One-Pot Synthesis of 5-Substituted 1*H*-Tetrazoles from Aryl Bromides with Potassium Hexakis(cyano-κC)ferrate(4−) ($K_4[Fe(CN)_6]$) as Cyanide Source

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A one-pot procedure for the synthesis of 5-substituted 1*H*-tetrazoles through the three-component reaction between an aryl bromide, potassium hexakis(cyano-κC)ferrate(4−) ($K_4[Fe(CN)_6]$) and NaN_3 catalyzed by $[Pd(OAc)_2]$ and $ZnBr_2$ in the presence of 1,4-diazabicyclo[2.2.2]octane (dabco) was developed. Furthermore, the reaction occurred under nonacidic conditions and involved a nontoxic cyanide source, making this method a quite attractive one.

Introduction. – Tetrazoles play important roles in coordination chemistry and found widespread application in pharmaceutical and material sciences, including photography [1] and specialty explosives [2]. Moreover, tetrazoles can be used in the synthesis of N-containing heterocycles [3].

Because of their potent usefulness, various synthetic methods have been developed for the construction of tetrazole frameworks [4]. Typically, they are prepared by the reaction of a hydrazoic acid source with nitriles [4a][4b]. In addition, trialkyltin azides are alternative reagents and have been shown to be effective in the synthesis of tetrazoles [4c][4d]. In general, the most direct and versatile method of the synthesis of 5-substituted 1*H*-tetrazoles is the [2 + 3]-cycloaddition between nitriles and azides [5]. Recently, a breakthrough for this reaction involving stoichiometric amounts of Zn^{II} salts was made by *Sharpless* and co-workers, the reaction being carried out under reflux in H_2O [6]. Other recent developments include the synthesis of 5-substituted 1*H*-tetrazoles under solvent-free conditions [7] and the application of new catalysts such as nanocrystalline ZnO [8], zinc hydroxyapatite [9], and Cu_2O [10]. However, despite these advances, papers reporting the synthesis of 5-substituted 1*H*-tetrazoles from *in situ* formed arenecarbonitriles have remained sparse. Successful examples include the direct transformation of primary alcohols and aldehydes into tetrazoles in aqueous media [11] and the one-pot synthesis of tetrazoles from aryl halides [12]. In the latter protocol, arenecarbonitriles were first prepared from aryl halides and elaborated further to the 5-aryl-1*H*-tetrazoles in a tandem reaction with NaN_3 in the presence of NH_4Cl. Nevertheless, the reaction of a hydrazoic acid source (NaN_3 and NH_4Cl) with nitriles could form the sublimed NH_4N_3 that may explode in dry form [13]. In an attempt to overcome this limitation, we wondered whether aryl halides, a cyanide source, and NaN_3 in the absence of NH_4Cl could be directly used for tetrazole formation without intermediate workup.

Results and Discussion. – To test this idea, we first focused on a brief optimization of the reaction conditions for the synthesis of 5-phenyl-1*H*-tetrazole (**2a**) from bromobenzene, potassium hexakis(cyano-κC)ferrate(4 –) ($K_4[Fe(CN)_6]$), and NaN_3 (*Table 1*). On the basis of the conditions reported for the reaction between aryl bromides and $K_4[Fe(CN)_6]$ [14], we treated bromobenzene (1 mmol) with $K_4[Fe(CN)_6]$ (20 mol-%) and NaN_3 (1.5 mmol) in the presence of $[Pd(OAc)_2]$ (1 mol-%) and Na_2CO_3 (1 mmol) in *N*,*N*-dimethylacetamide (DMAc) at 140° for 24 h. Unfortunately, the desired product **2a** could only be obtained in 30% yield (*Entry 1*). Replacing DMAc by *N*,*N*-dimethylformamide (DMF) afforded **2a** in a slightly higher yield of 45% (*Entry 2*). To improve the yield of **2a** further, we surveyed a series of reaction conditions and found that the addition of 1,4-diazabicyclo[2.2.2]octane (dabco) as a ligand promoted the formation of **2a** in 58% yield (*Entry 3*). However, it was found that other amines, including 2,2′-bipyridine (bpy), L-proline, *N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diamine (tmeda), *N*,*N*′-dimethylethane-1,2-diamine (dmeda), and 1,10-phenanthroline (1,10-phen), were less effective in comparison to dabco (*Entries 4–8*). Since $ZnBr_2$ has been used for the synthesis of tetrazoles from NaN_3 and nitriles [6], the yield of the desired product **2a** was enhanced to 69% when performing the reaction in the presence of $ZnBr_2$ (*Entry 9*). The use of other additives such as Cu_2O, $[Cu(OAc)_2]$, or CuI inhibited rather than facilitated the reaction (*Entries 10–12*).

