Monatsh Chem (2012) 143:925–930
DOI 10.1007/s00706-011-0670-8

ORIGINAL PAPER

Synthesis of arylaminotetrazoles by $ZnCl_2/AlCl_3$/silica as an efficient heterogeneous catalyst

Davood Habibi · Mahmoud Nasrollahzadeh

Received: 3 May 2011 / Accepted: 4 October 2011 / Published online: 17 November 2011

Abstract Arylaminotetrazoles were efficiently synthesized from secondary arylcyanamides by application of $ZnCl_2/AlCl_3$/silica as a reusable heterogeneous Lewis acid catalyst. 5-Arylamino-1*H*-tetrazoles can be obtained from arylcyanamides carrying electron-withdrawing substituents on the aryl ring, while with electron-releasing groups 1-aryl-5-amino-1*H*-tetrazoles will be produced. The former isomer is also produced within longer reaction times (~20 h) even with electron-releasing groups.

Keywords Arylaminotetrazole · Electron-releasing substituent · Electron-withdrawing substituent · Secondary arylcyanamide · Heterogeneous catalyst

Introduction

The chemistry of tetrazoles has gained increasing attention since the early 1980s [1]. Tetrazoles have a wide range of applications as lipophilic spacers and carboxylic acid surrogates in pharmaceuticals, as specialty explosives and information recording systems in materials, as ligands in coordination chemistry, and as precursors to a variety of nitrogen-containing compounds [2]. Furthermore, a range of aminotetrazoles have been reported as biologically active compounds [3, 4] and anticorrosive additives [5]. Nevertheless, the utility of these compounds is limited due to their insufficient synthetic availability.

Aminotetrazoles are conventionally synthesized by diazotation of aminoguanidine derivatives [6] or azidation of cyanamides [7, 8], carbodiimides [9], thioureas [10, 11], aminoiminomethanesulfonic acids [12], and benzotriazol-1-ylcarboximidamides [13]. 5-Amino groups can also be introduced into the tetrazole ring by nucleophilic substitution of the tetrazoles containing leaving groups in 5-position with the appropriate amines [14]. In addition, 5-(monosubstituted amino)-1*H*-tetrazoles were synthesized by thermal isomerization of 1-substituted 5-amino-1*H*-tetrazoles in boiling ethylene glycol or melt state (180–200 °C) [5, 8, 15].

These methods have disadvantages such as production of a mixture of isomers, i.e., 5-arylamino-1*H*-tetrazoles **3** and 1-aryl-5-amino-1*H*-tetrazoles **4** [7], application of hydrazoic acid, low yield, long reaction times, harsh reaction conditions, difficulty of work-up due to the application of homogeneous catalyst, use of expensive and toxic reagents, and in situ generation of hydrazoic acid.

In recent years great efforts have been devoted to the introduction and application of effective and safe heterogeneous acid catalysts [16, 17]. The high catalytic activity, low toxicity, recyclability, and particularly low price make the use of solid-supported reagents attractive alternatives to the conventional methods. It is strongly needed to develop a method without the application of a homogeneous system as well as avoiding the in situ generation of hydrazoic acid.

In the course of our researches on the synthesis of different heterocycles [18, 19] and applications of heterogeneous reagents [20], we report herein the synthesis of arylaminotetrazoles (**3a–3e** and **4f–4m**) from a wide variety of arylcyanamides **1a–1m** and sodium azide (**2**) in the presence of the $ZnCl_2/AlCl_3$/silica (ZAS) catalyst at

Electronic supplementary material The online version of this article (doi:10.1007/s00706-011-0670-8) contains supplementary material, which is available to authorized users.

