A Practical Synthesis of 5-(4'-Methylbiphenyl-2-yl)-1*H*-tetrazole

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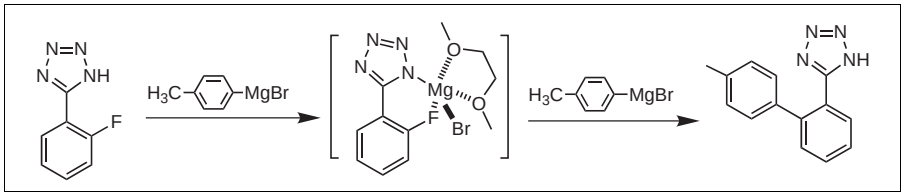

Practical synthesis of 5-(4'-methylbiphenyl-2-yl)-1*H*-tetrazole, key intermediate in several angiotensin II receptor antagonists from 2-fluorobenzonitrile in excellent yields and very high purity is described.

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Introduction.

Inhibition of renin angiotensin system (RAS) is the topic of pharmaceutical research for the last decade. Recently the discovery of heterocyclic agents that are angiotensin II receptor antagonists has produced yet another class of potential drugs **I-VIII**, for treatment of hypertension [1]. The major structural feature common in all these drug molecules is a biphenyl moiety with acidic tetrazole group in 2-position (Figure-1) [2-4]. The key steps involved in the synthesis of the biphenyl tetrazoles

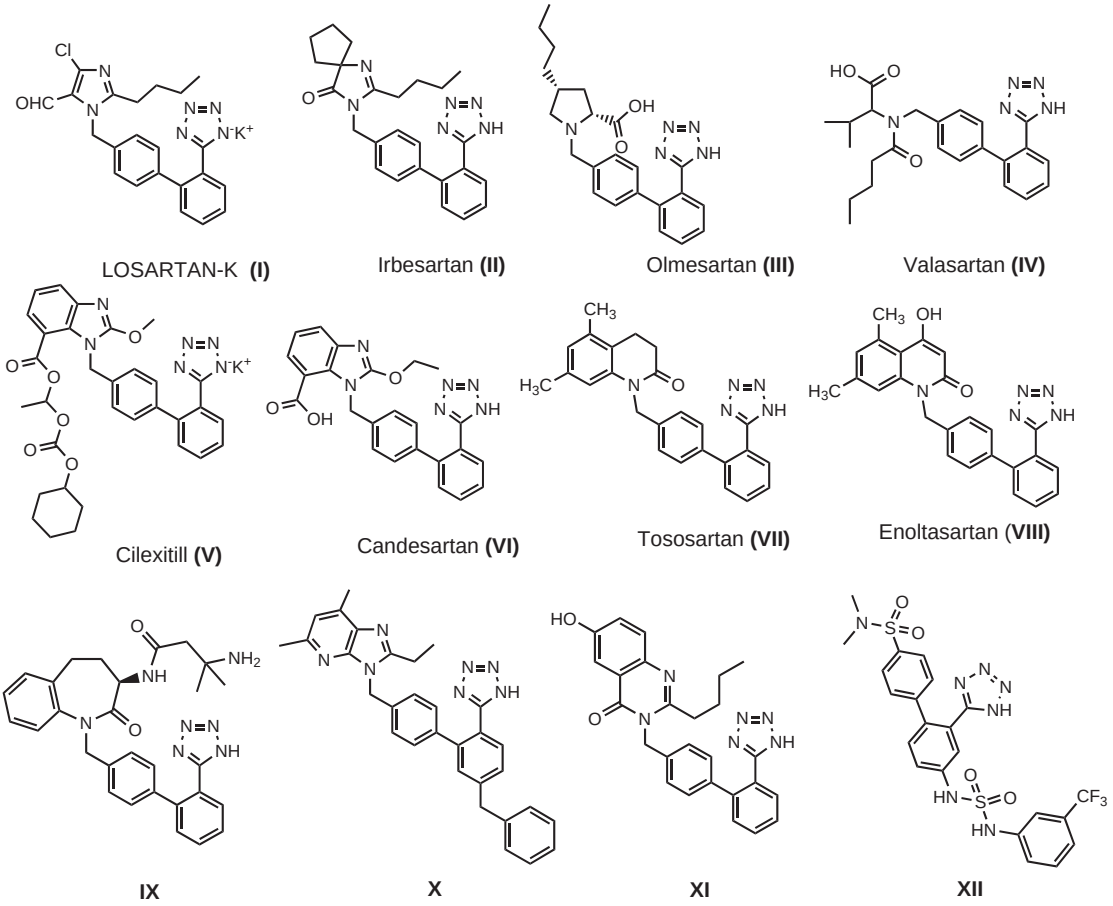
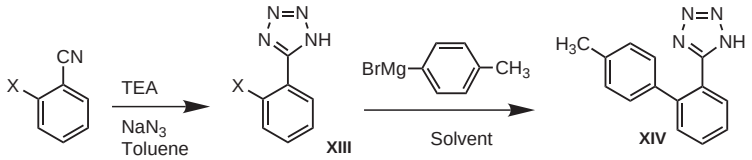


