

Ultrasound-Promoted Regioselective Synthesis of 1-Aryl-5-amino-1*H*-tetrazoles

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Received: 24.08.2012; Accepted after revision: 05.10.2012

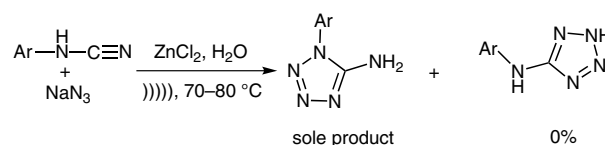
Abstract: A new method for the regioselective synthesis of 1-aryl-5-amino-1*H*-tetrazoles has been developed by the reaction of arylcyanamides with sodium azide using ZnCl₂ under ultrasound irradiation in excellent yields.

Key words: 1-aryl-5-amino-1*H*-tetrazole, cyanamide, sodium azide, ZnCl₂, sonochemical switching

Aminotetrazoles are important heterocyclic compounds from a biological point of view.¹ It is known that they have applications in the pharmaceutical arena,² as anticorrosive additives, as explosive and information recording systems,³ as ligands,⁴ and also as precursors to a variety of nitrogen-containing compounds.⁵ Aminotetrazoles have been reported as antiallergic and antiasthmatic,⁶ antiviral and anti-inflammatory,⁷ antineoplastic,⁸ and to have cognition disorder activities.⁹ For the synthesis of 1-substituted 5-amino-1*H*-tetrazoles, various methods have been reported including alkylation of 5-aminotetrazole with alkyl halides (which results in mixtures of isomers in very low yields),^{2,10} mercury(II)-promoted attack of an azide anion on a thiourea,¹¹ addition of a primary amine to cyanogen azide,¹² addition of hydrazoic acid to cyanamides (which often results in mixtures of 5-arylamino-1*H*-tetrazole and 1-aryl-5-amino-1*H*-tetrazole isomers),¹³ decomposition of 1-aryltetrazoles at –70 °C,¹⁴ and a three-step synthesis from aromatic amines via isolation of cyanamide intermediates in low yields in which *N*-arylureas and other byproducts were mostly formed.¹⁵ However, most of these synthetic methods suffer from different drawbacks such as employing toxic and volatile reagents such as hydrazoic acid and cyanogen bromide, harsh reaction conditions, complex catalysts or reagents, tedious isolation procedures, low yields, and formation of mixtures of isomers.

Therefore, it is desirable to develop more efficient and convenient methods for the regioselective synthesis of 1-substituted 5-amino-1*H*-tetrazoles without the application of hazardous reagents such as hydrazoic acid and cyanogen bromide.

To the best of our knowledge, ultrasound irradiation has not been used in the synthesis of tetrazoles so far. Due to our ongoing interest in heterocyclic chemistry and synthesis of the nitrogen-containing compounds,¹⁶ we wish to report a novel method for the regioselective synthesis of the 1-aryl-5-amino-1*H*-tetrazoles by reaction of aromatic cyanamides with sodium azide in the presence of ZnCl₂ under ultrasound irradiation (Scheme 1).



Scheme 1

ZnCl₂ in H₂O catalyzed the reaction of 4-nitrophenylcyanamide with sodium azide under ultrasonic irradiation, and 1-(4-nitrophenyl)-5-amino-1*H*-tetrazole was the sole product (Table 1). To study the combined effects of temperature and reaction times, additional experiments were performed in 40 °C, 60 °C, and 70–80 °C. The results shown in Table 1 clearly indicate that increasing the temperature and reaction time increases the yield.

Table 1 The Model Reaction at Different Temperatures and Reaction Times under Ultrasound Irradiation^a

Entry	Temp (°C)	Time (h)	Yield (%) ^b
1	r.t. ^c	5	30
2	40	5	41
3	60	5	52
4	70–80	8	63
5	70–80	15	79

^a Reaction conditions: 4-nitrophenylcyanamide (2 mmol), sodium azide (3 mmol), ZnCl₂ (2 mmol), H₂O (16 mL), 50 W, irradiation frequency 28 kHz (PARSONIC 2600s ultrasound cleaner).

^b Isolated yield.

^c Room temperature.

