J IRAN CHEM SOC (2012) 9:799–803
DOI 10.1007/s13738-012-0080-9

ORIGINAL PAPER

Ammonium acetate mediated synthesis of 5-substituted 1*H*-tetrazoles

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Received: 16 November 2011 / Accepted: 10 April 2012 / Published online: 24 April 2012

Abstract Synthesis of 5-substituted 1*H*-tetrazoles was achieved by [3+2] cycloaddition of nitriles and sodium azide in the presence of ammonium acetate. The reaction proceeds in situ formation of ammonium azide. Present protocol has advantage of good to excellent yields, short reaction times and simple isolation of products than reported methods.

Keywords 5-Substituted 1*H*-tetrazole · Nitrile · NaN_3 · Ammonium acetate · [3+2] Cycloaddition

Introduction

Tetrazoles are valuable heterocycles having wide range of applications [1, 2] in the field of material science including photography, information recording system and explosives. They behave as metabolically stable surrogates for carboxylic acid groups [3], important precursors for variety of nitrogen containing heterocycles and in coordination chemistry as ligands [4, 5]. Several syntheses of 5-substituted 1*H*-tetrazoles have been reported through [3+2] cycloaddition of nitriles and sodium azide. Recently, Sharpless and co-workers [6–8] reported a "click" chemistry approach for the synthesis of tetrazoles by [3+2] cycloaddition of nitriles and NaN_3 using stoichiometric amounts or 50 mol% of Zn(II) salts, but still requires tedious time consuming steps such as removal of zinc salts from acidic products. Earlier reported methods for the synthesis of 5-substituted 1*H*-tetrazole suffer from drawback such as the use of strong lewis acids or expensive and toxic metals. In order to overcome these difficulties, several pathways have been developed such as use of metal complexes [9, 10] as a catalyst, use of $TMSN_3$–TBAF [11], micellar media and ionic liquids [12, 13], $FeCl_3$–SiO_2 [14], Zn/Al-hydrocalcite [15], Fe_2O_3 [16], Zn hydroxyapatite [17], Sb_2O_3 [18], $NaHSO_4{\cdot}SiO_2$ or I_2 [19], $CuFe_2O_4$ [20], mesoporous ZnS nanospheres [21], use of clay-montmorillonite K-10, kaoline [22], use of various azide salts [23], microwave irradiation [24], $Et_3N{\cdot}HCl$ in nitrobenzene under microwave irradiation [25] and use of various amine salts in aromatic solvents [26]. However, some methods still require long reaction times to achieve reasonable yields and tedious purification of products.

An important objective of chemistry is to adopt classical process so that pollution effects are kept to a minimum with both reduction in energy and consumption of raw materials. Ammonium acetate is an example of salts having orthorhombic crystals that melts at low temperature. Quality like cheap and wide commercial availability, safe and easy handling, fair solubility in water and organic solvents, its nontoxic and ecofriendly nature makes ammonium acetate a popular reagent and effective alternative to gaseous ammonia [27]. In some cases, ammonium acetate shows excellent catalytic activities [28]. Ammonium acetate is an efficient reagent in low and high boiling organic solvents at room temperature as well as at refluxing condition. Its high efficiency as reagent in water, ionic liquid, microwave promoted solventless synthesis and supercritical water gives it a unique position in present scenario of green chemistry [27].

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Experimental

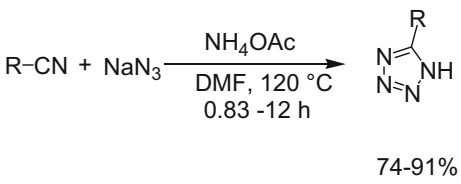
Materials

All reagents were purchased from Merck and Spectrochem and used without further purification. All yields refer to isolated products after purification. Products were characterized by comparing the physical data with those of authentic samples and spectroscopic (IR and NMR) data. The NMR spectra were recorded on a Bruker Avance-II spectrophotometer operating at 200 and 500 MHz instrument. The spectra were measured in DMSO relative to TMS (0.00 ppm). IR spectra were recorded on an IR affinity model-I spectrophotometer. Mass spectra were recorded on an LC–MS (Q-TOFF), LC operating at an ionization potential of 70 eV. Melting points were determined in open capillaries with a Lab Hosp melting point apparatus. TLC was performed on silica-gel polygram SILG/UV 254 plates.

