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Facile one-pot preparation of 5-aryltetrazoles and 3-arylisoxazoles from aryl bromides

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ABSTRACT

The successive treatment of aryl bromides with *n*-BuLi, DMF, hydroxylamine hydrochloride, and finally diphenylphosphoryl azide provided efficiently the corresponding 5-aryltetrazoles in good to moderate yields. Similarly, the successive treatment of aryl bromides with *n*-BuLi, DMF, hydroxylamine hydrochloride, and finally diethyl acetylenedicarboxylate and Oxone® provided efficiently the corresponding diethyl 3-arylisoxazole-4,5-dicarboxylates in good to moderate yields. Aromatic aldoximes are the key intermediates in both reactions, and 5-aryltetrazoles and 3-arylisoxazoles could be obtained from aryl bromides in one pot under transition-metal-free conditions.

1. Introduction

Nitrogen-containing heterocyclic compounds are very attractive due to their potent biological activities [1]. Tetrazoles [2a] and isoxazoles [3a], in particular, are one of the most important nitrogen-containing five-membered heterocyclic compounds and serve as units or cores of some pharmaceuticals and agrochemicals. For example, Losartan, a 5-(2′-biphenyl)tetrazole derivative, is an angiotensin II receptor blocker bearing antihypertensive activity [2b], and Valdecoxib, a 3-phenylisoxazole derivative, is a COX-2 inhibitor bearing anti-inflammatory activity [3d,3e], as shown in Fig. 1. Extensive synthetic studies of 5-substituted tetrazoles and 3-substituted isoxazoles have been carried out [2,3]. The conventional methods for the preparation of 5-aryltetrazoles and 3-arylisoxazoles include the reactions of aromatic nitriles with metal azides $[N_1 + N_3]^2$ and the reactions of aromatic nitrile oxides derived from aromatic aldoximes with alkynes [3], respectively.

As recent studies of the preparation of 5-aryltetrazoles, the reaction of aromatic nitriles and sodium azide in DMF [4a], the reaction of aromatic nitriles, sodium azide, and Amberlyst-15 in DMSO [4b], and other related reactions with aromatic nitriles [4c–4f] were reported. The Ugi reaction with aldehydes or ketones, amines, isonitriles, and $TMSN_3$ in CH_3OH was also reported [5a–5d]. For the preparation of 5-substituted tetrazoles using transition metals, the reaction of aldehyde hydrazones with $PhI(OAc)_2$ (DIB), $TMSN_3$, and $Cu(OAc)_2$ [6a], the reaction of arylboronic acids with NaN_3 and Pd(II) complex [6b], the reaction of allyl carbonates with *t*-butyl isonitrile, $TMSN_3$, and $Pd(OAc)_2$ [6c], and the reaction of aldoximes with NaN_3 and $InCl_3$ [6d] were reported. For the construction of 5-substituted tetrazoles via $[N_2 + N_2]$, the reaction of aromatic aldehydes, hydrazine, di-*t*-butylazodicarboxylate (DBAD), and [bis(trifluoroacetoxy)iodo] benzene (PIFA) [7a], the reaction of aryldiazonium salts, amidine, and I_2·KI [7b], and the reaction of aryldiazonium salts, 2,2,2-trifluorodiazomethane, and AcOAg [7c] were reported.

As recent studies of the preparation of 3-substituted isoxazoles, the reaction of benzylic chlorides with *N*-methylmorpholine *N*-oxide (NMO), NH_2OH·HCl, and then Oxone® in the presence of alkynes [8a], the reaction of α,α-difluoromethyl aldoxime with *N*-chlorosuccinimide (NCS) in the presence of alkynes [8b], the reaction of aldoximes and DIB in the presence of alkynes 8c], and other related reactions [8d–8k] under transition-metal-free conditions were reported. For the preparation of 3-substituted isoxazoles using transition metals, the reaction of terminal alkynes, primary amines, *t*-BuONO, $ZnCl_2$, and CuI [9a], the reaction of α-hydroxyimino acids with alkenes, Oxone®, and $Ru(bpy)_3Cl_2$ under irradiation with blue LED [9b], and other related reactions [9c–9e] were reported.

Among the above mentioned reactions, the reaction of aromatic aldoximes with diphenylphosphoryl azide (DPPA) $[N_1 + N_3]$ for the

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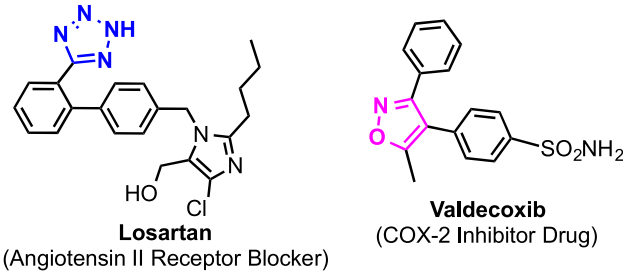


Fig. 1. Typical pharmaceuticals bearing 5-aryltetrazole or 3-arylisoxazole unit.