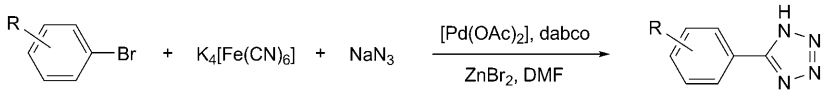
Table 1. *Optimization of the Synthesis of 5-Phenyl-1*H*-tetrazole* (**2a**)[a])

Entry	Amine[b]) [10 mol-%]	Additive	Solvent	Yield[c]) [%]
1	–	–	DMAc	30
2	–	–	DMF	45
3	dabco	–	DMF	58
4	bpy	–	DMF	25
5	L-proline	–	DMF	14
6	tmeda	–	DMF	50
7	dmeda	–	DMF	44
8	1,10-phen	–	DMF	9
9[d])	dabco	$ZnBr_2$	DMF	69
10[e])	dabco	Cu_2O	DMF	31
11[d])	dabco	$Cu(OAc)_2$	DMF	21
12[d])	dabco	CuI	DMF	51

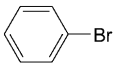
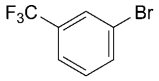
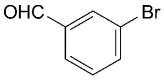
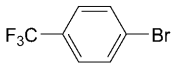
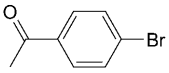
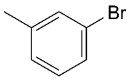
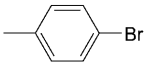
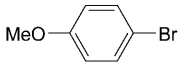
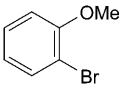
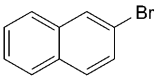
[a]) Reaction conditions: 1 mmol of bromobenzene, 1.5 mmol of NaN_3, 20 mol-% of $K_4[Fe(CN)_6]$, 1 mol-% of $[Pd(OAc)_2]$, 3 ml of solvent, 1 mmol of Na_2CO_3; 24 h at 140° under N_2. [b]) dabco = 1,4-diazabicyclo[2.2.2]octane, bpy = 2,2′-bipyridine, tmeda = *N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diamine, dmeda = *N*,*N*′-dimethylethane-1,2-diamine, 1,10-phen = 1,10-phenanthroline. [c]) Yield of isolated product. [d]) 20 mol-% of additive was used. [e]) 10 mol-% of additive was used.

On the basis of the above results, the scope of this reaction was further explored with different substrates. As shown in *Table 2*, most of the reactions afforded the corresponding products in moderate to good yields. The electronic nature of the substituents, either electron-withdrawing or electron-donating groups at the aryl bromides, did not have significant effects on the yields (*Entries 2–8*). However, steric

Table 2. *Synthesis of 5-Substituted 1*H*-Tetrazoles from Aryl Bromides*[a])



1 **2**

Entry	Aryl bromide **1**	Product **2**	Yield[b]) [%]
1		**2a**	69
2		**2b**	70
3		**2c**	65
4		**2d**	62
5		**2e**	64
6		**2f**	63
7		**2g**	61
8[c])		**2h**	60
9[c])[d])		**2i**	44
10		**2j**	73

[a]) Reaction conditions: 1 mmol of aryl bromide, 1.5 mmol of NaN_3, 20 mol-% of $K_4[Fe(CN)_6]$, 1 mol-% of $[Pd(OAc)_2]$, 3 ml of DMF, 1 mmol of Na_2CO_3, 10 mol-% of dabco, and 20 mol-% of $ZnBr_2$; 24 h at 140° under N_2. [b]) Yield of isolated product. [c]) 2 mol-% of $[Pd(OAc)_2]$ was used. [d]) Reaction time 32 h.

hindrance by *ortho*-positioned substituents at the aryl bromide seemed to be the cause of the reduced yield. For example, when 2-methoxyphenyl bromide was used as the substrate, the reaction resulted in a considerably lower yield in comparison with that of the less hindered 4-methoxyphenyl bromide, even when prolonging the reaction time

(*Entry 9 vs. Entry 8*). Also, the reaction of 2-bromonaphthalene gave the corresponding product in 73% yield (*Entry 10*).

In conclusion, 5-substituted 1*H*-tetrazoles were synthesized directly from aryl bromides, $K_4[Fe(CN)_6]$, and NaN_3 in the presence of the catalyst $[Pd(OAc)_2]$, the additive $ZnBr_2$, and the amine dabco. The reaction took place under nonacidic conditions and involved the readily accessible aryl bromides, NaN_3, and the nontoxic $K_4[Fe(CN)_6]$, making this protocol a quite attractive one. The method described here also represents a valuable complement relative to existing procedures for the synthesis of 5-substituted 1*H*-tetrazoles.

