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A New Synthetic Method for the Preparation of 5-Aryloxytetrazoles using Al_2O_3-SO_3H as an Effective Heterogeneous Catalyst under Solvent-free Conditions

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Abstract : A simple and efficient method is described for the preparation of 5-aryloxy tetrazoles (**3a-h**)in excellent yields and high purityfrom arylcyanates (**1a-h**)with usingAl_2O_3-SO_3H as an effective heterogeneous catalyst. The rate of product formation was enhanced by introduction of electron-donating substituents. The ^{1}H NMR spectral characterize are also discussed.

Keywords: 5-Aryloxy tetrazoles, arylcyanates, guanyl azides, Al_2O_3-SO_3H.

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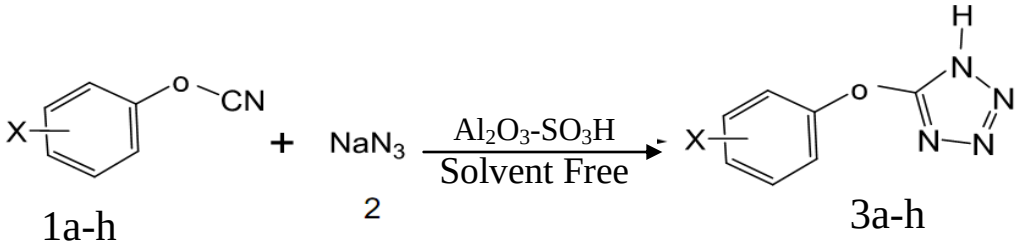
Introduction`

The tetrazole ring system has attracted considerable attention in recent years, [1-7] especially among medicinal chemists, as a potential surrogate for *cis*-peptide linkage and carboxylic acids.[3]Indeed, the number of patent claims and publications related to medicinal uses of tetrazoles continue to grow rapidly and cover a wide range of applications: Tetrazoles have been found to exhibit antihypertensive, antiallergic and antibiotic activities, and they are currently used, for example, as activator, anticonvulsants also in cancer and AIDS treatment.[1-5] Furthermore tetrazoles derivatives have been patented for muscle relaxation, anti-inflammatory, anti-arthritic, analgesic, ulcer therapeutic and coccidiostatic properties. Tetrazoles are also applied in agriculture, as plant growth regulators, herbicides and fungicides, stabilizers in photography and photoimaging and explosives in rocket propellants.[1-7] Another important application of tetrazoles is the preparation of imidoylazides.[8c] The addition of azide anion to nitriles, cyanates and cyanamides is the most common direction for preparing 5-substituted tetrazoles and 5-aryl/alkyl oxytetrazoles.[10-11] In most cases, reaction actually proceeds in solutions of hydrazoic acid in solvents such as benzene, toluene, xylene and chloroform. When hydrazoic acid is used, care must be taken by monitoring the concentration of hydrazoic acid in the reaction mixture to avoid an explosion. [1-7, 10-11]A substitute for hydrazoic acid is a mixture of sodium azide and ammonium chloride with dimethylformamide as the solvent. In dimethyl formamide, the reaction mixture must be heated at ~150 $^{\circ}$C from several hours to several days. Additional disadvantage of dimethyl formamide is the solubility in both organic solvents and water. Thus, removing the DMF from tetrazole is difficult. To resolve this problem, the reaction was carried out in several solvents, which allowed the temperature to be elevated to the necessary degree to enhance the reaction.[6] The published method for the preparation of 5-aryloxy-tetrazoles derivatives was reaction that including the addition of NaN_3 to arylcyanates in the presence of HCl and acetone under thermal conditions[17], lack of easy availability /preparation of the starting materials, difficulty of workup, use of expensive and toxic reagents and the in situ generated hydrazoic acid is highly toxic and explosive.[3,8b,8c,11,17] Because of the safety considerations, we required a method that did not use hydrazoic acid. Thus, a convenient and efficient method was required for preparation of the aryloxytetrazoles. In recent years, organic reactions on heterogeneous catalystshave received considerable attention in organic synthesis because of their ease of handling, enhanced reaction rates, greater selectivity, simple work-up, and recoverability of the catalysts.[1-7,22] From the standpoint of 'green chemistry', significant efforts have been made to find an alternative to organic solvents. A very attractive substitute for these solvents is a solvent–free reaction (industrially important due to reduced pollution, low cost, and simplicity in process and handling). In view of the importance of aryloxy tetrazoles and aryloxy imidoyl azides,[1-15,18-21] our aim was to find a facile and less hazardous method for syntheses of the 5-aryloxy tetrazoles(**3a-h**)from arylcyanates (**1a-h**)in quantitative yields by using Al_2O_3-SO_3Has an effective heterogeneous catalystin solvent-free.