The ^1H NMR spectrum of the product showed one peak at $\delta = 7.19$ ppm indicative of the NH_2 functional group and confirmed the formation of 1-(4-nitrophenyl)-5-amino-1*H*-tetrazole.^{16b,f}

To study the effects of the nature of the substituents on the benzene ring of the cyanamide, various 1-aryl-5-amino-1*H*-tetrazoles were synthesized from different aromatic cyanamides containing both electron-releasing and electron-withdrawing groups with sodium azide in the presence of ZnCl_2 in high yields under ultrasound irradiation (Table 2). We showed that the nature of the substituent had no effect on the reaction time and nature of the product which is in contrast with our previous reports for the synthesis of aminotetrazoles using Lewis acids.^{16a,b,f,g,j,k}

Table 2 Formation of 1-Aryl-5-amino-1*H*-tetrazoles via Secondary Arylcyanamides

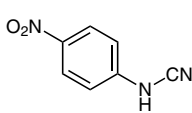
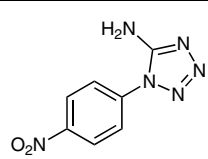
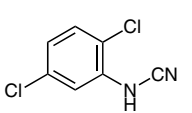
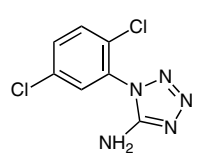
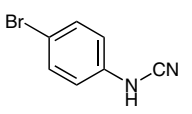
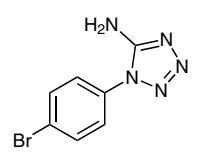
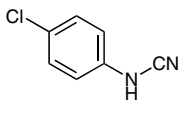
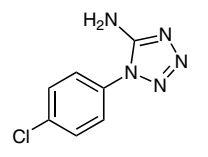
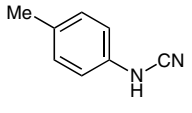
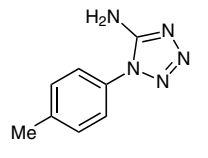
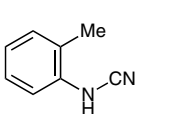
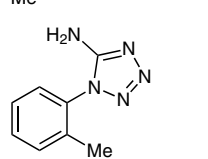
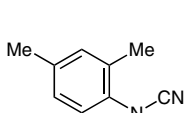
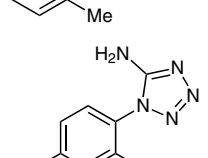
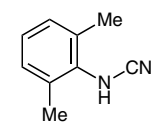
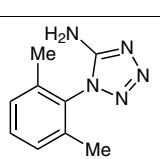
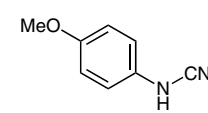
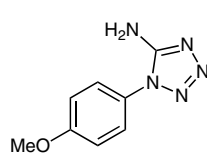
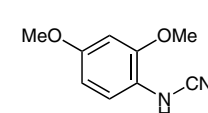
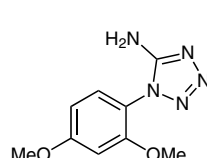
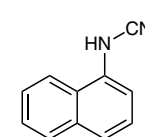
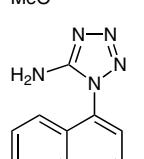
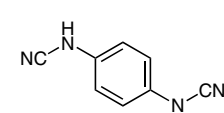
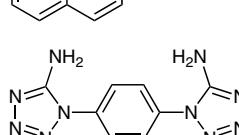
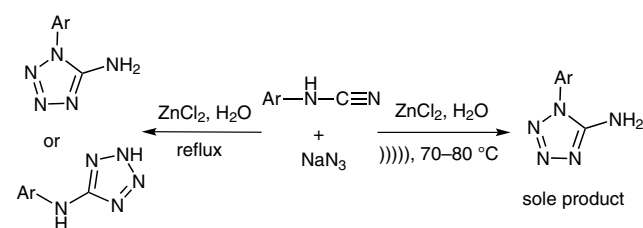
Entry	Cyanamide	Product	Yield (%) ^a
1			79
2			76
3			75
4			74
5			73
6			75
7			76

Table 2 Formation of 1-Aryl-5-amino-1*H*-tetrazoles via Secondary Arylcyanamides (continued)

Entry	Cyanamide	Product	Yield (%) ^a
8			77
9			79
10			76
11			78
12			80

^a Yields are after workup.

