# Efficient Synthesis of Conjugated 1,2,4-Triazole Derivatives under Suzuki Cross-Coupling Reactions in the Presence of Ionic Liquids

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***Abstract –*** ***The new derivatives of 4-phenyl-4H-1,2,4-triazole were synthesized under palladium catalyzed Suzuki cross-coupling reaction utilizing the intermediate 3,5-bis(4-bromophenyl)-4-phenyl-4H-1,2,4-triazole and boronic acids. The transformations conducted both in the presence of conventional solvents and in ionic liquids resulted in the formation of the conjugated 1,2,4-triazole arrangements in high yields.***

Keywords – Suzuki cross-coupling, heterocycles, 1,2,4-triazoles, ionic liquids, cyclocondensation.

## Introduction

1,2,4-Triazoles belong to the group of five-membered, non-naturally occurring aromatic heterocycles [1]. The first compound from this family was prepared by Fischer in 1878 and since then the large number of precious 1,2,4-triazole derivatives were produced. They have attracted the attention of many scientists due to a broad spectrum of biological activity. 1,2,4-Triazoles display mainly antifungal (*Fluconazole*, *Viroconazole*, *Ketoconazole*) and anticancer (*Letrozole*) activities, which makes them potentially useful agents in medicine [2]. They are also applied in agriculture as potential defoliants (*Amizole*). Conjugated macrocyclic arrangements based on the 1,2,4-triazole core exhibit interesting electron-transfer or luminescent properties and are used in organic light-emitting diodes (OLED) or corrosion inhibitors [3, 4]. The most popular method for preparation of these heterocyclic compounds involves the reaction of diacylhydrazines with aromatic amines, in the presence of the dehydrating agent, e.g. phosphorus pentoxide, zinc chloride or *N*,*N*'-diphenylphosphenimidous amide. Other methodologies include the reaction of acid hydrazides with imidoyl chlorides, esters, nitriles or the transformations of different five-membered heterocycles, just to mention 1,3,4-oxadiazoles, 1,3,4-thiadiazoles, but also dihydro-1,2,4,5-tetrazines [5].

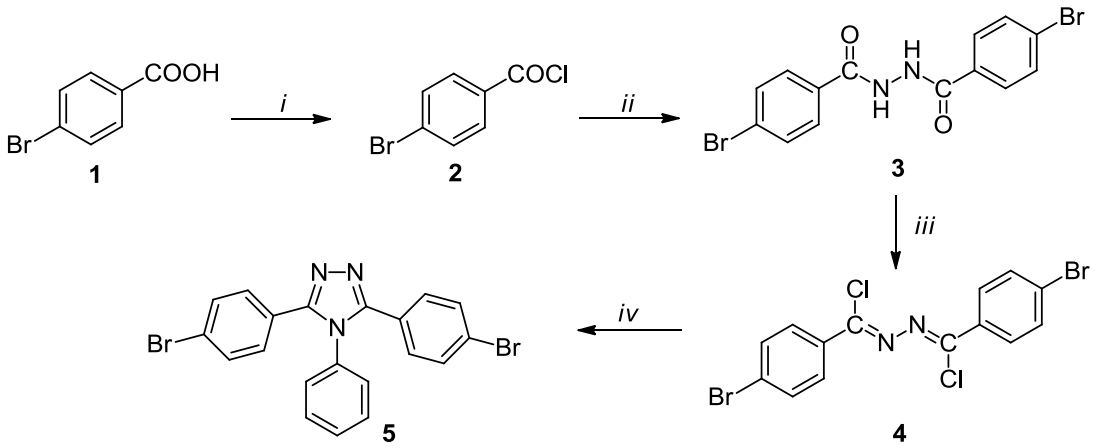
Over the last decades one may observe a particular interest in a new class of organic compounds called ionic liquids ILs. These modern solvents, exhibiting low vapor pressure, good thermal stability and wide liquid regions, perfectly match the principles of green chemistry in terms of process safety, environmental protection and the rational use of energy [6].

In our previous works on the application of acid hydrazides as effective reagents for synthesizing of some heterocyclic rings, we elaborated efficient few-step methodologies for the preparation of conjugated 1,3,4-oxadiazoles [7] and 1,3,4-thiadiazoles [8], making use of Suzuki cross-coupling reaction. The present study was undertaken to investigate the possibility of the preparation of another five-membered heterocyclic arrangements – 1,2,4-triazoles.