General experimental procedure for synthesis of 5-substituted 1*H*-tetrazoles

To a mixture of nitrile (10 mmol) and NaN_3 (15 mmol) in DMF (20 mL), NH_4OAc (15 mmol) was added. The mixture was stirred at 120 °C for appropriate time until reaction was completed (monitored by TLC). Then reaction was allow to cool at room temperature, carefully acidified by 5 M HCl with stirring, then ice cold water added, the solid obtained was filter and washed with water, dried and purified by simple recrystallization in ethanol or water–ethanol. In case of entry 8, 9, 10 (Table 3), the reaction mass on acidification was extracted with ethyl acetate, washed with water thrice. Organic layer dried over anhydrous Na_2SO_4, on solvent evaporation affords product which further purified by simple recrystallization. All compounds are characterized by FTIR, ^{1}H NMR, ^{13}C NMR, and mass spectroscopy, and found to be in good agreement with the literature data. Spectroscopic data of selected compounds:

5-phenyl-1*H*-tetrazole (Table 3, entry 1): yield: 85 %; IR (KBr) cm^{-1} = 2,459–3,213, 1,564, 1,608, 727; ^{1}H NMR (200 MHz, DMSO-d_6): δ = 7.62–7.65 (m, 3H, aromatic), 8.07–8.09 (m, 2H, aromatic); ^{13}C NMR (500 MHz, DMSO-d_6): δ = 124.05, 126.96, 129.45, 131.31, 155.62; MS: m/z = 147 $(M+1)^+$.



Scheme 1 Ammonium acetate mediated synthesis of 5-substituted 1*H*-tetrazole

Table 1 Synthesis of 5-phenyl 1*H*-tetrazole under various reaction conditions at 120 °C

Entry	NaN_3 (mmol)	NH_4OAc (mmol)	Solvent	Time (h)	Yield[a] (%)
1	10	10	DMF	3	75
2	13	13	DMF	2.5	78
3	15	15	DMF	2.25	85
4	15	–	DMF	24	–
5	15	15	H_2O	12	–
6	15	15	DMSO	6	50
7	15	15	Acetic acid	16	20
8	15	15	THF	12	Trace
9	15	15	Ethanol	15	30
10	15	15	PEG-400	12	38
11	15	15	–	12	–

Reaction condition: benzonitrile (10 mmol)

[a] Isolated yield

Table 2 Synthesis of 5-phenyl 1*H*-tetrazole by various reported catalyst

Entry	Catalyst	Time (h)	Yield (%)
1	$ZnBr_2$ (in H_2O) [6]	24	76
2	$TMSN_3$–TBAF·$3H_2O$[11]	18	86
3	$FeCl_3$–SiO_2 [14]	12	79
4	Zn/Al hydrocalcite [15]	12	84
5	Fe_2O_3 [16]	36	81
6	Zn hydroxyapatite [17]	12	78
7	Sb_2O_3 [18]	08	86
8	$CuFe_2O_4$ [20]	12	82
9	NH_4Cl [23]	07	59.6
10	$(n\text{-}C_4H_9)_2NH_2Cl$ [23]	07	51.6
11	$C_6H_5NH_3Cl$ [23]	07	73.8
12	$(CH_3)_4NCl$ [23]	07	40.4
13	NH_4Cl [24]	15 min	96[a]
14	Et_3N·HCl [25]	02	93[b]
15	Et_3N·HCl [26]	08	96[c]

[a] Under N_2 atmosphere and microwave irradiation (20 W)

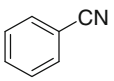
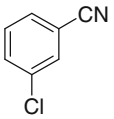
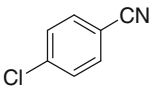
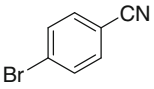
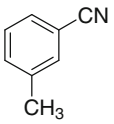
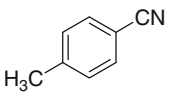
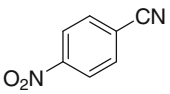
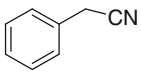
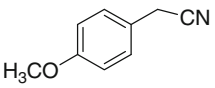
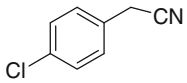
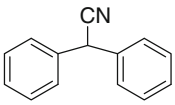
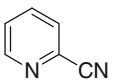
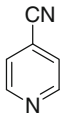
[b] Under microwave irradiation (75 W) in nitrobenzene

[c] Reactions were carried out in toluene

5-(4′-chlorophenyl)-1*H*-tetrazole (Table 3, entry 3): yield: 90 %; IR (KBr) cm^{-1} = 2,684–3,124, 1,610, 829, 744; ^{1}H NMR (200 MHz, DMSO-d_6): δ = 7.70 (d, 2H, J = 8.6 Hz, aromatic), 8.08 (d, 2H, J = 8.6 Hz, aromatic); ^{13}C NMR (500 MHz, DMSO-d_6): δ = 123.16, 128.70, 129.53, 135.94, 154.95; MS: m/z = 179 (M−1).

5-(3′-methylphenyl)-1*H*-tetrazole (Table 3, entry 5): yield: 87 %; IR (KBr) cm^{-1} = 3,338, 1,660, 1,598, 1,562,

Table 3 Synthesis of 5-substituted 1*H*-tetrazoles[a]

Entry	Substrate	Time (h)	Yield[b] (%)	M.p. (°C)	
				Found	Reported [Ref.]
1		2.25	85	218	217–218 [29]
2		0.83	89	140	138–139 [20]
3		1.5	90	254–256	250–252 [20]
4		2	84	267–268	268–269 [29]
5		2.5	87	152–153	–
6		3	91	250	251–252 [29]
7		1.5	84	218–220	219–220 [30]
8		8	87	121–123	123–124 [29]
9		8.25	82	163	–
10		4	82	162	160–162 [29]
11		12	74	165–166	165–166 [29]
12		1.5	78	209–210	208–210 [22]
13		1.25	83	257	254–258 [22]

[a] Reaction was carried out with nitrile (10 mmol), NaN_3 (15 mmol), ammonium acetate (15 mmol) in 20 mL of DMF at 120 °C

[b] Isolated yield

798; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 2.42$ (s, 3H), 7.43–7.89 (m, 4H, aromatic); ^{13}C NMR (500 MHz, DMSO-d_6): $\delta = 20.90$, 124.12, 127.39, 129.35, 131.93, 138.89, 155.32, 166.52; MS: $m/z = 160$ $(M)^+$.

