Preparation of Tetrazoles from Organic Nitriles and Sodium Azide in Micellar Media

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An effective method for the preparation of 5-substituted tetrazoles from the corresponding nitriles in micellar media is described. It was demonstrated that almost quantitative yields of tetrazoles can be obtained if the amount of water-surfactant is optimized. The advantages of the methods presented over many others currently used are the simplicity, facility of isolation of tetrazole products and elimination of using relatively expensive solvents and reagents.

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Introduction.

The tetrazole ring is a 6π-azapyrrole type system. Chemically, it differs considerably from other azole systems. Two possible tautomeric forms exist with hydrogen on the N_1 and N_2 ring atoms. Tetrazole nitogens have a considerable amount of local electron density, which consequently leads to a wide range of stable metallic and molecular complexes [1]. Furthermore, the tetrazole ring possesses a strong electron-withdrawing inductive efffect (-I), which surpasses the weak mesomeric effect (+M); therefore, the ring is a deactivating group [2].

Several tetrazoles have more profound biological activity [3] than many similar organic compounds due to their extraordinary stability under metabolic conditions. Further enhancement of biological activity is observed in some molecules when the carboxylic acid group is substituted with the tetrazole ring. Tetrazole analogs of amino acids have p*K*a values which are quite similar to the corresponding amino acids. Infrared spectra of these aminotetrazole analogs of amino acids coincide with zwitterionic structure [4].

Certain tetrazole derivatives are explosive and may be used as rocket propellants [5]. Their metallic salts can be used in primers, though silver salts are hypersensitive to mechanical stimuli [6]. Nitro derivatives of tetrazoles are potential primary explosives that are usually categorized with lead azide [7]. Furthermore, tetrazoles and tetrazole derivatives can be used as synthons in the preparation of some valuable compounds. Recently, the utilization of *N*-acyltetrazoles as reactive intermediates for the preparation of carboxylic acid derivatives [8] and the transformation of tetrazoles into 1,3,4-oxadiazoles [9] was reported.

There are several methods for the preparation of the tetrazole ring, the majority involve the cyclization of $RC(N_3)$=NR derivatives [10]. For example, the heating of $RC(N_3)$=NOH with acyl chloride gives cyclization of the 1-(acyl)hydroxy-5-substituted tetrazole derivative. Cyclization can be achieved by changing the *p*H of the reaction media [11]. The addition of the azide anion to nitriles is the most common route for preparing 5-substituted tetrazoles [12]. The reaction actually proceeds in solutions of hydrazoic acid in hydrocarbon solvents such as benzene, toluene or xylene; sodium azide in acetic acid and alcohol requires prolongated time (4-7 days) [13]. The reaction is facilitated by the presence of strong electron-withdrawing groups on the organic nitriles. Thus, 5-trifluoromethyltetrazole is obtained in 75% yield by bubbling trifluoroacetonitile into a suspension of sodium azide in acetonitrile. The reaction is exothermic and is controlled by the rate of trifluoroacetonitrile addition [14]. If hydrazoic acid is used, care must be taken by monitoring the concentration of hydrazoic acid in the reaction mixture to avoid an explosion [15]. A substitute for hydrazoic acid is a mixture of sodium azide and ammonium chloride with dimethlylformamide as the solvent [16]. To avoid the direct use of hydrazoic acid, an alternative approach that may be employed is the use of sodium azide and tributyltin chloride as reagents [17]. Relatively good yields of aliphatic and aromatic tetrazoles were achieved from the corresponding nitriles and metal azides such as aluminum azide and tributyltin azide [18]. Trimethylsilyl azide in the presence of a catalytic amount of dibutyltin oxide, accompanying toluene as the solvent, reacts to afford alkyl and aryl nitriles in high yield; however, at least two equivalents of trimethylsilyl azide are required for reaction completion [19].

Results and Discussion.