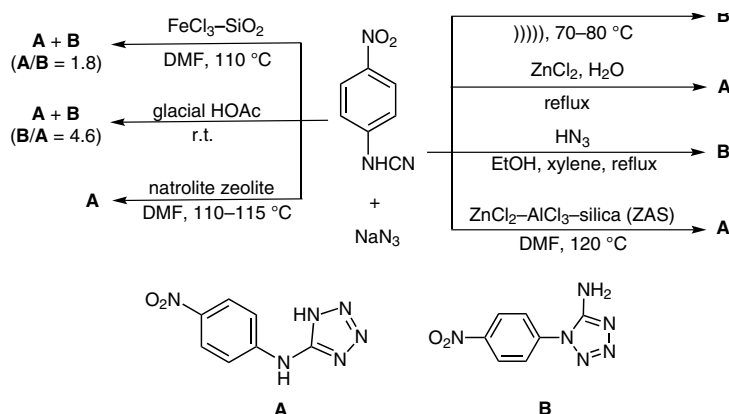
Under the same conditions but in the absence of sonication, the products are 1-aryl-5-amino-1*H*-tetrazoles or 5-arylamino-1*H*-tetrazoles depending on the nature of the substituents (Scheme 2).^{16f}



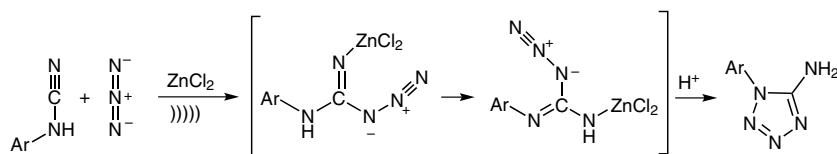
Scheme 2

As shown in Table 2, in contrast with previously reported methods using HN_3 ,¹³ AcOH ,^{16b} and $\text{FeCl}_3\text{-SiO}_2$,^{16g} in which a mixture of isomers was obtained, in our method, product formation was completely regioselective and solely 1-aryl-5-amino-1*H*-tetrazoles were obtained.

Interestingly, 4-nitrophenylcyanamide afforded 1-(4-nitrophenyl)-5-amino-1*H*-tetrazole (**B**, Table 2, entry 1), whereas by application of various Lewis acids, 5-(4-nitrophenyl)amino-1*H*-tetrazole (**A**) was obtained (Scheme 3). This result is in concordance with the synthesis of 1-(4-nitrophenyl)-5-amino-1*H*-tetrazole using hydrazoic acid¹³



Scheme 3



Scheme 4

or decomposition of 1-aryl- tetrazoles¹⁵ by consecutive ring opening, azidation, and intramolecular cyclization.

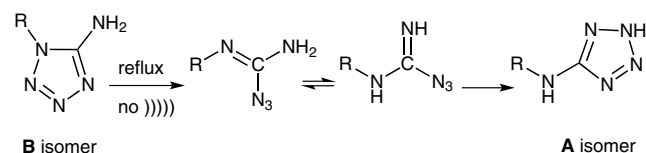
In addition, 2,5-dichlorophenylcyanamide (Table 2, entry 2) gave 1-(2,5-dichlorophenyl)-5-amino-1*H*-tetrazole, while with ZnCl_2 , Natrolite zeolite, $\text{ZnCl}_2/\text{AlCl}_3/\text{SiO}_2$, 5-(2,5-dichlorophenyl)amino-1*H*-tetrazole and with AcOH and $\text{FeCl}_3\text{-SiO}_2$, a mixture of isomers was obtained.

Compared to other procedures for the synthesis of 1-aryl-5-amino-1*H*-tetrazoles, the notable features of our method are: (1) The reaction system is simple; (2) organic solvents are not needed; (3) HN_3 , Brønsted acid, and organolithium reagents are not needed; (4) the yields of the products are high; (5) high reaction temperature and pressure are avoided; and (6) this method does not require column chromatography for the purification of products.

The mechanism of the reaction may originate from the nitrile group coordinating with ZnCl_2 and enhance its reactivity with sodium azide (Scheme 4) to yield a guanidine azide intermediate. However, the effect of ultrasound is not clear in this case, and further experiments are necessary to gain a clearer insight into these reactions. Herbst and Garbrecht have shown that cyanamides may be converted into aminotetrazoles using hydrazoic acid via the guanidine azide intermediate which often result in a mixture of isomers **A** and **B**, however.¹³

The 5-monosubstituted amino-1*H*-tetrazoles were synthesized before by thermal isomerization of 1-substituted 5-amino-1*H*-tetrazoles in boiling ethylene or melt state (180–200 °C).¹⁷ Furthermore, we have recently published an efficient synthesis of 5-arylamino-1*H*-tetrazoles in high yields from the corresponding cyanamides via isomerization of 1-aryl-5-amino-1*H*-tetrazoles over extended reaction times (ca. 20 h) in DMF at 120 °C.^{16j} In other

words, 5-arylamino-1*H*-tetrazoles **A** are the thermodynamic products which form in acidic environments or high temperatures via the guanidine azide intermediate using tetrazole ring opening. Generally, acidic environments and high reaction temperatures result in tetrazole ring opening and formation of 5-arylamino-1*H*-tetrazoles (**A** isomer).^{13,16b,f,i,j} This product is not depending on the nature of the substituent in the present method. In contrast, under reflux conditions,^{16f} it may be that ultrasound irradiation does not promote tetrazole ring opening and hence isomerization of 1-aryl-5-amino-1*H*-tetrazole (**B**, the kinetic product) to 5-arylamino-1*H*-tetrazole (**A**, the thermodynamic product, Scheme 5).



