Available online at www.sciencedirect.com
ScienceDirect
Chinese Chemical Letters 21 (2010) 892–896
CHINESE CHEMICAL LETTERS
www.elsevier.com/locate/cclet

Solvent-free preparation of arylaminotetrazole derivatives using aluminum(III) hydrogensulfate as an effective catalyst

Ferydoon Khamooshi, Ali Reza Modarresi-Alam *

Deparment of Chemistry, Faculty of Science, University of Sistan and Baluchestan, Zahedan, Iran

Received 24 November 2009

Abstract

An efficient and simple method for the preparation of 5-arylamino-1*H*-tetrazole and 1-aryl-5-amino-1*H*-tetrazole derivatives is reported using aluminum(III) hydrogensulfate ($Al(HSO_4)_3$) as an effective heterogeneous catalyst from secondary arylcyanamides. Generally, when the substitution in arylcyanamide is strongly electron-withdrawing the position of equilibrium would shift toward the isomer of 1-aryl-5-amino-1*H*-tetrazole (**B**) and as the electron-donating of substituent increased, the position of equilibrium is shifted toward the isomer of 5-arylamino-1*H*-tetrazole (**A**). The present methodology offers several advantages, such as excellent yields, short reaction times, easy work-up and greener conditions.

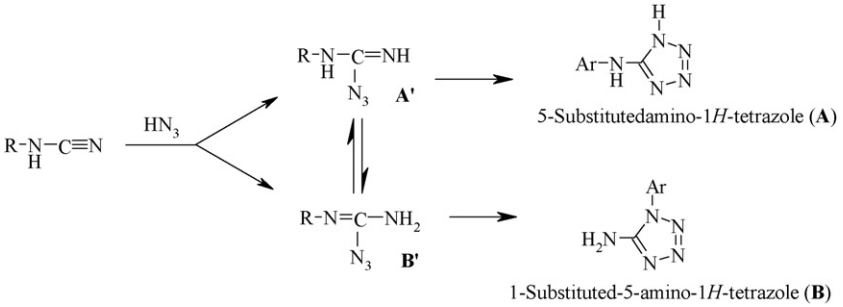
Keywords: 5-Arylamino-1*H*-tetrazole; 1-Aryl-5-amino-1*H*-tetrazole; Secondary arylcyanamide; Aluminum(III) hydrogensulfate ($Al(HSO_4)_3$); Heterogeneous catalyst; Solvent-free; Solid acid

The number of patent claims and publications related to medicinal uses of tetrazoles continue to grow rapidly and cover a wide range of applications [1,2]. They are currently used, for example, as a potential surrogate for *cis*-peptide linkage and carboxylic acids, as anticonvulsants and in cancer and AIDS treatment [2–7]. Tetrazoles are also applied in agriculture, as plant growth regulators, herbicides [1–8]. Tetrazoles also can play as explosives and rocket propellants [8–11]. Another important application of tetrazoles is the preparation of imidoylazides [12,13]. Recently, several synthesis of aryl and alkylaminotetrazoles have been reported using hydrazoic acid [14–16] and sodium azide under solution [17–19], Scheme 1. Congreve has reported two-step synthesis of 1-aryl-5-amino-1*H*-tetrazoles **B** from the corresponding 1-aryltetrazoles via cyanamide intermediate [20].

This reaction suffer from some drawbacks such as harsh reaction conditions, low temperatures (−70 °C), use of large excess of sodium azide and organolithium reagents making it fairly complicated and potentially dangerous. Vorobiov *et al*. published a three-step synthesis of 1-aryl-5-amino-1H-tetrazoles in low yields from the corresponding aromatic amines via isolation of intermediate cyanamides [21]. Unfortunately, this approach is not well developed due to insufficient stability of intermediate cyanamides. In most cases, *N*-arylureas and other by-products were mostly formed and the intermediate cyanamides were not stable enough to be isolated. Moreover, the above mentioned synthetic methods require the use of highly toxic and explosive hydrazoic acid. If hydrazoic acid is used, care must be taken by monitoring the concentration of hydrazoic acid in the reaction mixture to avoid an explosion [14–16,18,22].

* Corresponding author.
E-mail address: modaresi@chem.usb.ac.ir (A.R. Modarresi-Alam).