D. Habibi (✉) · M. Nasrollahzadeh
Faculty of Chemistry, Bu-Ali Sina University, 6517838683 Hamedan, Iran
e-mail: davood.habibi@gmail.com

Scheme 1

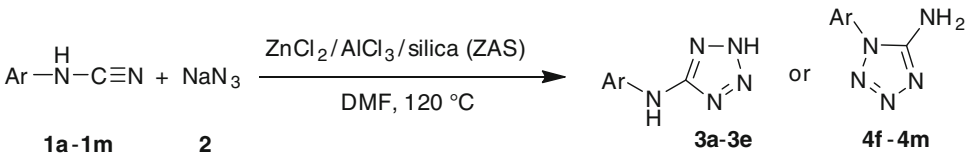
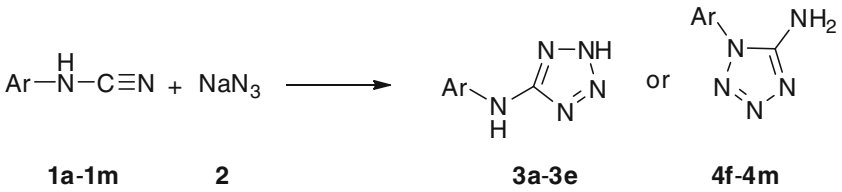


Table 1 Synthesis of arylaminotetrazoles



Entry	Ar	Product	Time/min	Yield/%[a]	M.p./°C (lit. m.p./°C) [Ref]
1	4-NO_2–C_6H_4–	**3a**	125	73	218–220 (218–220) [25]
2	2-Cl–C_6H_4–	**3b**	110	78	228–230 (228–230) [25]
3	2,5-Cl_2–C_6H_3–	**3c**	100	72	272–274 (272–274) [25]
4	4-Br–C_6H_4–	**3d**	100	77, 73[b]	249–250 (249–250) [25]
5	C_6H_5–	**3e**	80	70	215–217 (215–217) [25]
6	4-Cl–C_6H_4–	**4f**	110	78	217–219 (215–217) [8]
7	4-CH_3–C_6H_4–	**4g**	70	60	178–179 (175.5–177) [8]
8	2,4-$(CH_3)_2$–C_6H_3–	**4h**	65	70	199–201 (199–201) [25]
9	2-CH_3–C_6H_4–	**4i**	70	74	191–192 (191–192) [25]
10	1-Naphthyl	**4j**	70	75	220–221 (220–221) [25]
11	1,4-Phenylenebis	**4k**	35	77	264–266
12	4-CH_3O–C_6H_4–	**4l**	70	73	211–213 (211–213) [25]
13	2,4-$(CH_3O)_2$–C_6H_4–	**4m**	70	76	183–185 (183–185) [25]

[a] Isolated yield

[b] Yield after the third cycle

120 °C in DMF after appropriate times (Scheme 1; Table 1).

Results and discussion

To evaluate the efficiency of various reagents in the cycloaddition reaction, the activity of different catalytic systems was investigated in a model reaction between 2,5-dichlorophenylcyanamide (two equivalents) and sodium azide (three equivalents) at 120 °C. It was found that the ZAS catalyst was superior since the products are regiospecific, while a mixture of isomers was produced with the other reagents (Table 2).

Also, to optimize the yields, different amounts of ZAS were used for the synthesis of **3d** from the reaction of **1d** with **2**, the best result being obtained with 0.09 g ZAS (Table 2, entry 8).

As shown in Table 1, cyanamides having methyl as an electron-releasing group (entries 7–9) were completed at 120 °C after 65–70 min, while the species bearing the electron-withdrawing groups NO_2 or Cl (entries 1–3) require higher reaction times. The products were completely regiospecific. This observation is in contrast with those reports that the other reagents will often produce a mixture of isomers (Scheme 2) [7, 19].

The influences of various substituents in different *ortho*, *meta*, or *para* positions on the type of products were examined. The formation of isomers **3** or **4** is strongly influenced by the substituents in arylcyanamides **1** (Table 1). Generally, when the substituent on the aryl ring of **1** is electron-releasing, formation of 1-aryl-5-amino-1*H*-tetrazoles **4** is favored via the guanidine azide intermediate **B** (Table 1, entries 7–9, 12, and 13), while with electron-withdrawing substituents the product is shifted toward the formation of 5-arylamino-1*H*-tetrazoles **3** via the guanidine azide intermediate **A** (Table 1, entries 1–4). In the research carried out before, the nature of the substituent did not have any effect [2–5, 7, 8, 15, 21, 22]. No clear explanation was given by the previous workers about the isolation or

