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ORIGINAL PAPER

Green chemistry: $ZrOCl_2 \cdot 8H_2O$ catalyzed regioselective synthesis of 5-amino-1-aryl-1*H*-tetrazoles from secondary arylcyanamides in water

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Abstract A green and efficient method for the synthesis of 5-amino-1-aryl-1*H*-tetrazoles with excellent yields and high purity from secondary arylcyanamides is described. This method is completely green because no organic solvents or protic acid catalyst is used that can generate hydrazoic acid (HN_3). In addition, it is a very clean method for acquiring 5-amino-1-aryl-1*H*-tetrazoles without generating 5-arylamino-1*H*(2*H*)-tetrazoles in most cases.

Keywords 5-Amino-1-aryl-1*H*-tetrazoles · Arylcyanamides · $ZrOCl_2 \cdot 8H_2O$ · Regioselective synthesis · Green chemistry

Introduction

Tetrazoles are increasingly popular heterocycles [1] with various applications that were prepared by the reaction of anhydrous hydrazoic acid and hydrogen cyanide gas under pressure for the first time [2–10]. They are used as lipophilic spacers in pharmaceuticals [11] and in photography as stabilizing materials [12]. They provide a main skeleton in plant growth regulators, herbicides, and fungicides that are used in agriculture [12]. They are also used as a gas generator in automobile airbags and rocket propellants [13] because they produce non-toxic and high-temperature gas reaction products. The high burn rate and relative stability are other useful properties of tetrazoles [10]. Some tetrazoles with antihypertensive, anti-allergic, and antibiotic activity have been reported in the literature [14]. They are used in cancer and AIDS treatments [2, 15–18]. Furthermore, aminotetrazole derivatives have been patented for their anti-arthritic, muscle relaxation, anti-inflammatory, and analgesic properties [8]. 5-Substituted tetrazoles, 5-aryl/alkyloxytetrazoles, and 5-aryl/alkylaminotetrazoles are commonly prepared by the reaction of azide anion with nitriles, cyanates, and cyanamides, respectively [2–8, 19–21]. In most cases, the reaction actually proceeds in hydrazoic acid solutions. Hydrazoic acid is an unstable component and generates nitrogen and hydrogen under decomposition, which can produce an explosive gas mixture in combination with air or nitrogen at concentrations above 8–15 %. Therefore, care must be taken to monitor its concentration in the reaction mixture [2–8, 12, 21]. A mixture of sodium azide and ammonium chloride can be used as a substitute for hydrazoic acid with dimethylformamide as the solvent [2–8, 12, 21]; the reaction requires a long time and high temperatures.

Solubility in both organic solvents and water is another disadvantage of dimethylformamide that can cause many problems in the reaction workup. To resolve these problems, several solvents were employed at various temperatures to enhance the reaction [21]. Using sodium azide

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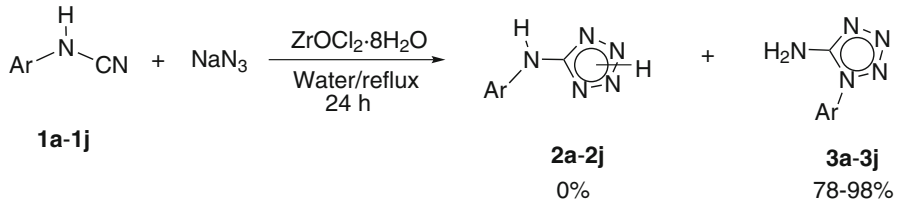
Scheme 1



in acetic acid at 50 °C for the synthesis of some amino-1*H*-tetrazoles in low yield (4–59 %) from the treatment of amino (imino) methanesulfonic acid derivatives was recently reported by Miller et al. [22]. Von Braun degradation of tertiary amines with carcinogen bromide is another way to prepare 5-monoalkylaminotetrazoles. Elimination of an alkyl group of 5-dialkylaminotetrazoles is possible with this method. Moreover, 5-monosubstituted amino-1*H*-tetrazoles can be synthesized by heating 5-amino-1-substituted-1*H*-tetrazoles in a thermal isomerization process [23]. Harsh reaction conditions, longer reaction times, low yield, use of toxic and expensive reagents, and in situ generation of hydrazoic acid, which is highly toxic and explosive, are some disadvantages of the above-mentioned methods.