Since tetrazole derivatives have proven valuable starting material for the preparation of other heterocycles such as oxadiazoles and furans, a simple and reliable method for the preparation of tetrazoles should be employed. In using dimethylformamide as the reaction solvent and heating the reaction mixture at 150° overnight, aromatic nitriles reacted to form the tetrazoles in high yields. When reacting less activated nitriles, the reaction time needs to be extended several more days. For example, the attempt to synthesize 5-heptyltetrazole from octyl cyanide and sodium azide plus ammonium chloride in dimethylformamide resulted in 70% completion.

Separating the product from the nitrile is a straight forward process. The tetrazole and nitrile are soluble in chloroform; fortunately, due to its acidic behavior, the tetrazole is separable from the nitrile through base-acid extraction. The separation is complete judging from ^1H nmr spectroscopy. Unfortunately, dimethylformamide is soluble in both chloroform and water. After multiple washings of the chlorofonn layer with water, the tetrazole still contained a considerable amount dimethylformamide. After evaporation of chloroform, a portion of dimethylformamide can be eliminated by high vacuum rotary evaporation, although approximately 10-15% seems to be residual. A similar problem was noted when tetrazoles were prepared from activated alkyl nitrites [14]. To resolve this problem, the reaction was attempted in several solvents, which allowed the temperature to be elevated to the degree necessary to enhance the reaction of inactivated nitriles [16]. For instance, since formamide and ethylene glycol are less soluble in chloroform than dimethylformamide, their separation from the product is easier; however, the yield of the reaction is considerably decreased (to ~5%). Considering that organic and inorganic reactants are combined, it is logical to introduce a micellar environment. Previous successes were experienced in performing organic reactions in micellar media [20]. Furthermore, our recent quantum mechanical calculations on azide addition to organic nitriles [21] demonstrate that the addition should go at relatively modest temperatures, if the organic nitriles are activated. Activated nitriles have a partial positive charge generated on the nitrile carbon atom. Electron-withdrawing substituents enhance the nitriles susceptibility to engage in cycloaddition with the azide anion.

Micellar environments should accommodate the necessary prerequisites for the cycloaddition; it is common media (solvent) for both organic nitriles and azide reactants (sodium azide and ammonium chloride). By nature, hexadecyltrimethylammonium bromide is acidic. Because of this characteristic, it should partially protonate the nitrile group and increase the partial positive charge on the nitrile carbon.

Finally, separating the product from the reaction mixture should be relatively facile. The major disadvantage of using a micellar media for this reaction is the rather low temperature permitted by the solvent. This may prolong the time required for practical completion of the reaction. Examples of tetrazoles synthesized by these methods are presented in Scheme 1. Two different methods of isolation of the tetrazole products from the reaction mixture can be employed based on their solubility in chloroform and reaction completion. Alkyl tetrazoles with structural type 4 usually require extended reaction time and produce low yields. They are soluble in chloroform or ethyl acetate and can be separated through acid-base extraction. When this procedure is used, it is important to initially acidify (*p*H~2) the reaction mixture. The unreacted nitrile and product are then extracted with the organic solvent. If the reaction mixture is first made basic, separating the aqueous layer from the organic layer is arduous and time consuming. Due to the very low reactivity of alkyl nitriles, only 5-15%, of the tetrazole products were isolated. Nevertheless, since the reactants are inexpensive, the procedure, product isolation, and purification are standard, this method is feasible for the preparation of alkyl tetrazoles in small quantities (Table 1).

Scheme 1

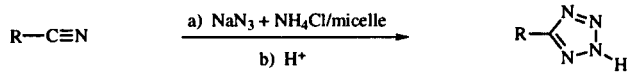

Table 1

Method of Preparation Yields and Melting Points for Tetrazoles Prepared in Micellar Media