Scheme 5

In conclusion, we have developed an efficient and simple procedure for the synthesis of 1-aryl-5-amino-1*H*-tetrazoles under ultrasound irradiation. The applied procedure is regioselective and has the advantages of excellent yields, simple methodology, easy workup, and elimination of hazardous hydrazoic acid and cyanogen bromide.

General Experimental Procedure for the Synthesis of 1-Aryl-5-amino-1*H*-tetrazoles

A mixture of the appropriate arylcyanamide (2 mmol), NaN_3 (3 mmol), and ZnCl_2 (2 mmol) in H_2O (16 mL) was ultrasonicated for 15 h at 70–80 °C. The reaction mixture was cooled to 25 °C, the solid residue was filtered, washed with H_2O and treated with 3 M HCl

(4 mL). Crystallization was performed using aq EtOH to give the desired pure products.

The physical data (mp, IR, NMR) of known compounds were found to be identical with those reported in the literature.^{16a,d,f,j} Elemental analyses (CHN), IR, ¹H NMR, and ¹³C NMR data of the novel tetrazoles (Table 2, entries 1, 2, and 8) are given as below.

1-(4-Nitrophenyl)-5-amino-1H-tetrazole (Table 2, Entry 1)

White color; yield 79%; mp 187–188 °C (lit.^{17b} 185–187 °C). IR (KBr): 3390, 3290, 3230, 3125, 3010, 2860, 1647, 1608, 1592, 1573, 1520, 1510, 1464, 1415, 1381, 1344, 1312, 1291, 1180, 1127, 1105, 1071, 1033, 1009, 992, 863, 747, 732, 689, 555, 525, 505, 458 cm⁻¹. ¹H NMR (500 MHz, DMSO-*d*₆): δ = 8.43 (d, *J* = 7.2 Hz, 2 H), 7.91 (d, *J* = 7.2 Hz, 2 H), 7.19 (s, 2 H). ¹³C NMR (125 MHz, DMSO-*d*₆): δ = 154.9, 147.1, 138.6, 125.3, 124.6. Anal. Calcd for C₇H₆N₆O₂: C, 40.78; H, 2.93; N, 40.77. Found: C, 40.88; H, 3.01; N, 40.67.

1-(2,5-Dichlorophenyl)-5-amino-1H-tetrazole (Table 2, Entry 2)

White color; yield 76%; mp 260–262 °C. IR (KBr): 3325, 3170, 3095, 2900, 2820, 1648, 1576, 1481, 1450, 1394, 1301, 1251, 1136, 1093, 1073, 1024, 983, 878, 821, 817, 754, 730, 698, 678, 660, 584, 510, 498 cm⁻¹. ¹H NMR (500 MHz, DMSO-*d*₆): δ = 7.90–7.72 (m, 3 H), 6.97 (s, 2 H). ¹³C NMR (125 MHz, DMSO-*d*₆): δ = 155.7, 132.5, 132.2, 131.8, 131.7, 130.3, 130.0. Anal. Calcd for C₇H₃N₅Cl₂: C, 36.52; H, 2.17; N, 30.43. Found: C, 36.64; H, 2.20; N, 30.54.

1-(2,6-Dimethylphenyl)-5-amino-1H-tetrazole (Table 2, Entry 8)

White color; yield 77%; mp 147–149 °C. IR (KBr): 3430, 3295, 3070, 2955, 2915, 2850, 1650, 1601, 1586, 1538, 1474, 1440, 1376, 1349, 1260, 1217, 1160, 1114, 917, 869, 760, 700, 662, 636, 546, 516, 496 cm⁻¹. ¹H NMR (500 MHz, DMSO-*d*₆): δ = 7.03 (s, 3 H), 5.24 (s, 2 H), 2.25 (s, 6 H). ¹³C NMR (125 MHz, DMSO-*d*₆): δ = 157.5, 137.1, 136.6, 128.3, 126.3, 18.6. Anal. Calcd for C₉H₁₁N₅: C, 57.12; H, 5.86; N, 37.02. Found: C, 57.18; H, 5.90; N, 37.09.

Acknowledgment

We gratefully acknowledge the Bu-Ali Sina University for the support of this work.

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