Table 2 Comparison of ZAS activity with other reagents in the synthesis of arylaminotetrazoles

Entry	Catalyst	Solvent	Time/min	Product	Yield/%[a]
1	PPh_3	DMF	120	**3** + **4**	75
2	LiCl	DMF	100	**3** + **4**	70
3	SiO_2-$HClO_4$	–[b]	25	**3** + **4**	85
4	Al_2O_3-SO_3H	–[b]	30	**3** + **4**	86
5	$Fe(HSO_4)_3$	–[b]	30	**3** + **4**	90
6	Glacial HOAc[c]		30 h[d]	**3** + **4**	87
7	ZAS (0.14 g)	DMF	100	**3**	77
8	ZAS (0.09 g)	DMF	100	**3**	77
9	ZAS (0.09 g)	DMSO	100	**3**	76
10	ZAS (0.08 g)	DMF	100	**3**	73
11	ZAS (0.07 g)	DMF	100	**3**	70
12	ZAS (0.06 g)	DMF	100	**3**	65

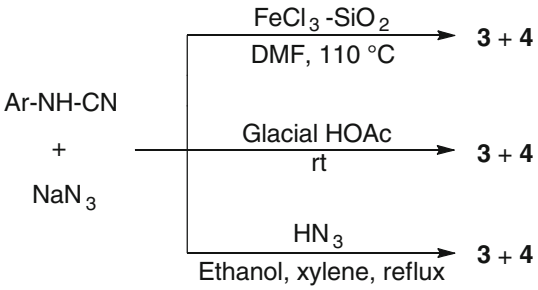
[a] Isolated yield

[b] Solvent-free

[c] Glacial acetic acid as both solvent and proton source

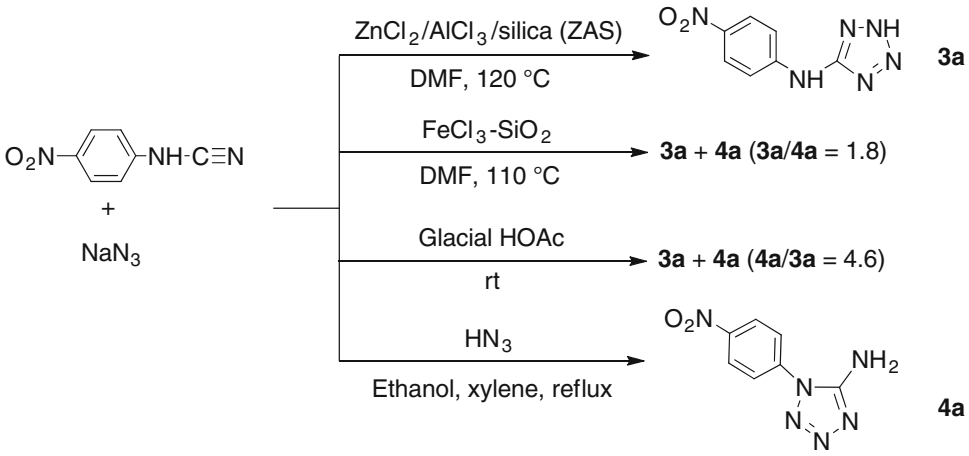
[d] Room temperature

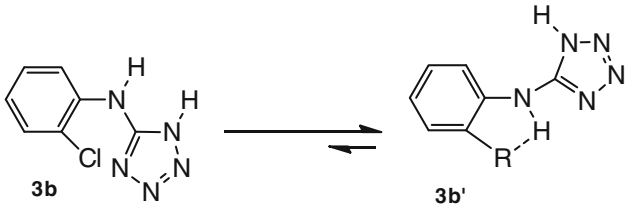
detection of other isomers, although Stolle and Heintz [11] reported the isolation of 5-anilinotetrazole in low yield from the reaction of phenylthiourea with lead oxide and sodium azide. In other words, in the synthesis of



Scheme 2

Scheme 3





Scheme 4

aminotetrazoles from cyanamides, only 1-aryl-5-amino-1*H*-tetrazole **4** or a mixture of isomers **3** + **4** was obtained [7, 19].