Tetrazole	Method of Preparation	Yield (%)	mp (°C)	lit mp (°C)
5-phenyltetrazole	A	74	215.5-216.0	217.0-218.0 [24]
5-(2'-nitrophenyl)tetrazole	A	92	157.2-157.6	N/A
5-(3'-nitrophenyl)tetrazole	A	65	144.7-145.6	145.0 [22]
5-(4'-nitrophenyl)tetrazole	A	67	218.6-219.7	219.0 [23]
5-(3',5'-dinitrophenyl)tetrazole	A	85	177.8-178.3	N/A
5-(2'-methylphenyl)tetrazole	A	89	153.2-153.8	157.0-158.0 [24]
5-(3'-methylphenyl)tetrazole	A	75	149.8-150.0	152-152.5 [24]
5-(4'-methylphenyl)tetrazole	A	62	247.5-247.7	250.0-250.5 [24]
5-benzyltetrazole	B	34	123.2-124.0	125.6-126.0 [24]
5-(diphenylmethyl)tetrazole	B	66	164.2-165.2	165.0 [23]
5-octyltetrazole	B	7.5	41.0-42.0	41.5-42.5 [24]
5-(1'-naphthyl)tetrazole	B	87	199.4-199.7	N/A

This method seems appropriate for the preparation of aromatic tetrazoles. Because the products are usually insoluble in low polarity solvents such as choroform, a different isolation method should be used. The reaction mixture is cooled down and acidified (*p*H~2). The product, which precipitates upon acidification, is suction filtered washed several times with cold water and allowed to air dry. In many instances recrystallization is not necessary. Examples of tetrazoles prepared by these schemes are presented in Table 1. It is well documented that the ratio of water to surfactant for chemical reactions is very important in order to reach the critical micellar concentration. For instance, we have mentioned in Table 1 that the isolated yield for the preparation of 5-phenyltetrazole is 75% under the experimental conditions presented in procedure A. The yield of 5-phenyltetrazole was found to be inversely proportional to the amount of water in the reaction media. If the experiment is performed with twice the amount of reagents and surfactant as in procedure A and the amount of water is varied to 8, 12, 20 and 50 ml, the isolated yields of 5-phenyltetrazole are 99, 96, 60 and 45% respectively.

Conclusion.

In conclusion, it has been demonstrated that a micellar media might be a method of choice for obtaining 5-aryl-substituted tetrazoles. The preparation is simple and gives solvent free product in good yield. This is not true for the preparation of alkyl tetrazoles, in which poor yields were obtained.

EXPERIMENTAL

Mass spectra were recorded on a 70 eV gc-ms Hewlett Packard 5890 series II, ^{13}C (75 MHz) and ^{1}H nmr (300 MHz) spectra were recorded on a Gemini nmr spectrometer in dimethyl sulfoxide-d_6 as the solvent. Infared spectra were recorded on a Nicolet 550 FT-IR at 2 cm^{-1} resolution with potassium bromide plates. Thin layer chromatography (tlc) was performed on 0.2 mm silica gel 60 F254 plates from E. Kodak in a chloroform-petroleum ether mixture. Melting points (uncorrected) were determined on an Electrothermal IA 9000 Digital Melting Point Apparatus. Elemental analysis was performed by Atlantic Microlab, Inc., Norcross, Ga. All reagents and starting materials were obtained from Aldrich and used as such.

Procedure A. Preparation of 5-Phenyltetrazole.

Benzonitrile (2.5661 g, 24.88 mmoles) was combined with ammonium chloride (1.7860 g, 33.39 mmoles) and sodium azide (1.9837 g, 30.51 mmoles) and dodecyltrimethylammonium bromide as surfactant (0.3847 g, 1.25 mmoles), 5 ml waler was added and the mixture refluxed for 75 hours, 10 ml water was then added and the mixture was refluxed another 29 hours. The mixture was then removed from heat, allowed to cool to room temperature and 20 ml of water was added. It was acidified with 12*M* hydrochloric acid. The white precipitate, which appeared upon acidification, was suction filtered, slurried with cold water (3 x 100 ml) and allowed to air dry. The yield was (2.6819 g, 18.35 mmoles) (74%), (mp 215.5-216.0), >99% pure (gc); ir (potassium bromide); 3130, 3058, 2981, 2914, 2841, 2701, 2609, 2554, 2484, 1608, 1564, 1487, 1466, 1412, 1408, 1165, 1086, 1057, 1036, 1016, 993, 791, 725, 704 and 688 cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 7.87 (2H, *meta*), 7.27 (3H, *ortho* + *para* hydrogens); ^{13}C nmr (dimethyl sulfoxide-d_6): 153 (tetrazole carbon), 129, 127, 125 and 122 (benzene carbons); ms: m/z 77 ($C_6H_5^+$), 91 ($C_6H_5CH_2^+$), 105 ($C_6H_5CN^+$), 118 ($C_6H_5CN_2H^+$), and 146 ($C_6H_5CH_2CN_4H^+$, M^+).