1001-8417/$ – see front matter
doi:10.1016/j.cclet.2010.03.008

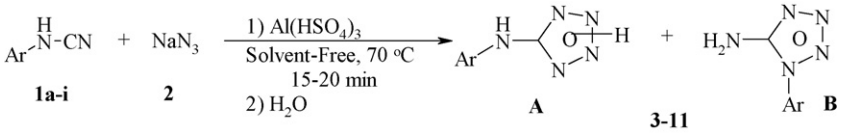


Scheme 1.

Due to safety considerations, we required a method that did not use hydrazoic acid or an azide source that produce hydrazoic acid in situ because of the associated hazards. Therefore, it is desirable to develop a more efficient and convenient methods for the synthesis of arylaminotetrazoles. In recent years, organic reactions on aluminum(III) hydrogensulfate ($Al(HSO_4)_3$) catalyst have received considerable attention in organic synthesis because of their ease of handling, enhanced reaction rates, greater selectivity, simple work-up [23]. We have recently reported synthesis of 5-arylamino-1*H*-tetrazole and 1-aryl-5-amino-1H-tetrazole from arylcyanamides in glacial acetic acid [24]. In continuation of our recent works on the application of heterogeneous reagents for the development of useful synthetic methodologies [25–27], herein we wish to report a new protocol for the preparation of arylaminotetrazole **3–11** derivatives from secondary arylcyanamides **1** using a amount of $Al(HSO_4)_3$ as a solid acid catalyst (Scheme 2 and Table 1). However, to the best of our knowledge there is not any report on synthesis of aminotetrazoles using of solid acid catalysts in solvent-free.

1. Experimental

All reagents were purchased from Merck and Aldrich and used without further purification. ^{13}C NMR and ^{1}H NMR spectra were recorded on Brucker using TMS as internal standard. Chemical shifts are reported in ppm, and coupling



Scheme 2.

Table 1
Synthesis of arylaminotetrazole derivatives **3–11** in the presence of $Al(HSO_4)_3$ by the reaction of sodium azide **2** and aromatic cyanamides **1** at 70 °C.

Entry	Cyanamide	Ar	Product (tetrazole)	Reaction time (min)	Ratio of isomers (**B/A**)[b]	Yield (%)[a]	M.p. (°C) of isomers [24]
1	**1a**	4-$NO_2C_6H_4$	**3A, 3B**	18	4.88	90 (17% **A**, 83% **B**)	**3a**: 218–220; **4a**: 187–188
2	**1b**	2,5-$Cl_2C_6H_3$	**4A, 4B**	20	2.03	83 (33% **A**, 67% **B**)	**4A**: 272–274; **4B**: 260–262
3	**1c**	2-ClC_6H_4	**5A, 5B**	17	1.94	86 (36% **A**, 64% **B**)	**5A**: 227–229; **5B**: 187–189
4	**1d**	4-BrC_6H_4	**6A, 6B**	20	1.33	82 (43% **A**, 57% **B**)	**3b**: 245–247; **4b**: 239–240
5	**1e**	4-$CH_3OC_6H_4$	**7A, 7B**	15	0.49	88 (67% **A**, 33% **B**)	**7A**: 200–202; **7B**: 211–213
6	**1f**	2,4-$(CH_3)_2C_6H_3$	**8A, 8B**	15	0.33	72 (75% **A**, 25% **B**)	**8A**: 190–192; **8B**: 196–198
7	**1g**	2,6-$(CH_3)_2C_6H_3$	**9A, 9B**	15	0.33	74 (75% **A**, 25% **B**)	**9A**: 245–247; **9B**: 146–149
8	**1h**	4-$CH_3C_6H_4$	**10A, 10B**	15	0.49	82 (67% **A**, 33% **B**)	**10A**: 202–204; **10B**: 176–178
9	**1i**	2-$CH_3C_6H_4$	**11A, 11B**	15	0.49	77 (67% **A**, 33% **B**)	**11A**: 201–203; **11B**: 192–194

[a] Yields refer to the pure isolated products.
[b] Determined by ^{1}H NMR analysis.

constants are reported in Hz. IR spectra were recorded on a Shimadzu 470 spectrophotometer. TLC was performed on Merck-precoated silica gel 60-F254 plates.