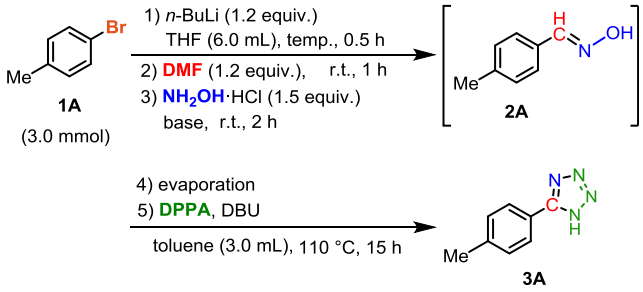
preparation of 5-aryltetrazoles [10] and the reaction of aromatic nitrile oxides derived from aromatic aldoximes with alkynes for the preparation of 3-arylisoxazoles are very attractive due to the simple operation and the ease of handling of the reagents. On the other hand, aryl bromides are either commercially available or can be easily obtained from the reactions of arenes with brominating reagents, such as Br_2, Br_2 with Fe, NBS, 1,3-dibromo-5,5-dimethylhydantoin (DBH), *etc.* In this report, we would like to present a one-pot and transition-metal-free preparation of 5-aryltetrazoles and 3-arylisoxazole-4,5-dicarboxylates through the reaction of aryl bromides with *n*-BuLi, DMF, and then $NH_2OH·HCl$, followed by the reactions with DPPA and Oxone® in the presence of diethyl acetylenedicarboxylate, respectively.

2. Results and discussion

First, the one-pot preparation of 5-aryltetrazoles from aryl bromides via aromatic aldoximes was studied. The reaction of 4-methylphenyl bromide **1A** with *n*-BuLi (1.55 M in hexane, 1.2 equiv.) in THF at −70 °C for 0.5 h, followed by the reaction with DMF (1.2 equiv.) at room temperature for 1 h and then the reaction with $NH_2OH·HCl$ (1.5 equiv.) and Et_3N (1.5 equiv.) at room temperature for 2 h, gave the corresponding aldoxime **2A** in over 90% yield. Based on this result, the same successive treatment of 4-methylphenyl bromide **1A** with *n*-BuLi, DMF, and $NH_2OH·HCl$, followed by solvent evaporation and treatment of the residue with DPPA (2.0 equiv.) and DBU (4.0 equiv.) in toluene for 15 h at refluxing conditions [10], was carried out to give 5-(4′-methylphenyl)tetrazole **3A** in 28% yield, as shown in Table 1 (entry 1). To improve the yield of **3A**, K_2CO_3 (0.75 equiv. and 1.5 equiv.) instead of Et_3N was used in the 3rd step, the amount of DPPA (2.5 equiv. and 3.0 equiv.) was increased, and the amount of DBU was reduced in the 5th step under the same procedure and conditions except that the reaction temperature was −50 °C in the 1st step (entries 2–5). Consequently, it was found that the treatment of 4-methylphenyl bromide **1A** with *n*-BuLi (1.2 equiv.) at −50 °C for 0.5 h in the 1st step, DMF (1.2 equiv.) at room temperature for 1 h in the 2nd step, and $NH_2OH·HCl$ (1.5 equiv.) and K_2CO_3 (1.5 equiv.) at room temperature for 2 h in the 3rd step, followed by solvent evaporation and final treatment of the residue with DPPA (2.5 equiv.) and DBU (3.5 equiv.) in toluene for 15 h under refluxing conditions gave 5-(4′-methylphenyl)tetrazole **3A** in 70% yield (entry 4). As a gram-scale experiment, the treatment of 4-methylphenyl bromide **1A** (6 mmol) with *n*-BuLi, DMF, $NH_2OH·HCl$ and K_2CO_3, solvent removal, and then treatment with DPPA and DBU under the same procedure and conditions gave **3A** in 64% yield, as shown in Scheme 1.

Based on those results, the treatment of 3-methylphenyl bromide **1B**, 3,4-dimethylphenyl bromide **1C**, 4-isopropylphenyl bromide **1D**, phenyl bromide **1G**, 4-biphenyl bromide **1H**, and 4-methoxyphenyl bromide **1I** with *n*-BuLi, DMF, and then $NH_2OH·HCl$ with K_2CO_3, followed by solvent evaporation and the reaction of the residue with DPPA and DBU in toluene under the same procedure and conditions, gave the corresponding 5-aryltetrazoles **3B~3D** and **3G~3I** in good to moderate yields, respectively, as shown in Scheme 1. The same treatment of aryl bromides **1J** and **1K** bearing an *O*-methoxymethyl (*O*-MOM) group and aryl bromide **1L** bearing a cyclic acetal group gave 5-aryltetrazoles **3J** and **3K**, both of which were deprotected by extraction of the reaction mixture after acidification with aq. HCl, and **3L** in good to moderate yields, respectively. As examples of aryl bromides bearing electron-withdrawing groups, such as chloro and trifluoromethyl groups, 4-chlorophenyl bromide **1M**, 3-chlorophenyl bromide **1N**, and 4-trifluoromethylphenyl bromide **1O** were also treated with *n*-BuLi, DMF, and $NH_2OH·HCl$ with K_2CO_3. Then, the solvent was evaporated and the reaction with DPPA and DBU under the same procedure and conditions was

Table 1
Transformation of 4-methylphenyl bromide **1A** to 5-(4′-methylphenyl)tetrazole **3A**.



entry	Temp. (°C)	base	DPPA (equiv.)	DBU (equiv.)	Yield (%)
1[a]	−70	Et_3N (1.5 equiv.)	2.0	4.0	28
2	−50	K_2CO_3 (0.75 equiv.)	2.5	3.5	67
3[b]	−50	K_2CO_3 (0.75 equiv.)	2.5	3.5	46
4	**−50**	**K_2CO_3 (1.5 equiv.)**	**2.5**	**3.5**	**70**
5	−50	K_2CO_3 (1.5 equiv.)	3.0	3.5	59

The bold values represent the best conditions.
[a] The mixture was warmed at 0 °C for 5 min before addition of DMF at 2nd step reaction.
[b] Reaction was carried out without evaporation, before addition of DPPA.