivatives has been achieved by Hajra et al.[10] from alkenes, N-bromosuccinimide (NBS), nitriles, and trimethyl silyl azide ($TMSN_3$). Demko and Sharpless reported an innovative and safe procedure for the synthesis of tetrazoles by the addition of sodium azide to nitriles using stoichiometric amounts of Zn(II) salts in H_2O.[5] Amantini et al. efficiently synthesized tetrazoles by the addition of $TMSN_3$ to organic nitriles using 10 mol% Bu_4NF as catalyst.[6] Recently, Lakshmi Kantham et al.[11] have developed a simple and efficient method for the preparation of 5-substituted 1H-tetrazoles via [2 + 3]-cycloaddition using nano-ZnO as a heterogeneous catalyst. Various nitriles reacted with NaN_3 at 120–130°C to yield the corresponding 5-substituted 1*H*-tetrazoles with moderate to good yields. The catalyst could also be readily recovered and reused. Keith[12] has developed a single-step protocol, in which pyridine *N*-oxides were converted to tetrazolo[1,5-a]pyridines in good yield in the presence of sulfonyl or phosphoryl azides and pyridine by heating in the absence of solvent. Diphenyl phosphorazidate (DPPA) was the most convenient reagent. Smoleski et al.[13] developed an easy metal-mediated synthesis and isolation of 5-substituted tetrazoles using water-soluble azido- and derived tetrazolato-platinum(II) complexes with purified terephthalic acid (PTA) as catalyst. The reactions afforded good yields of end products.

Catalysis plays an ever-increasing role in pharmaceutical and industrial manufacturing because of process efficiency. $CdCl_2$ is an economically cheap Lewis acid used in a variety of reactions as an efficient catalyst.[14–16] Electron-deficient olefins undergo rapid aza-Michael reaction with a wide range of amines catalyzed by $CdCl_2$ at room temperature.[14] $CdCl_2$ is described as an efficient catalyst for a one-pot synthesis of 3,4-dihydropyrimidin-2-ones from a three-component Biginelli reaction of acetoacetate, aldehydes, and urea.[13] An improved



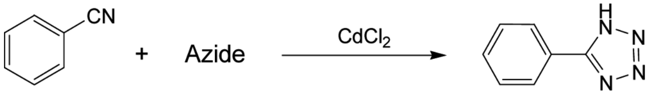
Scheme 1. Synthesis of 5-substituted 1*H*-tetrazoles catalyzed by $CdCl_2$.

safe method that does not contaminate the environment with cadmium chloride, a toxic heavy-metal salt, was developed for the synthesis of phosphatidylcholine.[14] However, to the best of our knowledge, $CdCl_2$ has not been employed as a catalyst for the synthesis of tetrazoles. In this communication, we report the synthesis of 5-substituted 1*H*-tetrazoles from a wide variety of organic nitriles with NaN_3 using $CdCl_2$ as a Lewis acid catalyst for the first time (Scheme 1).

RESULTS AND DISCUSSION

In an effort to develop a better catalytic system, various reaction parameters were screened for [2 + 3]-cycloaddition of benzonitrile with NaN_3 to yield 5-phenyltetrazole and are presented in Table 1. The solvent has a pronounced effect in these reactions (Table 1, entries 1–4), in which dimethylformamide (DMF) proved to be the best solvent to give good yields of the corresponding tetrazole, whereas dimethylsulfoxide (DMSO) and N-methylpyridine (NMP) provided moderate yields and H_2O gave poor yields of 5-phenyltetrazole. $TMSN_3$ is also used in the reaction with benzonitrile in DMF at about 80°C (Table 1, entry 5).

Table 1. Screening of reaction parameters for the formation phenyltetrazole[a]

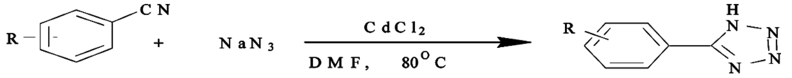


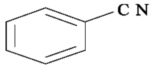
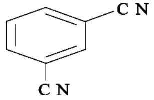
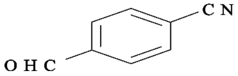
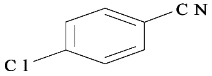
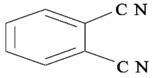
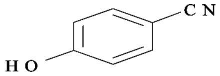
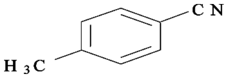
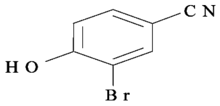
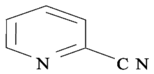
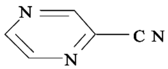
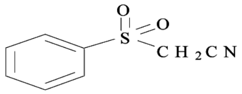
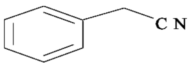
Entry	Solvent	Azide	Yield (%)[b]
1	Water	NaN_3	10
2	DMSO	NaN_3	26
3	NMP	NaN_3	29
4	DMF	NaN_3	91
5	DMF	$TMSN_3$	62