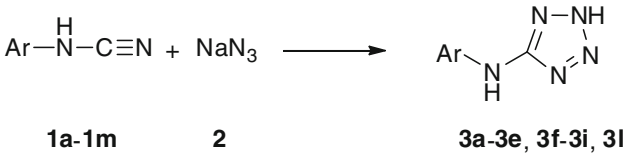
Due to presence of the two CN groups, **1k** (Table 1, entry 11) interestingly afforded the double-addition product. 4-Nitrophenylcyanamide (Table 1, entry 1) interestingly gave 5-(4-nitrophenylamino)-1*H*-tetrazole (**3a**), while with the methods reported before, 1-(4-nitrophenyl)-5-amino-1*H*-tetrazole (**4a**) or a mixture of isomers was obtained (Scheme 3).

According to Table 1, even though entry 6 has an electron-withdrawing group, the product (**4f**) is not the same as the products in entries 1–4 (**3a**–**3d**). This is in concordance with the report which was published before for the synthesis of aminotetrazoles using $ZnCl_2$ in water [18]. Formation of the 5-arylamino-1*H*-tetrazole isomer (**3b** and **3c** in Table 1) is probably favored through the intramolecular hydrogen bonding (Scheme 4) in **3b** (chlorine atom at *ortho* position) and **3c** (chlorine atom at *ortho* and *meta* positions).

The tendency towards formation of 5-arylamino-1*H*-tetrazoles **3** relative to 1-aryl-5-amino-1*H*-tetrazoles **4** increases as the reaction time is increased (Table 3). The isomer **3** is favored with longer reaction times (~20 h) even with electron-releasing groups (Scheme 5).

Substitution on the R group of monosubstituted guanyl azides will change the distribution of charge in the intermediate by induction or resonance effect. Electronegative

Table 3 Synthesis of arylaminotetrazoles at longer reaction times (~20 h)



1a-1m **2** **3a-3e**, **3f-3i**, **3l**

Entry	Ar	Product	Yield/ %[a]	M.p./°C (lit. m.p./°C) [Ref]
1	4-NO_2-C_6H_4-	**3a**	73	218–220 (218–220) [25]
2	2-Cl-C_6H_4-	**3b**	76	228–230 (228–230) [25]
3	2,5-Cl_2-C_6H_3-	**3c**	71	272–274 (272–274) [25]
4	4-Br-C_6H_4-	**3d**	75	249–250 (249–250) [25]
5	C_6H_5-	**3e**	73	215–217 (215–217) [25]
6	4-Cl-C_6H_4-	**3f**	74	226–228
7	4-CH_3-C_6H_4-	**3g**	75	201–203 (200.5–201) [8]
8	2,4-$(CH_3)_2$-C_6H_3-	**3h**	70	192–193
9	2-CH_3-C_6H_4-	**3i**	65	201–203
10	4-CH_3O-C_6H_4-	**3l**	76	200–202 (200–202) [8]

[a] Isolated yield

substitution will decrease the electron density around the nitrogen to which R is bonded, increasing the percentage of **A** and thus increase the amount of 5-arylamino-1*H*-tetrazoles **3**. Electropositive substitution exerts the opposite effect, increasing the percentage of **B** and so increasing the amount of 1-aryl-5-amino-1*H*-tetrazoles **4**. In other words, the distribution of isomeric tetrazoles **3** and **4** is probably a direct measurement of the distribution of the tautomeric guanyl azides **A** and **B** at equilibrium.

2-Methylphenylcyanamide (Table 1, entry 9) interestingly gave 1-(2-methylphenyl)-5-amino-1*H*-tetrazole (**4i**), while with HOAc and $FeCl_3$–SiO_2, 5-(2-methylphenylamino)-1*H*-tetrazole (**3i**) and a mixture of isomers were obtained, respectively (Scheme 6) [23].