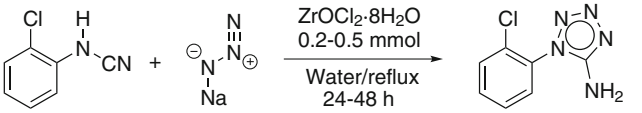
Due to their availability and low toxicity, Zr (IV) salts have recently attracted much attention, which is reflected in their applications in several organic transformations such as electrophilic amination of activated arenes [24], transthioacetylization of acetals [25], deoxygenation of heterocyclic *N*-oxides [26], reduction of nitro compounds [27], conversion of carbonyl compounds to 1,3-oxathiolanes [28], synthesis of nitriles from *O*-arylaldoximes [29], Michael reaction of 1,3-dicarbonyls and enones [30], opening of epoxide rings by amines [31], reactions of indole, 1-methylindole, and pyrrole with α,β-unsaturated ketone [32], and other organic transformations [33–42]. There are only a few reports on metal oxysalt-based organic reactions [43].

In this work, we describe a simple and green route to the regioselective synthesis of 5-amino-1-aryl-1*H*-tetrazoles using arylcyanamides, sodium azide, and $ZrOCl_2$ as catalyst in good yields. This reaction does not produce any hydrazoic acid, and no organic solvent is used (Scheme 1).

Results and discussion

Different cyanamide derivatives [44, 45] **1a-1j** were reacted with sodium azide in the presence of zirconium oxychloride as catalyst in water to afford corresponding 5-amino-1-aryl-1*H*-tetrazoles. Water was selected as a green and environmentally friendly reaction medium that can dissolve sodium azide and simplify the separation of products from other reactants. Different reaction conditions were examined for synthesis of 5-amino-1-(2-chlorophenyl)-1*H*-tetrazole using 2-chlorophenyl cyanamide (1 mmol) to acquire the best results, which are summarized in Table 1. As shown in the data in Table 1, the procedure in entry 4 was selected for other cyanamide derivatives. The results are shown in Table 2.

Table 1 Reaction of 2-chlorophenylcyanamide with sodium azide under different conditions



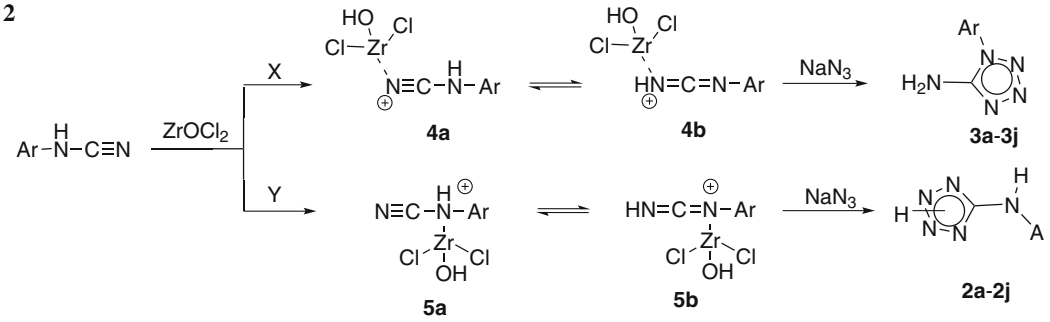
1c 1 mmol — 1-3 mmol — **3c**

Entry	NaN_3/mmol	$ZrOCl_2·8H_2O$/mmol	Conversion/%	Time/h
1	1	0.2	20	48
2	2	0.3	60	24
3	3	0.4	85	24
4	3	0.5	100	24
5	3	0.2	50	24
6	3	0.3	65	24
7	1	0.5	35	48
8	2	0.5	70	24