2. Caution

Although aminotetrazoles are kinetically stable and in most cases are insensitive to electrostatic discharge, friction, and impact, they are nonetheless energetic materials and appropriate safety precautions should be taken, especially when these compounds are prepared on a larger scale [9–11]. Hydrazoic acid is an unstable component which may decompose violently, forming nitrogen and hydrogen. Depending on the literature source, an explosive gas mixture can be formed with air or nitrogen above a concentration of more than 8–15% [22].

All of the products are known compounds and identified by comparison of some their spectral data (IR, ^{1}H and ^{13}C NMR) and physical properties with those of authentic samples [24,28]. All starting materials and solvents were purified with the proper purification techniques before use, when necessary [29]. The cyanamides **1** were prepared according to the literature [30].

2.1. General procedure for preparation of arylaminotetrazole derivatives *3–11* using $Al(HSO_4)_3$

A mixture of the cyanamide **1** (1 mmol), aluminum hydrogensulfate [23] (0.7 mmol) and sodium azide (1.5 mmol) was heated at 70 °C under solid-state conditions. The reaction mixture was stirred for the appropriate time (Table 1). The progress of the reaction was followed by TLC. After completion, the reaction mass was cooled to 25 °C, then water was added and the mixture stirred for 5 min. The solid residue was filtered from the mixture. The desired pure products was characterized by IR and NMR spectra [24]. As isomers **3–11B** were not soluble in spirit alcohol, they were separated from isomers **3–11A** via a simple procedure [24]. Isomers **3–11B** precipitated from spirit alcohol and were easily collected on filter paper. The filtrates contained a small amount of isomers **3–11B** and residue of isomers **3–11A**. The remaining isomers **3–11B** in the stock solution were precipitated and removed by adding EtOH/H_2O (3:1). The filtrate solution contained only isomers **3–11A**. Removing the solvents gave pure isomers **3–11A**.

3. Results and discussion

Aluminum(III) hydrogensulfate ($Al(HSO_4)_3$) as an effective heterogeneous catalyst was prepared from the reaction of anhydrous aluminum chloride with sulfuric acid [23].

In order to improve yield and due to the biological importance of aminotetrazole derivatives, we started to study this reaction by examining the different amounts of $Al(HSO_4)_3$ reagent to afford the product under thermal conditions where best results was obtained with a 0.7 mmol of $Al(HSO_4)_3$ and the optimized results depicted for 4-Br-phenylcyanamide in Table 2. Indeed, arylaminotetrazoles **3–11** were obtained from reaction of secondary arylcyanamides **1** with sodium azide **2** in the presence of $Al(HSO_4)_3$ as a solid acid at 70 °C for appropriated time in excellent yields, as summarized in Table 1. In order to include a reasonable range of electrical and steric effects the arylsubstituted cyanamides studied included various groups in *ortho*, *meta* and *para* positions. The reaction of arylsubstituted cyanamides resulted in mixture of isomers (**A** + **B**) (Table 1). Since isomers **B** were not soluble in spirit alcohol they were separated from isomers **A** via a simple procedure as described elsewhere [24]. As shown in Table 1, among the various cyanamides tested, electron-rich aromatic cyanamides reach completion at 70 °C after 15 min,

Table 2
Preparation of 4-Br drivative from the reaction of 4-Br-phenylcyanamide and sodium azide using variety amount of $Al(HSO_4)_3$ under solid-phase condition at 70 °C.

Entry	$Al(HSO_4)_3$ (mmol%)	Time (min)	Yield[a] %
1	33	70	75
2	38	62	81
3	42	40	84
4	60	19	90
5	70	19	91

[a] Isolated yield.

Table 3
Comparison effect of different catalysts in the synthesis of 5-(2-chlorophenyl)amino-1*H*-tetrazole (**5A**) and 5-amino-1-(2-chlorophenyl)-1*H*-tetrazole (**5B**).