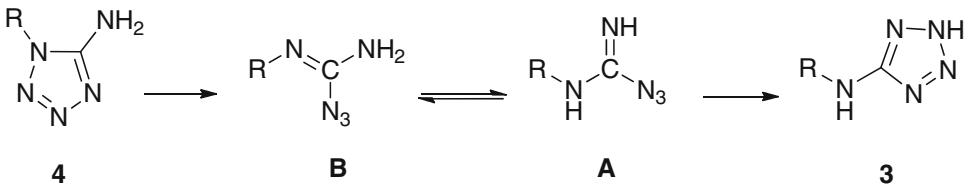
The isomers **3** and **4** have different chemical properties. 5-Arylamino-1*H*-tetrazoles **3** are acidic substances, while 1-aryl-5-amino-1*H*-tetrazoles **4** have basic properties due to their NH_2 functional group.

The mechanism of the catalysis may originate from the nitrile group coordinating with the surface of the solid acid. The solid acid is supposed to activate the nitriles and enhance their reactivity with sodium azide (Scheme 7). However, further experiments are necessary to gain a clearer insight into these reactions.

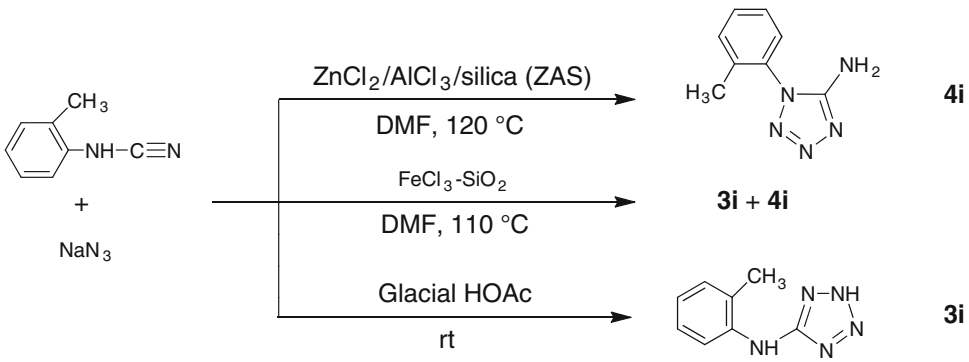
Conclusions

We developed an effective cyclization reaction of various cyanamides with sodium azide under thermal conditions in the presence of $ZnCl_2$/$AlCl_3$/silica (ZAS) as an effective heterogeneous catalyst. The significant advantages of this methodology are high yields, regiospecific products, short reaction times, elimination of dangerous and harmful hydrazoic acid, easy and simple work-up procedure, low cost, and easy preparation and handling of the catalyst. ZAS is an ecofriendly catalyst because it produces little waste and can be recovered by simple filtration and successively reused without significant loss of activity.