Figure I. Examples of pharmaceutically relevant biphenyl tetrazoles **I-XII**

are (1) aryl-aryl coupling reaction to form the biphenyl moiety and (2) conversion of nitrile group in the 2-position to tetrazole. Methods generally employed are Ullmann coupling between two iodoaryl derivatives [5] or nickel [6], manganese [7] or palladium [8] catalyzed coupling of aryl halides with 2-halobenzonitrile. In the subsequent reaction, nitrile group at 2-position was converted to tetrazole using either trialkyltin azide [9] or TMS-N_3 [10]. Aside from the expense and potential concerns associated with the recovery of $Pd°L_4$ catalysts from pilot-scale procedures, it was difficult to satisfactorily remove trace levels of palladium contamination from products. Moreover, serious problems are also encountered in the conversion of biphenyl nitrile to biphenyl tetrazole due to the use of highly toxic trialkyltin azide [9] or TMS-N_3 [10] which make rigorous purification absolutely necessary in order to obtain the high purity product as required by pharmaceutical industry.

An alternate approach described by Russel and Murry [11] involve the tetrazolylation of 2-fluorobenzonitrile by refluxing with sodium azide in acetic acid. Subsequently the formed 5-(2-fluorophenyl)-1*H*-tetrazole is reacted with *p*-tolylmagnesium bromide to yield the desired biphenyl tetrazole. Here *in situ* generation of poisonous hydrazoic acid and use of ether solvent in Grignard reaction for biphenyl formation make this method unsuitable for large-scale preparations. In our attempts [12] to develop an efficient process for the preparation of angiotensin II antagonists such as Losartan-K (I) we require a suitable procedure for large-scale preparation of 5-(4'-methylbiphenyl-2-yl)-1*H*-tetrazole XIV. In this paper we describe a practical and economically viable synthesis of 5-(4'-methylbiphenyl-2-yl)-1*H*-tetrazole XIV from 5-(2-fluorophenyl)-1*H*-tetrazole XIIIa *via* Grignard reaction with *p*-tolylmagnesium bromide in 93% yield and 99.6% HPLC purity (Scheme-I).

Scheme I



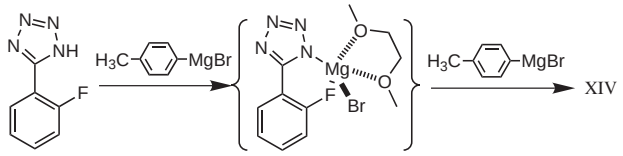
a) X= F
b) X= Cl
c) X= Br

Results and Discussion.

Having developed [13] a suitable high yield and high purity procedure for the preparation 5-(2-halophenyl)-1*H*-tetrazoles **XIIIa-c** by reacting 2-halobenzonitrile with sodium azide and triethyl ammonium chloride in toluene at 98-100 °C, we now concentrated our efforts in the preparation of Grignard reagent and its coupling in suitable solvent to give **XIV** (Scheme-I). For better recoverability and reusability of solvent, we initially used single solvent for the preparation of *p*-toluene magnesium bromide and its coupling with 5-(2-fluorophenyl)-1*H*-tetrazole.

Our preliminary experiments using ether and THF as single solvent did not give fruitful results and ended with only poor yields of biphenyl tetrazole **XIV** (entry 1 & 2, Table-I). As observed in the literature [11], when we carried out the coupling reaction in dimethoxy ethane (DME) by adding *p*-toluene magnesium bromide in ether, **XIV** was obtained in reasonably good yield (entry 3, Table-I). This observation made us think that probably DME solvent is essential for the formation of some sort of complex with magnesium to facilitate the coupling reaction. Further when both the Grignard reagent and the subsequent coupling reaction were carried out in DME, increasingly good yields of the required compound **XIV** with greater purity was obtained (entry 4, Table-I). For

Scheme II



Plausible mechanism for the formation of **XIV**

Table I

Effect of solvent and reaction conditions on the yield of the product.

S.No	Solvent for Grignard preparation	Coupling reaction: Solvent	Reaction Temp. (°C)	Reaction Time (h)	Yield of **XIV** (%)
1	Ether	Ether	Reflux	48	3
2	THF	THF	Reflux	48	10
3	Ether	DME	Reflux	24	67
4	DME	DME	85	20	74
5	THF	DME	80	12	93

the first time, we achieved highest yield (93%) and best purity (99.6%) by adding *p*-toluene magnesium bromide in THF to 5-(2-fluorophenyl)-1*H*-tetrazole in DME and heating the mixture at 80 °C (entry 5, Table-I).