Procedure B. Preparation of 5-Benzyltetrazole.

Benzyl cyanide (23.06 ml, 0.1995 mole) was combined with ammonium chloride (13.1 g, 0.245 mole) and sodium azide (14.8 g, 0.228 mole) in a 500 ml round bottom flask with a magnetic stirring bar; 100 ml of tap water and (0.5 g, 1.4 mmoles) of hexadecyltrimethylammonium bromide as a surfactant was added. An oil bath was maintained at 130° and the reaction mixture was refluxed while stirring for three days. After heating was

Table 2

Elemental Analysis for Some Tetrazoles Prepared in Micellar Media

5-(2'-nitrophenyl)tetrazole		
	Anal. Calcd. for $C_7H_5N_5O_2$ (191.15): [a]	C, 43.98; H, 2.64; N, 36.64
	Found:	C, 44.05; H, 2.70; N, 36.55
5-(3'-nitrophenyl)tetrazole		
	Anal. Calcd. for $C_7H_5N_5O_2$ (191.15): [b]	C, 43.98; H, 2.64; N, 36.64
	Found:	C, 43.80; H, 2.60; N, 36.93
5-(3',5'-dinitrophenyl)tetrazole		
	Anal. Calcd. for $C_7H_4N_6O_4$ (236.141): [a]	C, 35.60; H, 1.71; N, 35.59
	Found:	C, 35.64; H, 1.71; N, 35.46
5-(3'-methylphenyl)tetrazole		
	Anal. Calcd. for $C_8H_7N_4$ (160.18): [b]	C, 59.99; H, 5.04; N, 34.98
	Found:	C, 59.77; H, 5.05; N, 34.81
5-(1'-naphthyl)tetrazole		
	Anal. Calcd. for $C_{11}H_8N_4$ (196.213): [a]	C, 67.34; H, 4.11; N, 28.55
	Found:	C, 66.93; H, 4.11; N, 28.57

[a] New tetrazoles prepared with our method; [b] Tetrazoles previously prepared with elemental analysis not reported.

discontinued and the reaction mixture was allowed to cool to room temperature, cold water (100 ml) was added and the reaction mixture was acidified to *p*H~2 with 12*M* hydrochloric acid (**caution ammonia evolved**) and extracted with chloroform (4 x 50 ml). The chloroform layer was washed with 10% sodium hydroxide solution (4 x 50 ml). The combined water layers were acidified with 12*M* hydrochloric acid and extracted with chloroform (4 x 50 ml). The chloroform layers were combined, dried over magnesium sulfate and the chloroform was evaporated. The white crystalline residue was slurried in petroleum ether and suction filtered. The yield was (10.8 g, 0.067 mole) (34%) of 5-benzyltetrazole (mp 123.1-123.8°); ir (potassium bromide); 3150-2300 broad, 1549, 1533, 1494, 1458, 1074, 1056, 892, 715, 711, 696 and 673 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): 7.27 (5H, broad singlet, phenyl), 4.32 (2H, s, CH_2); ^{13}C nmr (dimethyl sulfoxide-d_6): 153 (tetrazole carbon), 134, 126.5, 126.3, 125 (phenyl carbon) and 27 (methylene carbon); ms: m/z 65, 77 ($C_6H_5^+$), 91 ($C_6H_5H_2^+$), 117 ($C_6H_5CH_2CN^+$), 132 ($C_6H_5CH_2CN_2H^+$), and 160 ($C_6H_5CH_2CN_4H^+$, M^+).

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