Scheme 1

Results and Discussion

A simple and efficient method is described for the preparation of 5-aryloxy tetrazoles (**3a-h**)in excellent yields and high purity from arylcyanates (**1a-h**) with using Al_2O_3-SO_3H as an effective catalyst in solvent-free (Scheme 1).

The cyanates **1a-h** were prepared according to literature.[8a,8b,8c,11,17] Thenature of the substituent appears to play an important role for directing the course of the reaction. As shown in Table 1, among the various cyanates tested, electron-rich aromatic cyanates reach completion after (15-20)h, whereas electron-poor aromatic species require little higher times (compare entries 1-4 with 5-6 in Table 1). In addition, there is an excellent correlation between the effect of substitution on the benzene ring and the time of reaction. Scheme 1 and Table 1.

The following important results is extracted from data in Table 1. In general, when the substitution is electron-donating group reaction is completed at shorter reaction time (starting cyanate **1a-c** consumes faster) than when the substitution is electron-with-drawing (compare entries 5 and 6 with 1, 2, 3 and 4 in Table 1). The entries 5 (24 h) and 6 (29 h) confirms this result. The rate of reaction was found to decrease with increasing the electronegativity of a substituent on the aryl group. These results are the reverse of what was reported for the nitriles.[3] When the substitution on aryl ring is electron-donating in arylcyanates **1** the oxygen attached to aryl ring has more basic character. On the other hand, the electron-donating group acts to increase the electron density on the oxygen attached to aryl group, and thus assists in the cyclisation of guanyl azides to give 5-aryloxy tetrazoles. Furthermore, it is worthy to mention that reaction of α– and β–naphthol (entries 7 and 8) did not proceed completely in the recently reported method. [8b, 8c,11,17] Indeed, considerable amounts of starting material remained even after long times, and/or at high temperatures.However, the time to complete reaction in solvent-free and room temperature (Table 1) is a good indication that, the first step, addition of hydrogen ion to arylcyanate **1a-h** the most important step or the rate determining step of reaction, because when the substitution is electron-donating, reaction is completed at shorter reaction period.

Conclusions

A facile, convenient and less hazardous synthetic method for 5-aryloxy tetrazoles **3** from arylcyanates in solvent-free was achieved giving quantitative yields and high purity without involvement of expensivereagents or the formation of undesirable side products.To show the advantages of Al_2O_3-SO_3H as a catalyst in comparison with other materials, we

Table 1. The preparation of 5-aryloxy tetrazoles **(3a-h)** from arylcyanates by using Al_2O_3-SO_3H at r.t.

Entry	Cyanate	Ar	Product (tetrazole)	Reactiontime (h)	Yield (%)[a]
1	**1a**	4-$CH_3C_6H_4$	**3a**	22	94
2	**1b**	2,6-$(CH_3)_2C_6H_3$	**3b**	18	92
3	**1c**	4-$CH_3OC_6H_4$	**3c**	15	95
4	**1d**	C_6H_5	**3d**	20	84
5	**1e**	4-ClC_6H_4	**3e**	24	77
6	**1f**	4-$NO_2C_6H_4$	**3f**	29	51
7	**1g**	α-naphthyl	**3g**	21	79
8	**1h**	β-naphthyl	**3h**	20	83

[a] Yields refer to the pure isolated products.