In order to have broader applicability, we carried out coupling reaction with 5-(2-chlorophenyl)-1*H*-tetrazole (**XIIIb**) in DME by adding *p*-toluene magnesium bromide in THF and heating at 80-85 °C. Contrary to our expectation, the reaction did not proceed even after refluxing the mixture for longer hours (72 h). With bromo derivative **XIIIc**, the reaction was sluggish and did not give the desired product. This observation revealed that, apart from DME solvent, fluoro group at 2-position on the phenyl ring containing tetrazole moiety was also essential for the success of the reaction.

Based on these observations, we propose that, initial addition of Grignard reagent to 5-(2-fluorophenyl)-1*H*-tetrazole forms an electron rich magnesium tetrazolate complex that is stabilized by interactions with nucleofugic fluoro group at 2-position (Scheme-II). The stability of the complex may be further increases by forming a binding pocket with dimethoxyethane (DME) [8b]. On further addition of Grignard reagent, the fluoro group activated by magnesium tetrazolate undergoes nucleophilic displacement reaction (S_NAr) to give the required biphenyl product **XIV**. In the preparation of Grignard reagent it is not essential whether we use DME or THF as solvent [14]. In case of chloro and bromophenyl magnesium tetrazolates, probably the interactions involving chloro or bromo groups with magnesium are not strong enough to facilitate nucleophilic displacement (S_NAr) reaction.

In conclusion, we described here an efficient and industrially viable practical procedure for the synthesis of 5-(4'-methylbiphenyl-2-yl)-1*H*-tetrazole, key intermediate in several angiotensin II receptor antagonists from 2-fluorophenyltetrazole 93% yield and 99.6% purity.

EXPERIMENTAL

General.

Melting points were recorded on Buchi 535 melting point apparatus and are uncorrected. All the reactions were monitored by thin layer chromatography performed on precoated silica gel $60F_{254}$ plates (Merck). Compounds were visualized with UV light at 254nm and 365nm, iodine and heating plates after dipping in 2% phosphomolybdic acid in 15% aq. H_2SO_4 solution. All solvents used were purified and dried according to the standard procedures. IR spectra were recorded on Perkin-Elmer 683 or 1310 FT-IR spectrometer with KBr pellets. NMR spectra were recorded on Varian Unity-400 MHz and BRUKER AMX 300 MHz spectrometers using tetramethyl silane as an internal standard. ^{13}C NMR was recorded on Varian Unity at 100 MHz using $CDCl_3$ as internal standard. Mass spectra were recorded on a VG Micromass 7070H and Finnigan Mat 1020B mass spectrometers operating at 70 eV. 2-Fluoro phenyltetrazole **XIIIa**, 2-chlorophenyl tetrazole **XIIIb** and 2-bromophenyl tetrazole **XIIIc** were prepared according to the reported procedure [12].

Typical Procedure for the Preparation of 5-(4'-Methylbiphenyl-2-yl)-1*H*-tetrazole.

To the suspension of activated magnesium turnings (46.7 g, 1.92 mol) in anhydrous tetrahydrofuran (200 mL), *p*-bromotoluene (330 g, 1.92 mol) in tetrahydrofuran (1 L) was added drop wise in such a way that the reaction temperature is maintained at 40-50 °C. Following the addition, the mixture was stirred at 50 °C until the magnesium was entirely dissolved (1 h). The resulting reagent was cooled to room temperature and added drop wise to the solution of 2-fluorophenyl tetrazole (100 g, 0.61 mol) in dimethoxyethane (1.5 L) at 5-10 °C (1 h) under N_2. After complete addition, the mixture was brought to room temperature, heated to distill out tetrahydrofuran till the temperature of reaction mixture reached to 80 °C and then stirred for 12 h. With ice bath cooling, the mixture was slowly quenched with 6 *N* HCl (400 mL), dimethoxyethane was removed under reduced pressure. The resulting aqueous residue was extracted with dichloroethane (4x150ml) and the combined organic layer was washed with 2 *N* NaOH (3x200mL). The alkaline portion was acidified to pH 2 with conc. HCl, the precipitate formed was collected by filtration, washed with water and dried at 60 °C. Recrystalization from toluene afforded a tan color solid 5-(4'-methylbiphenyl)-2-yl)-1*H*-tetrazole **XIV** (133.2 g) in 93% yield and 99.6% HPLC purity; m.p. 146 °C (Lit. [11] m.p. 144-148 °C). The product was fully characterized by NMR and mass spectral analysis and compared with authentic sample.

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