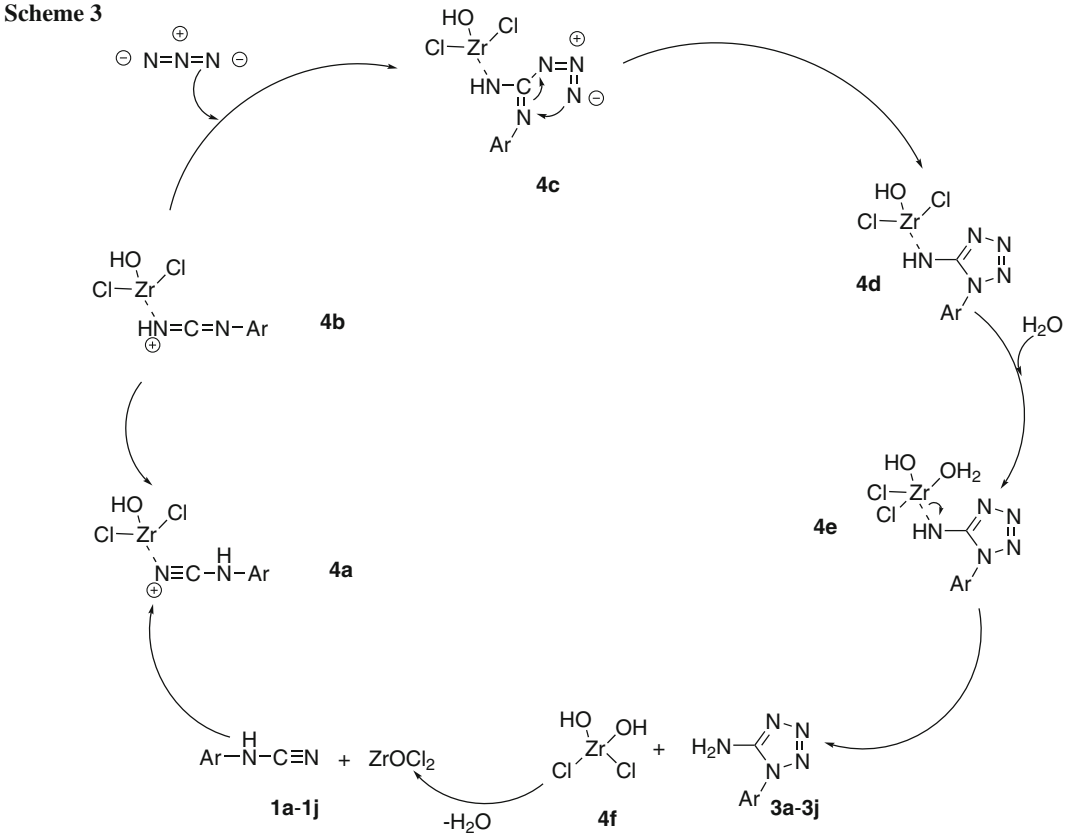
Table 2 Reaction of arylcyanamides with sodium azide (3 eq) catalyzed by zirconium oxychloride (0.5 eq) (Scheme 1)

Entry	Product	Ar	Yield/%	M.p./°C	Lit. m.p./°C
1	**3a**	4-NO_2–C_6H_4	78	186–188	185–187 [22]
2	**3b**	4-Cl–C_6H_4	96	214–216	215–217 [22]
3	**3c**	2-Cl–C_6H_4	98	186–189	185–190 [22]
4	**3d**	4-Br–C_6H_4	91	238–240	239–240 [8]
5	**3e**	4-CH_3–C_6H_4	95	174–176	175–177 [22]
6	**3f**	2,5-Cl_2–C_6H_3	92	260–263	260–262 [8]
7	**3g**	2-CH_3–C_6H_4	95	190–192	191–192 [22]
8	**3h**	3-Cl–C_6H_4	94	174–177	174–175 [22]
9	**3i**	4-CH_3O–C_6H_4	90	210–212	209–210 [22]
10	**3j**	2,4-$(CH_3)_2$–C_6H_3	93	197–199	199–201 [22]