Table2. Comparison of different catalysts in the synthesis of 5-(4-Chlorophenoxy)-tetrazole (**3e**)

Entry	Catalyst	Solvent	Time (min)	Temperature (°C)	Yield%
1	PPh_3	DMF	120	120	57
2	HCl[b]	CH_3COCH_3	80	65	46
3	LiCl	DMF	110	120	55
4	CH_3COOH[a]	CH_3COOH	35h	25	59
5	$SnCl_4$	DMF	120	120	58
5	ZnCl2	DMF	100	120	71
6	Al_2O_3-SO_3H	-	24h	25	77

[a] Glacial acetic acid as both solvent and proton donor source. [b] add in work up[8b,8c,11].

compared the reaction of Al_2O_3-$SO_3H$with $ZnCl_2$, glacial acetic acid,PPh3, HCl [8a,8b,8c,11], $SnCl_4$ and LiClin the synthesis of 5-(4-chlorophenoxy)-tetrazole (**3e**) (Table 1, Entry 5). As shown in Table 2, Al_2O_3-$SO_3H$is a better catalyst in the synthesis of 5-(4-Chlorophenoxy)- tetrazole (**3e**).

Experimental Section

CAUTION: Although aryloxytetrazoles 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. 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 concentration of 8-15%.[3]All products are known compounds andare identified by comparison of their spectral data (IRand^{1}H-NMR) specify instruments work and physical properties with those of authentic samples.[8a,8b,8c,11]All starting materials and solvents were purified with the specific proper purification techniques before use, when necessary.Al_2O_3-$SO_3H$was prepared according to the literature.[22]

Typical experimental procedure for the preparation of 5-Aryloxy tetrazoles 3 usingAl_2O_3-SO_3H

Thecyanate (1 mmol) ,Al_2O_3-SO_3H(1.05 g, 3 mmol) and sodium azide (3 mmol) wereadded. the mixture was pulverized in a mortar (or the mixture was stirred by a magnet in a test tube) at room temperature for an appropriate time (Table 1). Thereaction was monitored via TLC. After completion of the reaction, $CHCl_3$ was added and the mixture was filtered for separating the reagent. A portion of the solvent ($CHCl_3$) was evaporated and the pure productwas then filtered. Pure products were obtained in high yields, as summarized in Table 1. The desired pure products characterized by ^{1}H NMR and IR spectroscopy and melting points. The spectral data of 5-aryloxy tetrazoles are given below.

Data for5-aryloxy tetrazoles (3a-h):

5-(4-Methylphenoxy)-tetrazole(3a): M.p. = 139-140 °C. lit[8]140-142°C. IR (KBr, cm^{-1}): 3005 (m), 2900 (m), 2705 (m), 2550 (m), 2455 (m), 2350 (m), 1620 (s), 1590 (s), 1500 (s), 1440 (m), 1190 (s), 1120 (m), 1050 (m), 820 (s).cm^{-1}. ^{1}H-NMR (500 MHz, $(CD_3)_2CO$), δ ppm:2.20 (s , 6H), 7.12 (s, 3H), 10.3 (s, 1H).

5-(2,6-Dimethylphenoxy)-tetrazole(3b): M.p. = 171-173°C. lit[8]173-174°C. IR (KBr, cm^{-1}): 3010 (m), 2905 (s), 2855 (s), 2705 (s),2605 (s), 2450 (s), 1605 (s), 1570 (s), 1470(s), 1440 (s), 1410 (s), 1160 (s), 1045 (s), 785 (s), 775 (s).cm^{-1}. ^{1}H-NMR (500 MHz, $(CD_3)_2CO$), δ ppm:2.38 (s , 3H), 7.30 (s, 4H), 9.8 (s, br , 1H).

5-(4-Methoxyphenoxy)-tetrazole(3c): M.p. = 150-151°C. lit[8] 149-150°C. IR (KBr, cm^{-1}): 3060 (m), 2950 (m), 2900 (m), 2850 (m), 2750 (m), 2600 (m), 1620 (m), 1600 (m), 1590 (m), 1500 (s), 1470 (m), 1440 (s), 1190 (m), 1180 (m), 1040 (m),1030 (m), 820 (s).cm^{-1}. ^{1}H-NMR (500 MHz, $(CD_3)_2CO$), δ ppm:3.88 (s , 3H), 7.00 (d , J = 10.5 Hz , 2H), 7.4 (d , J = 10.5 Hz , 2H), 8.4 (s, 1H).