Entry	Catalyst	Solvent	Time (min)	Temperture (°C)	Yield%
1	PPh_3	DMF	120	115	64
2	$FeCl_3$–SiO_2	DMF	120	115	75
3	SiO_2–$HClO_4$	–[a]	30	110	87
4	Al_2O_3–SO_3H	–[a]	30	110	88
5	Zeolite	DMF	95	115	81
6	Zeolite	H_2O	95	100	48
7	Zeolite	DMSO	95	115	80
8	LiCl	DMF	100	115	65
9	CH_3COOH[b]	CH_3COOH	24 h	25	86
10	$Al(HSO_4)_3$	–[a]	17	70	97

[a] Solvent-free.
[b] Glacial acetic acid as both solvent and proton donor source.

whereas electron-poor aromatic species require little higher times (compare entries **1–4** with **5–8** in Table 1). In addition, there is an excellent correlation between the effect of substitution on the benzene ring and the position of equilibrium. In other words, isomers ratio in tetrazoles **3–11** are under effect of type of substituents in arylcyanamide **1**. The detailed mechanism was described elsewhere so that tautomers **A** and **B** are formed via guanidine azide intermediates **A′** and **B′**, Scheme 1 [24].

Generally, when the substitution on aryl ring is strongly electron-donating the position of equilibrium would shift toward the isomer of 5-arylamino-1*H*-tetrazole **A** via guanidine azide intermediate **A′** (Table 1 and entries **5–8**) and as the electronegativity of substituent increased, the position of equilibrium is shifted toward the isomer of 1-aryl-5-amino-1*H*-tetrazoles **B** via guanidine azide intermediate **B′** (Table 1 and entries **1–4**). This is in contrast to the substituent effect on aryl ring of mechanism that was presented by Henry and coworkers for thermal isomerization [14]. All of the products are known compounds and identified by comparison of their spectral data (IR, ^1H and ^{13}C NMR) and physical properties with those of authentic samples [24,28]. Elimination of one strong and sharp absorption band (CN stretching band), and appearance of two absorption bands in the range of 3140–3550 cm^{-1} (NH stretching bands) in IR spectrum, confirmed the formation of arylaminotetrazoles. ^{13}C NMR spectra display signals for tetrazole ring carbons of arylaminotetrazoles in the range of 154–157 ppm (depending on the nature of the substituents in the amino functionality) [24,31]. To show the advantages of aluminum hydrogensulfate as a catalyst in comparison with other reported results in the literatures [24,32], we compared the reaction of $Al(HSO_4)_3$ with PPh_3, LiCl, SiO_2–$HClO_4$, Al_2O_3–SO_3H, zeolite, glacial acetic acid and $FeCl_3$–SiO_2 in the synthesis of 5-(2-chlorophenyl)amino-1*H*-tetrazole (**5A**) and 5-amino-1-(2-chlorophenyl)-1*H*-tetrazole (**5B**) with comparison effect of these different catalysts have been incorporated in Table 3. As shown in Table 3, aluminum hydrogensulfate is a better catalyst in the synthesis of arylaminotetrazole.

4. Conclusions

In conclusion, we have developed a novel and highly efficient method for the synthesis of various arylaminotetrazoles by the treatment of secondary arylcyanamides with sodium azide in the presence of $Al(HSO_4)_3$ as an effective catalyst. The significant advantages of this methodology are excellent yields, short reaction times, solvent-free reaction conditions, elimination of dangerous and harmful hydrazoic acid, simple work-up procedure and easy preparation and handling of the catalyst and no chromatographic separation is necessary to get the spectra-pure compounds.

Acknowledgment

The authors are thankful to Sistan and Baluchestan University Research Council for support of this work.