Experimental Part

*5-Substituted 1*H*-Tetrazoles: General Procedure.* Procedure exemplified for **2a**: After standard cycles of evacuation and filling with dry and pure N_2, an oven-dried tube was charged with bromobenzene (1 mmol), $K_4[Fe(CN)_6]$ (20 mol-%), $[Pd(OAc)_2]$ (1 mol-%), dabco (10 mol-%), $ZnBr_2$ (20 mol-%), Na_2CO_3 (1 mmol), NaN_3 (1.5 mmol), and DMF (3 ml). The tube was evacuated and filled with N_2. Then, the tube was sealed, and the mixture was stirred at 140° for 24 h. After cooling to r.t., aq. 1M HCl (10 ml) and AcOEt (25 ml) were added, and the mixture was vigorously stirred. The org. layer was separated, and the aq. layer was extracted with AcOEt (2 × 25 ml). The combined org. layer was dried ($MgSO_4$), filtered, and concentrated and the residue subjected to column chromatography (silica gel): 5-phenyl-1*H*-tetrazole **2a**.

*5-Phenyl-1*H*-tetrazole* (**2a**) [6a]: M.p. 214 – 215°. ^{1}H-NMR: 7.58 – 7.64 (*m*, 3 H); 8.01 – 8.06 (*m*, 2 H).

*5-[3-(Trifluoromethyl)phenyl]-1*H*-tetrazole* (**2b**) [15]: M.p. 155 – 156°. ^{1}H-NMR: 7.87 (*t*, *J* = 8.1, 1 H); 7.96 (*d*, *J* = 8.1, 1 H); 8.31 – 8.38 (*m*, 2 H).

*3-(1*H*-Tetrazol-5-yl)benzaldehyde* (**2c**) [16]: M.p. 196 – 198°. ^{1}H-NMR: 7.81 (*t*, *J* = 7.7, 1 H); 8.09 (*d*, *J* = 7.7, 1 H); 8.33 (*d*, *J* = 7.7, 1 H); 8.54 (*s*, 1 H); 10.10 (*s*, 1 H).

*5-[4-(Trifluoromethyl)phenyl]-1*H*-tetrazole* (**2d**) [17]: M.p. 218 – 219°. ^{1}H-NMR: 7.98 (*d*, *J* = 8.3, 2 H); 8.27 (*d*, *J* = 8.3, 2 H).

*1-[4-(1*H*-Tetrazol-5-yl)phenyl]ethanone* (**2e**) [7]: M.p. 173 – 175°. ^{1}H-NMR: 2.64 (*s*, 3 H); 8.13 (*d*, *J* = 8.2, 2 H); 8.23 (*d*, *J* = 8.2, 2 H).

*5-(3-Methylphenyl)-1*H*-tetrazole* (**2f**) [5a]: M.p. 151 – 152°. ^{1}H-NMR: 2.41 (*s*, 3 H); 7.40 (*d*, *J* = 7.8, 1 H); 7.56 (*t*, *J* = 7.8, 1 H); 7.88 –7.91 (*m*, 2 H).

*5-(4-Methylphenyl)-1*H*-tetrazole* (**2g**) [18]: M.p. 248 – 249°. ^{1}H-NMR: 2.47 (*s*, 3 H); 7.49 (*d*, *J* = 8.0, 2 H); 8.01 (*d*, *J* = 8.0, 2 H).

*5-(4-Methoxyphenyl)-1*H*-tetrazole* (**2h**) [6a]: M.p. 231 – 232°. ^{1}H-NMR: 3.83 (*s*, 3 H); 7.14 (*d*, *J* = 8.8, 2 H); 7.97 (*d*, *J* = 8.8, 2 H).

*5-(2-Methoxyphenyl)-1*H*-tetrazole* (**2i**) [19]: M.p. 159 – 160°. ^{1}H-NMR: 3.85 (*s*, 3 H); 7.15 – 7.19 (*m*, 2 H), 7.55 (*t*, *J* = 8.5, 1 H); 7.92 (*d*, *J* = 8.5, 1 H).

*5-(Naphthalen-2-yl)-1*H*-tetrazole* (**2j**) [6a]: M.p. 205 – 206°. ^{1}H-NMR: 7.59 – 7.68 (*m*, 2 H); 7.98 – 8.18 (*m*, 4 H); 8.65 (*s*, 1 H).

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