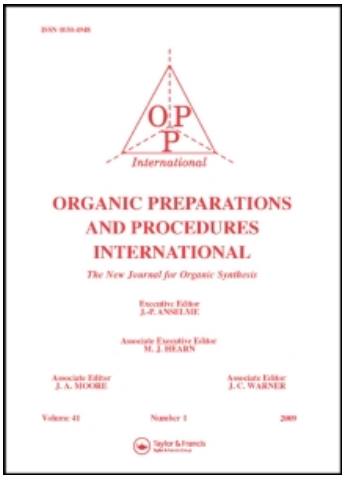

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AN IMPROVED SYNTHESIS OF 5-(2-FLUOROPHENYL)-1H-TETRAZOLE

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OPPI BRIEFS

AN IMPROVED SYNTHESIS OF 5-(2-FLUOROPHENYL)-1H-TETRAZOLE

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(04/22/03)

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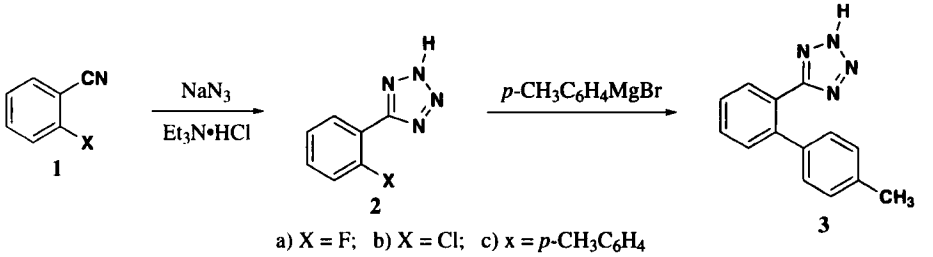
The preparation of *Losartan-K*, a non-peptide angiotensin II receptor antagonist, requires 5-(4'-methylbiphenyl-2-yl-1H-tetrazole (**3**) as an intermediate.[1] It is generally prepared[2] by the tetrazolylation of 2-cyano-4'-methylbiphenyl (**1c**) using tributyltin azide. This protocol requires a long reaction time and the use of highly toxic trialkyltin azide. Rigorous purification of stannous compounds is necessary to obtain the desired tetrazole in the high purity as demanded by the pharmaceutical industry. Further, attempts by us[3] and others[4,5] on tetrazolylation of 2-cyano-4'-methylbiphenyl (**1c**) with sodium azide and triethylammonium chloride at high temperatures (99-120°C) in dimethylformamide (DMF) or toluene took longer and gave only a moderate yield of the product. Russell and Murray[6] reported an alternate approach involving the reaction of 5-(2-fluorophenyl)-1*H*-tetrazole (**3a**) with *p*-tolylmagnesium bromide to give 5-(4'-methylbiphenyl-2-yl)-1*H*-tetrazole (**3c**) in excellent purity.



a) X = F; b) X = Cl; c) x = *p*-$CH_3C_6H_4$

The method reported[6] for the preparation of 5-(2-fluorophenyl)-1*H*-tetrazole (yield 69%), involved refluxing 2-fluorobenzonitrile (**1a**) in a mixture of sodium azide and acetic acid in *n*-butanol for two days. It is not practical for large scale preparation because of the *in situ* generation of hydrazoic acid, which is poisonous and explosive.

We report herein an improved method for the preparation of 5-(2-chlorophenyl)- and 5-(2-fluorophenyl)-1*H*-tetrazoles by treatment of 2-halobenzonitriles with triethylammonium chloride and sodium azide in toluene at reflux for 8-10 h. In this procedure, instead of hydrazoic acid, triethylammonium azide is generated *in situ* and reacts with the nitrile to give a 93% yield of tetrazole **3a** in 99.6% HPLC purity. This method has the advantages of shorter reaction time, lower temperature, safe handling and purity of the product.

EXPERIMENTAL SECTION

1H NMR spectra were recorded using Varian FT 200 MHz (Gemini) instrument with TMS as the internal standard. Mass spectra were recorded on VG Micro mass 7070 H.

5-(2-Fluorophenyl)-1*H*-tetrazole. Typical Procedure.- To a suspension of triethylammonium chloride (89 g, 0.65 mol) and toluene (200 mL) taken in to a 2 L four necked RB flask equipped with a mechanical stirrer and thermometer and reflux condenser, was slowly added sodium azide (4.2 g, 0.64 mol) as a solid at RT with stirring. A solution of 2-fluorobenzonitrile (51 g, 0.422 mol) in toluene (250 mL) was slowly added, stirred at RT for 5 min and then heated to gentle reflux (98-100°C) for 8 h. After cooling the reaction mixture to RT, distilled water (200 mL) was added, the aqueous layer was separated; the toluene layer was washed with water (3 x 50 mL). The light brown colored aqueous layer (pH 8) was cooled to 0-5°C, acidified to pH 2 using conc. HCl (65 mL) with stirring for 10 min. The solid precipitate formed was collected and washed with water. The cream colored solid was dried in a vacuum oven (64 g, 93% yield) and purity 99.64 by HPLC). The 2-chloro analogue was obtained similarly. The analytical data of the products were consistent with those of the previously reported compounds.[7,8]

5-(2-Fluorophenyl)-1*H*-tetrazole (3a), mp. 162-163°C, *lit.*[7] 160-162°C; *^{1}H NMR ($CDCl_3$+ DMSO)*: δ 8.15 (m, 1H), 7.50 (m, 1H), 7.15-7.30 (m, 2H); *MS (EI 70eV) m/z (%)*: 164 (M^+, 100), 136 (90), 107 (90).

5-(2-Chlorophenyl)-1*H*-tetrazole (3b), mp. 179-180°C, *lit.*[8] 180-181°C; *^{1}H NMR ($CDCl_3$)*: δ 7.90 (m, 1H), 7.40-7.60 (m, 3H); *MS (EI 70eV) m/z (%)*: 180 (M^+, 60), 89 (100).

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A NEW SIMPLIFIED METHOD FOR THE PREPARATION OF *N,N'*-DIPHENYLUREA

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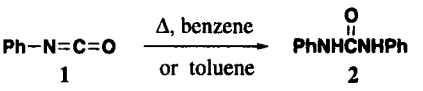
Ureas constitute a family of organic molecules of great interest.[1] *N,N'*-Diphenylurea (**2**, carbanilide) is widely used in numerous applications.[2-10] Consequently, the synthesis of **2** has been the subject of several previous studies[11-18] utilizing a variety of solvents and metallic inorganic catalysts. However, these methods required large excesses of solvents, long reaction times, tedious work-ups, and elaborate purification procedures. Since **2** is relatively expensive, we have developed a new, inexpensive and clean approach to prepare **2** from phenyl isocyanate (**1**) in anhydrous benzene or toluene.[19] The approach is attractive because of its



simplicity, ease of operation, and high yield of a very pure product **without** recrystallization. Moreover, no catalyst is required, and the reaction time is short. The Table below contains pertinent results which are the average of two separate experiments.

Table. Self-condensation of Phenyl Isocyanate (**1**) in benzene and toluene to N,N'-Diphenylurea

Solvent	Yield (%)	mp (°C)
Benzene	62	239-240, *lit*[2] mp 238-240°C
Toluene	62	241.5-242