5-(4′-methylphenyl)-1*H*-tetrazole (Table 3, entry 6): yield: 91 %; IR (KBr) $cm^{-1} = 2{,}476$–$3{,}082$, 1,614, 820; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 2.39$ (s, 3H), 3.60 (brs, 1H), 7.42 (d, 2H, $J = 8$ Hz, aromatic), 7.93 (d, 2H, $J = 8$ Hz, aromatic); ^{13}C NMR (500 MHz, DMSO-d_6): $\delta = 21.02$, 121.15, 126.87, 129.96, 141.32, 155.17; MS: $m/z = 161$ $(M+1)^+$.

5-(4′-chlorobenzyl)-1*H*-tetrazole (Table 3, entry 10): yield: 82 %; IR (KBr) $cm^{-1} = 2{,}480$–$3{,}116$, 1,585; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 4.31$ (s, 2H), 7.32 (d, 2H, aromatic), 7.41 (d, 2H, aromatic); ^{13}C NMR (500 MHz, DMSO-d_6): $\delta = 28.18$, 128.66, 130.62, 131.78, 134.81, 155.12; MS: $m/z = 195$ $(M+1)^+$.

5-benzhydryl-1*H*-tetrazole (Table 3, entry 11): yield: 74 %; IR (KBr) $cm^{-1} = 2{,}455$–$3{,}103$, 1,566, 1,496, 725; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 5.98$ (s, 1H), 7.20–7.40 (m, 10H, aromatic); ^{13}C NMR (500 MHz, DMSO-d_6): $\delta = 45.73$, 127.27, 128.40, 128.75, 140.00, 158.10; MS: $m/z = 236$ (M^+).

2-(1*H*-tetrazol-5′-yl) pyridine (Table 3, entry 12): yield: 78 %; IR (KBr) $cm^{-1} = 2{,}466$–3109, 1,639, 1,558; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 3.87$ (s, 1H), 7.73–8.90 (m, 4H, aromatic); ^{13}C NMR (500 MHz, DMSO-d_6): $\delta = 122.64$, 126.17, 138.31, 143.70, 150.12, 154.84; MS: $m/z = 148$ $(M+1)^+$.

Results and discussion

The aim of study was to find a protocol for synthesis of tetrazoles that has advantages of previous procedures including good yields in short reaction times, versatility and easy isolation of product without column chromatography. For optimization of reaction condition, we synthesized 5-phenyl 1*H*-tetrazole under various reaction conditions (see Scheme 1; Table 1) and the DMF found to be the best solvent regarding to yield. The quantity of NaN_3 and ammonium acetate used also has effect on yields significantly (Table 1). In order to check the efficiency of this method, we compare our results with some literature methods in response with reaction time and yields (see Table 2). The best reaction condition was found at entry 3 (Table 1). In the absence of ammonium acetate (entry 4, Table 1), reaction does not proceed even at long reaction time confirms the role of ammonium acetate. Ammonium acetate may produce ammonium azide in situ by reaction of ammonium acetate and sodium azide making availability of azide ion for [3+2] cycloaddition with nitrile easily. The use of DMF as a stable solvent at high temperature does not allows the sublimation of ammonium azide even at longer reaction times, thereby increasing the overall safety of the procedure. The advantage of this method is a substantial decrease in reaction times compared with literature methods and easy isolation of product by acidification, making ammonium acetate as a better catalyst for these reactions.

We examined a variety of structurally divergent benzonitriles, possessing a wide range of functional groups to understand the scope and generality of ammonium acetate promoted [3+2] cycloaddition reaction using DMF as a solvent affording tetrazoles by complete conversion within 0.83–12 h (checked by TLC) with good to excellent yields. The effects of substituent on aromatic ring were found to be less significant. The reaction time increases for benzyl nitriles (entries 8–10, Table 3) due to the absence of electronic effect of aromatic ring. The heteroaromatic nitrile such as 2-pyridinecarbonitrile and 4-pyridinecarbonitrile (entries 12, 13, Table 3) gives desire product with 78 and 83 %, respectively, with short reaction time.

Conclusions

In conclusion, an efficient practical method has been developed for synthesis of 5-substituted 1*H*-tetrazoles which has combined advantages of short reaction time than previously reported methods, good to excellent yields, simple experimental setup and workup procedure and purification of products without column chromatography. Note that the procedure also be scaled up to 70 g of starting nitrile without decreasing the yield.

Acknowledgments The authors thank to DST and UGC, New Delhi for financial assistance.

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