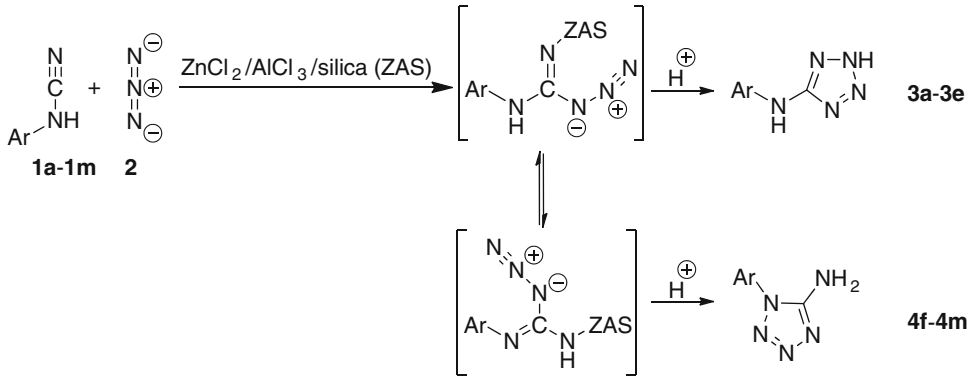
Scheme 5



Scheme 6



Scheme 7



Experimental

All reagents were purchased from Merck and Aldrich chemical companies and used without further purification. Products were characterized by infrared (IR), Fourier-transform (FT)-IR, ^{1}H and ^{13}C nuclear magnetic resonance (NMR), elemental analysis (CHN), and melting points. ^{1}H NMR spectra were recorded on Bruker Avance DRX 300- and 500-MHz instruments. NMR spectra were recorded in DMSO-d_6 and acetone-d_6. Chemical shifts (δ) are reported in ppm relative to tetramethylsilane (TMS) as internal standard. J values are given in Hz. ^{13}C NMR spectra were recorded at 125 and 75 MHz. IR (KBr) and FT-IR (KBr) spectra were recorded on Shimadzu 470 and PerkinElmer 781 spectrophotometers, respectively. Melting points were taken in open capillary tubes with a BÜCHI 510 melting point apparatus. The elemental analysis was performed using a Heraeus CHN-O-Rapid analyzer. Thin-layer chromatography (TLC) was performed on silica gel polygram SIL G/UV 254 plates. The cyanamides **1a**–**1m** were prepared according to the literature [24].

Caution! All reactions of azides and tetrazole compounds must be treated as potentially explosive and conducted behind a rigid safety screen.

General procedure for the preparation of $ZnCl_2/AlCl_3$/silica (ZAS)

Anhydrous $AlCl_3$ (1.27 g, 9.5 mmol) and 1.27 g $ZnCl_2$ (9.3 mmol) were added to 5.1 g silica gel (grade 60, 230–400, washed with 1 M HCl, and dried under vacuum at 80 °C for 72 h) in 50 cm^3 carbon tetrachloride. The mixture was stirred and refluxed for 2 days in the absence of light under N_2 atmosphere, filtered, washed with dry CCl_4, and then dried under vacuum at 70 °C for 5 h.

General procedure for the synthesis of arylaminotetrazoles using $ZnCl_2/AlCl_3$/silica

A mixture of arylcyanamide **1a**–**1m** (2 mmol), 0.2 g NaN_3 (**2**, 3 mmol), and 0.09 g ZAS in 7 cm^3 distilled DMF was heated up to 120 °C for the appropriate time (Table 1) and stirred. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to 25 °C and the catalyst was filtered and washed with water and ethanol. The solution was treated with 35 cm^3 ethyl acetate and 20 cm^3 4 N HCl and stirred vigorously. The resultant organic layer was separated, and the aqueous layer was again extracted with 25 cm^3 ethyl acetate. The combined organic layers were washed with water, concentrated, and washed with ethanol to give different arylaminotetrazoles. The physical data (m.p., IR, NMR) of known compounds were found to be identical to those reported in the literature [8, 18, 25].

N-(4-Chlorophenyl)-1H-tetrazol-5-amine (**3f**, $C_7H_6ClN_5$)
M.p.: 226–228 °C; FT-IR (KBr):$\overline{\nu}$ = 3,269, 3,210, 3,130, 3,071, 1,625, 1,579, 1,546, 1,493, 1,246, 1,093, 1,057, 835, 782, 728, 503 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.35 (d, J = 8.9 Hz, 2H), 7.56 (d, J = 8.9 Hz, 2H), 9.97 (s, 1H), 15.40 (s, br, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 156.1, 139.8, 129.3, 125.1, 118.7 ppm.

N-(2,4-Dimethylphenyl)-1H-tetrazol-5-amine (**3h**, $C_9H_{11}N_5$)
M.p.: 192–193 °C; FT-IR (KBr): $\overline{\nu}$ = 3,255, 3,130, 2,920, 1,629, 1,605, 1,580, 1,542, 1,495, 1,268, 1,216, 1,158, 1,116, 1,067, 991, 869, 827, 781, 726, 600, 559 cm^{-1}; ^{1}H NMR (300 MHz, aceton-d_6): δ = 2.29 (s, 6H), 7.04 (d, J = 7.9 Hz, 2H), 7.66 (d, J = 7.9 Hz, 1H), 8.30 (s, br, 1H) ppm; ^{13}C NMR (75 MHz, aceton-d_6): δ = 156.6, 136.3, 134.1, 132.2, 129.9, 128.1, 121.8, 20.7, 17.9 ppm.