[a] Reaction conditions: Benzonitrile (1 mmol), NaN_3 (2 mmol), $CdCl_2$ (0.1 mmol), and DMF (5 mL); reaction time (6 h); 80°C.

[b] Yields of isolated products.

Table 2. $CdCl_2$-mediated preparation of 5-substituted 1*H*-tetrazoles[a]



Entry	Substrate	Time (h)	Yield (%)[b]
1		6	91
2		5	82
3		5	80
4		4	95
5		6	75
6		6	90
7		8	76
8		5	72
9		3	85
10		4	72
11		12	65
12		12	62

[a] Reaction conditions: Benzonitrile (1 mmol), NaN_3 (2 mmol), $CdCl_2$ (0.1 mmol), and DMF (5 mL) at 80–90°C.

[b] Isolated yields.

To clarify the scope and limitations of the $CdCl_2$-mediated [2 + 3]-cycloaddition reaction, various structurally divergent benzonitriles possessing a wide range of functional groups were reacted with NaN_3 to give the corresponding tetrazoles, and the results are summarized in Table 2. The various nitriles tested are aromatic, heteroaromatic, and benzylic; the aromatic benzonitrile gave moderate to good yields (Table 2, entries 1–11). 4-Chlorobenzonitriles provided the corresponding tetrazole with good yield, whereas 2-chlorobenzonitriles (not included in the table) gave slightly less yield compared to their paracounterpart. This might be due to a more pronounced steric effect of the chloro group at orthoposition. Compared with electron-withdrawing groups such as hydroxy, chloro, cyano, and formyl groups present on the aromatic ring (Table 2, entries 2–7), 4-formylbenzonitrile gave only 1*H*-tetrazole with carbonyl (aldehyde) functionality untouched (Table 2, entry 3). 1,2-Dicyanobenzene and 1,4-dicyanobenzene afforded mono addition product (Table 2, entries 2 and 5). Aliphatic nitriles such as 4-chlorophenyl acetonitrile, phenyl acetonitrile, and (phenylsulfonyl) acetonitrile provided moderate yields of corresponding tetrazoles with long duration of time (Table 2, entries 11 and 12). Heteroaromatic nitriles such as 2-pyridinecarbonitrile and cyanopyrazine gave the corresponding tetrazoles in shorter reaction times with excellent yields (Table 2, entries 9 and 10).

In conclusion, an efficient and clean method has been developed for the synthesis of 5-substituted 1*H*-tetrazoles via [2 + 3]-cycloaddition using an economically cheap $CdCl_2$ catalyst. A number of structurally divergent nitriles were used with NaN_3 in the reactions at 80°C to yield the corresponding 5-substituted 1*H*-tetrazoles with moderate to good yields. The methodology developed in this work may find widespread use for the preparation of 5-substituted 1*H*-tetrazoles in the field of organic synthesis.

EXPERIMENTAL

$CdCl_2$ was added (0.1 mmol) to a mixture of benzonitrile (1 mmol) and sodium azide (2 mmol) in DMF (5 mL) and stirred at 80°C for 6 h. After completion of reaction (as monitored by thin-layer chromatography, TLC), the reaction mixture was treated with ethyl acetate (30 mL) and washed with distilled water, and then the organic layer was treated with 5 N HCl (20 mL) and stirred vigorously. The resultant organic layer was separated, and the aqueous layer was again extracted with ethyl acetate (20 mL). The combined organic layers were washed with water and concentrated to give the crude solid crystalline 5-phenyltetrazole. Column chromatography was performed using silica gel (100–200 mesh) to afford pure 5-phenyltetrazole.

^{1}H NMR (200 MHz, $CDCl_3$ + DMSO) δ 8.04 (m, 2H), 7.61 (m, 3H); MS (70 eV) m/z (%) 146 (M^+, 12.65%), 118 (100%), 103 (13.94%), 91 (36.70%), 77 (30.37%), 63 (26.58%), 39 (17.72%).

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