References

[1] R.N. Bulter, in: C.W. Ress, E.F.V. Scriven (Eds.), Comprehensive Heterocyclic Chemistry, vol. 4, Pergamon, Oxford, UK, 1996, pp. 621.
[2] R.J. Herr, Bioorg. Med. Chem. 10 (2002) 3379.
[3] R.R. Wexler, W.J. Greenlee, J.D. Irvin, et al. J. Med. Chem. 39 (1996) 625.
[4] S.C.S. Bugalho, E.M.S. Macoas, L.S. Cristiano, et al. Phys. Chem. 3 (2001) 3541, and references cited therein.
[5] A.R. Katritzky, C.W. Ress, Comprehensive Heterocyclic Chemistry, Pergamon Press, Oxford, 1984.
[6] A.R. Katritzky, C.W. Ress, E.F.V. Scriven, Comprehensive Heterocyclic Chemistry II, Pergamon Press, Oxford, 1996.
[7] Y. Tamura, F. Watanabe, T. Nakatani, et al. J. Med. Chem. 41 (1998) 640.
[8] B.S. Jursic, B.W. LeBlanc, J. Heterocyclic Chem. 35 (1998) 405.
[9] E.O. John, R.L. Kirchmeier, J.M. Shreeve, Inorg. Chem. 28 (1989) 4629.
[10] C.Z. Xu, X. Heming, Int. J. Quantum Chem. 79 (2000) 350.
[11] G. Steinhauser, T.M. Klapotke, Angew. Chem. Int. Ed. 47 (2008) 3330.
[12] A.R. Modarresi-Alam, H. Keykha, F. Khamooshi, et al. Tetrahedron 60 (2004) 1525.
[13] A.R. Modarresi-Alam, F. Khamooshi, Synth. Comun. 34 (2004) 129.
[14] W.G. Finnegan, R.A. Henry, E. Lieber, J. Org. Chem. 18 (1953) 779.
[15] W.L. Garbrecht, R.M. Herbst, J. Org. Chem. 18 (1953) 1014.
[16] W.L. Garbrecht, R.M. Herbst, J. Org. Chem. 18 (1953) 1003.
[17] P.Z. Demko, K.B. Sharpless, Org. Lett. 3 (2001) 4091.
[18] S. Wittenberger, J. Org. Prep. Proced. Int. 26 (1994) 499.
[19] A.R. Katritzky, B.V. Rogovoy, K.V. Kovalenko, J. Org. Chem. 68 (2003) 4941.
[20] (a) M.S. Congreve, Synlett (1996) 359;
(b) L.A. Flippin, Tetrahedron Lett. 32 (1991) 6857.
[21] (a) A.N. Vorobiov, P.N. Gaponik, P.T. Petrov, Vestsi Nats. Akad. Navuk Belarusi, Ser. Khim. Navuk (2003) 50;
(b) A.N. Vorobiov, P.N. Gaponik, P.T. Petrov, Chem. Abstr. 140 (2004) 16784g.
[22] J. Wiss, C. Fleury, U. Onken, Org. Proc. Res. Develop. 10 (2006) 349.
[23] (a) F. Shirini, M.A. Zolfigol, P. Salehic, et al. Curr. Org. Chem. 12 (2008) 183;
(b) F. Shirini, M.A. Zolfigol, M. Abedini, Bull. Chem. Soc. Jpn. 78 (2005) 1982;
(c) B.F. Mirjalili, M.A. Zolfigol, A. Bamoniri, et al. J. Braz. Chem. Soc. 16 (2005) 877;
(d) F. Shirini, M.A. Zolfigol, M. Abedini, Monatshefte fur Chem. 135 (2004) 279;
(e) F. Shirini, M.A. Zolfigol, M. Abedini, et al. Bull. Korean Chem. Soc. 24 (2003) 1683;
(f) P. Salehi, M.M. Khodaei, M.A. Zolfigol, et al. Bull. Chem. Soc. Jpn. 76 (2003) 1863;
(g) F. Shirini, M.A. Zolfigol, M. Abedini, et al. Mendeleev Commun. (2003) 265.
[24] A.R. Modarresi-Alam, M. Nasrollahzadeh, Turk J. Chem. 33 (2009) 267.
[25] A.R. Modarresi-Alam, M. Nasrollahzadeh, F. Khamooshi, ARKIVOC xvi (2007) 238.
[26] A.R. Modarresi-Alam, F. Khamooshi, M. Nasrollahzadeh, et al. Tetrahedron 63 (2007) 8723.
[27] A.R. Modarresi-Alam, M. Rostamizadeh, P. Najafi, Turk J. Chem. 30 (2005) 269.
[28] T. Schelenz, W. Schäfer, J. Prakt. Chem. 342 (2000) 197.
[29] (a) M. Casey, J. Leonard, B. Lygo, G. Procter, Advanced Practical Organic Chemistry, Chapman & Hall, Int. New York, 1990;
(b) W.L.F. Armarego, D.D. Perrin, Purification of Laboratory Chemicals, Butter worth-Heinmam, Oxford, 1996.
[30] R.J. Crutchley, M.L. Nakicki, Inorg. Chem. 28 (1989) 1955.
[31] I. Goljer, J. Svetlik, I. Hrusovsky, Monatshefte fur Chem. 114 (1983) 65.
[32] M. Nasrollahzadeh, D. Habibi, Z. Shahkarami, et al. Tetrahedron 65 (2009) 10715.