N-(2-Methylphenyl)-1H-tetrazol-5-amine (**3i**, $C_8H_9N_5$)
M.p.: 201–203 °C; FT-IR (KBr): $\overline{\nu}$ = 3,435, 3,315, 2,910, 1,646, 1,606, 1,577, 1,542, 1,457, 1,352, 742, 593 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.17 (s, 3H), 5.99 (s, 1H), 6.86 (t, J = 7.0 Hz, 1H), 7.04–7.11 (m, 2H), 7.66 (s, 1H), 7.77 (d, J = 8.0 Hz, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 156.2, 138.2, 130.0, 126.9, 125.9, 121.9, 120.8, 17.9 ppm.

1,1′-(1,4-Phenylene)bis(1H-tetrazol-5-amine)
(**4k**, $C_8H_8N_{10}$)
M.p.: 264–266 °C; FT-IR (KBr):$\overline{\nu}$ = 3,357, 3,139, 1,652, 1,588, 1,519, 1,426, 1,293, 1,141, 1,070, 843 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): $\delta = 7.03$ (s, 4H), 7.83 (s, 4H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 155.9$, 134.6, 126.3 ppm.

Catalyst reuse and stability

The reusability of the catalyst was tested in the synthesis of 5-(4-bromophenylamino)-1*H*-tetrazole. In a typical experiment, after completion of the reaction, ZAS was isolated from the reaction mixture by simple filtration and washed with water and ethanol, followed by drying in an oven at 100 °C for 50 min. The recovered catalyst (98%) was reused three times without any loss of activity (Table 1, entry 4). This reusability demonstrates the high stability of the catalyst under the operating conditions.

Acknowledgments The authors gratefully acknowledge the financial support from the Bu-Ali Sina University, Hamedan 6517838683, Iran.

References

1. Bulter RN (1996) In: Katritzky AR, Rees CW, Scriven EFV (eds) Comprehensive heterocyclic chemistry II, vol 4. Pergamon, Oxford
2. Butler RN (1977) Adv Het Chem 21:323
3. Wittenberger SJ (1994) Org Prep Proced Int 26:499
4. Herr RJ (2002) Bioorg Med Chem 10:3379
5. Zhilin AY, Ilyushin MA, Tselinskii IV, Kozlov AS, Lisker IS (2003) Russ J Appl Chem 76:572
6. Finnegan WG, Henry RA, Lieber E (1953) J Org Chem 18:779
7. Garbrecht WL, Herbst RM (1953) J Org Chem 18:1014
8. Henry RA, Finnegan WG, Lieber E (1954) J Am Chem Soc 76:88
9. Svetlik J, Hrusovsky I, Martvon A (1979) Collect Czech Chem Commun 44:2982
10. Batey RA, Powell DA (2000) Org Lett 2:3237
11. Stolle R, Heintz K (1937) J Prakt Chem 147:286
12. Miller AE, Feeney DJ, Ma Y, Zarcone L, Aziz MA, Magnuson E (1990) Synth Commun 20:217
13. Katritzky AR, Rogovoy BV, Kovalenko KV (2003) J Org Chem 68:4941
14. Klich M, Teutsch G (1986) Tetrahedron 42:2677
15. Henry RA, Finnegan WG, Lieber E (1955) J Am Chem Soc 77:2264
16. Ley SV, Baxendale IR, Bream RN, Jackson PS, Leach AG, Longbottom DA, Nesi M, Scott JS, Storer RI, Taylor SJ (2000) J Chem Soc Perkin Trans 1:3815
17. Gorte RJ (1999) Catal Lett 62:1
18. Habibi D, Nasrollahzadeh M, Faraji AR, Bayat Y (2010) Tetrahedron 66:3866
19. Habibi D, Nasrollahzadeh M (2010) Synth Commun 40:3159
20. Modarresi-Alam AR, Nasrollahzadeh M, Khamooshi F (2007) Arkivoc (xvi):238
21. Koldobskii GI, Ostrovskii VA, Popavskii VS (1982) Chem Heterocycl Comp 18:965
22. Garbrecht WL, Herbst RM (1953) J Org Chem 18:1003
23. Modarresi-Alam AR, Nasrollahzadeh M (2009) Turk J Chem 33:267
24. Crutchley RJ, Naklicki ML (1989) Inorg Chem 28:1955
25. Nasrollahzadeh M, Habibi D, Shahkarami Z, Bayat Y (2009) Tetrahedron 65:10715