Scheme 2



Scheme 3



All products are known compounds and were identified by comparison of their spectral data (IR, and ^{1}H, and ^{13}C NMR) and physical properties with those of authentic samples [22, 23]. ^{13}C-NMR spectra displayed a signal at $\delta = 155$–157 ppm for C5 of the tetrazole ring [46–49]. Arylcyanamide molecules **1a**-**1j** can be complexes with zirconium oxychloride in two pathways (*X* and *Y*) and produce two intermediates, **4a** and **5a**, each of which can tautomerize to **4b** and **5b**, respectively. According to these results, pathway **X** is the predominate one (Scheme 2).

The proposed mechanism involves an attack of azide anion on compound **4b**, which is made from complexion of arylcyanamide molecule **1a**-**1j** with zirconium oxychloride followed by cyclization of intermediate **4c** to give compound **4d** in water to release the target molecules **3a**-**3j**. Hydrated zirconium oxychloride **4f** can start a new cycle after elimination of one H_2O molecule (Scheme 3).

In this work, we describe a new methodology to acquire 5-amino-1-aryl-1*H*-tetrazoles without generation of 5-arylamino-1*H* (2*H*)-tetrazoles in most cases. This methodology has important advantages over previous methods; for example,

the reactions were carried out in water solvent. Using Lewis acid as catalyst prevents making any hydrazoic acid during the reaction. Syntheses of 5-amino-1-aryl-1*H*-tetrazoles are regioselective in most cases (only in the case of **1a** was a trace amount of **2a** obtained). The workup is very simple and includes washing the crude products three times with water. This method does not generate any by-products. In conclusion, this methodology is completely green, environmentally benign, and simple.

Experimental

General procedure for synthesis of 5-amino-1-aryl-1H-tetrazoles

To a solution of sodium azide (3 mmol) in 10 cm^3 water was added cyanamide (1 mmol) and catalyst (0.5 mmol). The reaction mixture was refluxed for 24 h with vigorous stirring until all the cyanamide was consumed (monitored by TLC). The reaction mixture was filtered and washed with water three times (3×15 cm^3) to remove excess sodium azide and catalyst. The products were dried under vacuum and characterized by IR and NMR spectra and melting points (Tables 1 and 2). Isomer **3a** was not soluble in ethanol and was separated from isomer **2a** via a simple procedure. Isomer **3a** was precipitated from ethanol and was collected on filter paper. The remaining isomer **3a** in the stock solution was precipitated and removed by adding $EtOH/H_2O$ (3:1). The filtrate solution contained only isomer **2a**. Removing the solvents gives pure isomer **2a**.