5-(phenoxy)-tetrazole(3d): M.p. = 136-138°C. lit[8]137-138°C. IR (KBr, cm^{-1}): 2450-3000 (m), 1615 (s), 1575 (s), 1485 (s), 1440 (s), 1185 (s), 1050 (s),680-820 (m).cm^{-1}. ^{1}H-NMR (500 MHz, $(CD_3)_2CO$), δ ppm:7.20 (s, 5H), 13.00 (br , 1H).

5-(4-Chlorophenoxy)-tetrazole(3e): M.p. = 156-158°C. lit[8]166-167°C. IR (KBr, cm^{-1}): 3010 (m), 3000 (m),2850 (m), 2700 (s), 2600 (m), 2450 (s), 1610 (s), 1590 (s), 1480 (s), 1410 (m), 1190 (s), 1175 (m), 1080 (m), 1050 (s), 825 (s).cm^{-1}. ^{1}H-NMR (500 MHz, $(CD_3)_2CO$), δ ppm:7.35 (s, 4H), 8.66 (br , 1H).

5-(4-Nitrophenoxy)-tetrazole(3f): M.p. = 161-163 °C. lit[8]162-163 °C. IR (KBr, cm^{-1}): 3120 (m), 3100 (s), 3000(m), 2750 (s), 2600 (s), 2450 (s), 1650 (vs), 1600 (s), 1570 (vs), 1540 (vs), 1480 (vs), 1450 (s), 1410 (s), 1350 (vs), 1310 (s), 1200 (vs), 1190 (s), 1120 (s), 1100 (s), 1060 (vs),860 (s), 850 (s). cm^{-1}. ^{1}H-NMR (500 MHz, $(CD_3)_2CO$), δ ppm: 7.55 (d , J=9Hz ,2H), 8.33 (d , J=9Hz, 2H), 14.1 (s , 1H).

5-(Naphthalen-1-yloxy)-tetrazole(3g): M.p. = 174-176°C. IR (KBr, cm^{-1}):2750-3060 (m), 1630 (s), 1600 (s), 1500 (m), 1485 (m), 1390 (m),1280 (m), 1170(s),1105 (m), 1050 (w), 680-950 (m).cm^{-1}. ^{1}H-NMR (500 MHz, $(CD_3)_2CO$), δ ppm:7.20 (d, J = 7.5 Hz, 1H), 7.35-7.45 (m, 3H),7.63 (d, J = 8.2 Hz, 1H), 7.78 (dd, J = 9.3 Hz, J = 2.1Hz, 1H), 7.92 (dd, J = 8.8 Hz, J = 2.1 Hz, 1H), 11.1 (s , 1H).^{13}C-NMR(500 MHz, $(CD_3)_2CO$), δppm: 117.7, 120.8, 124.8,124.9, 125.6, 125.7, 126.9, 127.3, 134.0, 146.2, 156.7.Analysis Calcd for $C_{11}H_8N_4O$: C, 62.26; H, 3.77; N, 26.42%. Found: C, 62.46; H, 3.66; N, 26.53%.

5-(Naphthalen-2-yloxy)-tetrazole(3h): M.p. = 152-154 °C. IR (KBr, cm^{-1}): 2800-3070 (m), 1625(s), 1590(s), 1510 (m), 1475 (m), 1400 (m), 1275 (m), 1170(s), 1110 (m), 1070 (w), 660- 970 (m). cm^{-1}. ^{1}H-NMR (500 MHz, $(CD_3)_2CO$), δ ppm; 7.20 (dd, J = 8.7 Hz,J = 2.1 Hz, 1H), 7.34-7.41 (m, 2H), 7.49 (d, J = 2.1 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 8.7Hz, 2H).,11.3 (s , 1H).^{13}C-NMR(500 MHz, $(CD_3)_2CO$), δ ppm; 117.9, 121.2, 124.8, 125.8, 126.9, 127.1, 128.5, 130.5, 133.1, 148.3, 156.5. Analysis Calcd. for $C_{11}H_8N_4O$: C, 62.26; H, 3.77; N, 26.42%. Found: C, 61.87; H, 3.61; N, 26.50%.

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