## Results and Discussion

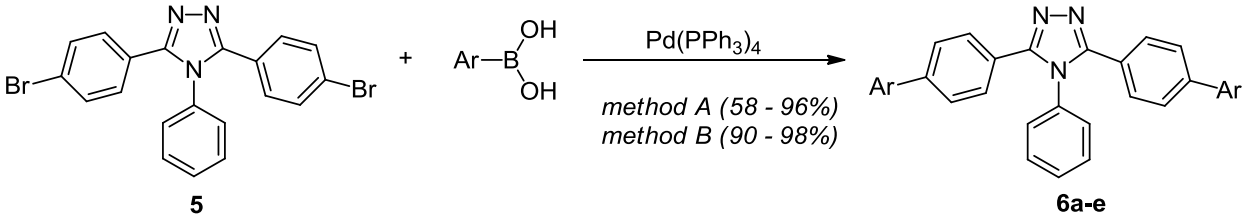
The key 3,5-bis(4-bromophenyl)-4*H*-1,2,4-triazole substituted with phenyl group at the position 4 was used as a starting material. It was prepared from commercially available 4-bromobenzoic acid (**1**), which was transferred into the corresponding acid chloride (**2**) and then substituted with hydrazine hydrate yielding the symmetrically substituted *N,N'*-bis(4-bromobenzoyl)hydrazine (**3**). The latter intermediate was transformed into the more reactive chloro-derivative (**4**) in the presence of phosphorus pentachloride and in the non-polar solvent

toluene. The subsequent heating with excess aniline ($C_6H_5NH_2$) generated the key 4-phenyl-4*H*-1,2,4-triazole derivative (**5**).




Scheme 1. Synthesis of 3,5-bis(4-bromophenyl)-4-phenyl-4*H*-1,2,4-triazole (**5**) – the precursor for Suzuki cross-coupling reactions. Reagents and conditions: (*i*) $SOCl_2$, toluene, reflux; (*ii*) $NH_2NH_2 \bullet H_2O$, TEA, $CHCl_3$, rt; (*iii*) $PCl_5$, toluene, reflux; (*iv*) $C_6H_5$-$NH_2$, toluene, reflux.

The next stage in the preparation of the conjugated 1,2,4-triazole derivatives was the Suzuki cross-coupling reaction - one of the most popular catalytic methods of C-C bond construction. The transformation was realized according to two methods: the conventional, making use of typical solvents (Scheme 2, *method A*) and alternative, applying ionic liquids ILs instead of common solvents (Scheme 2, *method B*).




Ar = phenyl (**a**), tiophen-3-yl (**b**), tiophen-2-yl (**c**), 4-(*N,N*-diphenylamino)phenyl (**d**), thianthren-1-yl (**e**)

Scheme 2. The conventional and alternative Suzuki cross-coupling reaction for 3,5-bis(4-bromophenyl)-4-phenyl-4*H*-1,2,4-triazole (**5**). Reagents and conditions: *method A* - aryl dibromide **5** (1.00 mmol), arylboronic acid **a-e** (2.50 mmol), $Pd(PPh_3)_4$ (0.05 mmol), $NBu_4Br$ (0.10 mmol), $K_2CO_3$ (10 mmol), toluene/$H_2O$/EtOH (10:6:3 mL), oil bath 130 °C, 4-12 h; *method B* - aryl dibromide **5** (1.00 mmol), arylboronic acid **a-e** (2.50 mmol), $Pd(PPh_3)_4$ (0.05 mmol), choline-OH (10 mL), MW, 125 °C, 10 min.

Regardless of the method used, each reaction between the starting 4-phenyl-4*H*-1,2,4-triazole (**5**) and boronic acid (**a-e**) was conducted in the presence of 5 mol% palladium catalyst $Pd(PPh_3)_4$. The conventional transformation (*method A*) proceeded in a two-phase toluene/$H_2O$/EtOH solvent system and in the presence of $K_2CO_3$, playing a role of base, and a phase transfer catalyst $NBu_4Br$. The second alternative transformation (*method B*) was successfully conducted in choline hydroxide solution (IL), acting here both as a green solvent and as a base, necessary to facilitate the transmetallation step. Additionally, we found that the IL can be regenerated and recycled into the reaction with only a slight decrease in product yield after five cycles. Both presented methodologies have led to obtain a new symmetrical conjugated 1,2,4-triazole derivatives **6a-e** in high yields. However, the alternative methodology making use of ionic liquid IL has the advantage of providing the desired products rapidly, and in high yields

which makes it a useful addition to the conventional synthetic protocol. The new products were characterized by elemental analysis and spectroscopic methods.

## Conclusion

We have prepared a series of new 4*H*-1,2,4-triazole derivatives as extended π-conjugated systems. The leading 4-phenyl-4*H*-1,2,4-triazole ring has been coupled at the position 3 and 5 *via* a 1,4-phenylene linker with selected aromatic arrangements under Suzuki cross-coupling reaction. Two methodologies, the conventional, applying typical solvents and alternative, using ionic liquids, led to the final products which may be of a potential interest of optoelectronics.

## Acknowledgments

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