References

1. Butler RN, Katritzky AR, Rees CW, Scriven EFV (1996) Comprehensive heterocyclic chemistry, vol 4. Pergamon, Oxford
2. Herr RJ (2002) Bioorg Med Chem 10:3379
3. Monderhack D (1998) J Prakt Chem 340:687
4. Wittenberger SJ (1994) Org Prep Proced Int 26:499
5. Benson FR (1947) Chem Rev 47:1
6. Koldobskii GI, Ostrovskii VA, Popavskii VS (1981) Chem Heterocycl Comp 17:965
7. Butler RN (1977) Adv Heterocycl Chem 21:323
8. Modarresi Alam AR, Nasrollahzadeh M (2009) Turk J Chem 33:267
9. Hodges JC, Hamby JM, Blankley CJ (1992) Drugs Future 17:575
10. Satchell JF, Smith BJ (2002) Phys Chem Chem Phys 4:4314
11. Singh H, Chawla AS, Kapoor VK, Paul D (1980) Prog Med Chem 17:151
12. Jursic BS, Blanc BW (1998) J Heterocycl Chem 35:405
13. Kharaghiosoff K, Klapotke TM, Mayer P (2006) J Org Chem 71:1295
14. Wexler RR, Greenlee WJ, Irvin JD (1996) J Med Chem 39:625
15. Sproat B, Colonna F, Mullah B (1995) Nucleosides Nucleotides 14:255
16. Desarro A, Ammendola D, Zappala M (1995) Antimicorb Agents Chemother 39:232
17. Wood E, Crosby RM, Dickerson S (2001) Anti-Cancer Drug Des 16:1
18. May BCH, Abell AD (2002) J Chem Soc Perkin Trans 1:172
19. Modarresi-Alam AR, Khamooshi F, Rostamizadeh M (2007) J Mol Struc 841:61
20. Katritzky AR, Rogovoy BV, Kovalenko KV (2003) J Org Chem 68:4941
21. Demko PZ, Sharpless KB (2001) Org Lett 3:4091
22. Miller AE, Feeney DJ, Ma Y, Zircon L, Aziz MA, Magnuson E (1990) Synth Commun 20:217
23. Schelenz T, Schäfer W (2000) J Prakt Chem 342:197
24. Lenarsic R, Kocevar M, Polanc S (1999) J Org Chem 64:2558
25. Firouzabadi H, Iranpoor N, Karimi B (1999) Synlett 1999(3):319
26. Chary KP, Mohan GH, Iyengar DS (1999) Chem Lett 12:1339
27. Chary KP, Ram SR (2000) Synlett 2000(5):683
28. Karimi B, Seradj H (2000) Synlett 2000(6):805
29. Tsuji C, Miyazawa E, Sakamoto T (2002) Synth Commun 32:3871
30. Smitha G, Patnaik S, Reddy CS (2005) Synthesis 2005(5):711
31. Chakraborti AK, Kondaskar A (2003) Tetrahedron Lett 44:8315
32. Shi M, Cui SC, Li QJ (2004) Tetrahedron 60:6679
33. Bora U (2003) Synlett 2003(7):1073
34. Mo LP, Zhang ZH (2011) Curr Org Chem 15:3800
35. Zhang ZH, Li TS (2009) Curr Org Chem 13:1
36. Lu HY, Li JJ, Zhang ZH (2009) Appl Organomet Chem 23:165
37. Karami B, Kiani M (2011) Catal Commun 14:62
38. Fioravanti S, Pellacani L, Vergari MC (2012) Org Biomol Chem 10:8207
39. Movassagh B, Rakhshani A (2012) Synth Commun 42:2121
40. Eftekhari-Sis B, Abdollahifar A, Hashemi MM, Zirak M (2006) Eur J Org Chem 2006(22):5152
41. Hashemi MM, Eftekhari-Sis B, Abdollahifar A, Khalili B (2006) Tetrahedron 62:672
42. Matloubi Moghaddam F, Ismaili H, Rezanejade Bardajee G (2006) Heteroat Chem 17:136
43. Anderson AM, Blazek JM, Garg P (2000) Tetrahedron Lett 41:1527
44. Crutchley RJ, Nakicki ML (1989) Inorg Chem 28:1955
45. Niwa R, Kamada H, Shitara E (1996) Chem Pharm Bull 44:2314
46. Butler RN, Garvin NL (1981) J Chem Soc Perkin Trans 1:390
47. Butler RN, Mc Evoy TM, Scott FL (1977) Can J Chem 55:1564
48. Butler RN (1972) Can J Chem 51:2315
49. Batterhan TJ (1973) NMR spectra of simple heterocycles. Wiley, New York, p 226