Potassium tert-Butoxide Promoted Synthesis of 4,5-Diaryl-2H-1,2,3-triazoles from Tosylhydrazones and Nitriles

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Abstract Intermolecular cycloaddition of tosylhydrazones with nitriles was investigated. t-BuOK was shown to be an excellent base for increasing the effectiveness of the reaction in this protocol, and homocoupling of the tosylhydrazones was significantly inhibited by using xylene as a solvent. Through this transformation, a variety of 4,5-diaryl-2H-1,2,3-triazoles were prepared in good to excellent yields and with high purities. The process is azide-free and transition-metal-free.

Key words triazoles, tosylhydrazones, cycloaddition, potassium tert-butoxide

NH-1,2,3-Triazoles, as a class of special 1,2,3-triazoles, are found in a number of bioactive molecules (for examples, see Figure 1). Consequently, their synthesis has become an important issue in 1,2,3-triazole chemistry and medicinal chemistry. Since the discovery of the copper-catalyzed Huisgen cycloaddition of azides and alkynes for the synthesis of 1,2,3-triazoles with exclusive regioselectivity and high efficiency, several elegant protocols have been used to prepare NH-1,2,3-triazoles from azides through cycloaddition reactions of azides, multicomponent reactions, and other reactions. Although various NH-1,2,3-triazole motifs have been synthesized, 4,5-diaryl-NH-1,2,3-triazoles have received little attention.

Generally, 4,5-diaryl-NH-1,2,3-triazoles have been synthesized by [3+2]-cycloaddition of diarylalkynes with trimethylsilyl azide or sodium azide (Scheme 1a). Because of the potential explosivity and toxicity of azides, the concept of azide-free synthesis has been widely adopted in the synthesis of 1,2,3-triazoles. This progress has also influenced the synthesis of NH-1,2,3-triazoles. It is therefore imperative to explore azide-free protocols for the synthesis of 4,5-diaryl-1,2,3-triazoles. In 1988, Grundon and Khan reported that the reactions of aryldiazomethanes with arylaldehyde azines or aryl nitriles gave the corresponding 4,5-diaryl-NH-1,2,3-triazoles in moderate yields (Scheme 1b). Perhaps, the instability, hazardous nature, and difficulty in handling of diazo compounds has restricted the use of this cycloaddition reaction and, consequently, this work is rarely mentioned in the literature on 1,2,3-triazoles.

Scheme 1 Synthetic approaches to 4,5-diaryl-NH-1,2,3-triazoles
In recent decades, tosylhydrazones have attracted intense interest from the organic-synthesis community and have been widely used in many reactions as excellent and safe precursors of diazo compounds. Furthermore, the use of tosylhydrazones as versatile synthons has been explored in many novel reactions to afford various heterocycles, including 1,2,3-triazoles. Recently, the groups of Sakač and Mani reported a synthesis of NH-1,2,3-triazoles through 1,3-dipolar cycloadditions of diazo compounds generated in situ from tosylhydrazones. Obviously, the preparation of 4,5-diaryl-NH-1,2,3-triazoles by 1,3-dipolar cycloadditions of nitriles with diazo compounds generated in situ from tosylhydrazones would constitute an elegant protocol.

In 2017, the group of Maity and Manna described regioselective syntheses of 1,2,3-triazoles and pyrazoles from tosylhydrazones. They succeeded in synthesizing 4,5-diaryl-NH-1,2,3-triazoles in moderate to good yields by coupling tosylhydrazones. They also showed that the electronic nature of tosylhydrazones influenced the coupling process. As the results, when cross-couplings of different tosylhydrazones were carried out, the corresponding homocoupled 1,2,3-triazole similarly decreased the yields and the purities of the products (Scheme 1c). The challenge therefore remained of inhibiting the homocoupling of the tosylhydrazones similarly decreased the yields and the purities of the products (Scheme 1c). The challenge therefore remained of inhibiting the homocoupling of the tosylhydrazones similarly decreased the yields and the purities of the products (Scheme 1c).17

Initially, we chose benzaldehyde tosylhydrazone (1a) and benzonitrile (2a) as model substrates for the optimization of the reaction conditions (Table 1). 

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (equiv)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K₂CO₃ (2.0)</td>
<td>n.d.</td>
</tr>
<tr>
<td>2</td>
<td>DBU (2.0)</td>
<td>n.d.</td>
</tr>
<tr>
<td>3</td>
<td>t-BuOK (2.0)</td>
<td>38</td>
</tr>
<tr>
<td>4</td>
<td>Cs₂CO₃ (3.0)</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>t-BuOK (3.0)</td>
<td>90</td>
</tr>
</tbody>
</table>

*Reaction conditions: 1a (1.0 mmol), 2a (1.2 mmol), DMF (6 mL), 90 °C, 4 h, under Ar.

Suitable as a base in intramolecular cycloadditions did not facilitate the intermolecular reaction. However, when 2.0 equivalents of t-BuOK were used as the base, the desired product was isolated in 38% yield, along with benzoaldehyde azine as a byproduct in a yield of 35% (entry 3). Encouraged by this result, and with the aim of restraining the formation of the benzoaldehyde azine byproduct, we increased the amount of t-BuOK to 3.0 equivalents, and this gave the desired product in an excellent yield of 90%. Cs₂CO₃ as a base gave a lower yield of 30%. When we screened other suitable bases in intramolecular cycloadditions, did not facilitate the intermolecular reaction. However, when 2.0 equivalents of t-BuOK were used as the base, the desired product was isolated in 38% yield, along with benzoaldehyde azine as a byproduct in a yield of 35% (entry 3). Encouraged by this result, and with the aim of restraining the formation of the benzoaldehyde azine byproduct, we increased the amount of t-BuOK to 3.0 equivalents, and this gave the desired product in an excellent yield of 90%. Cs₂CO₃ as a base gave a lower yield of 30%. When we screened other suitable bases in intramolecular cycloadditions, did not facilitate the intermolecular reaction. However, when 2.0 equivalents of t-BuOK were used as the base, the desired product was isolated in 38% yield, along with benzoaldehyde azine as a byproduct in a yield of 35% (entry 3). Encouraged by this result, and with the aim of restraining the formation of the benzoaldehyde azine byproduct, we increased the amount of t-BuOK to 3.0 equivalents, and this gave the desired product in an excellent yield of 90%. Cs₂CO₃ as a base gave a lower yield of 30%. When we screened other suitable bases in intramolecular cycloadditions, did not facilitate the intermolecular reaction. However, when 2.0 equivalents of t-BuOK were used as the base, the desired product was isolated in 38% yield, along with benzoaldehyde azine as a byproduct in a yield of 35% (entry 3). Encouraged by this result, and with the aim of restraining the formation of the benzoaldehyde azine byproduct, we increased the amount of t-BuOK to 3.0 equivalents, and this gave the desired product in an excellent yield of 90%. Cs₂CO₃ as a base gave a lower yield of 30%. When we screened other suitable bases in intramolecular cycloadditions, did not facilitate the intermolecular reaction. However, when 2.0 equivalents of t-BuOK were used as the base, the desired product was isolated in 38% yield, along with benzoaldehyde azine as a byproduct in a yield of 35% (entry 3). Encouraged by this result, and with the aim of restraining the formation of the benzoaldehyde azine byproduct, we increased the amount of t-BuOK to 3.0 equivalents, and this gave the desired product in an excellent yield of 90%. Cs₂CO₃ as a base gave a lower yield of 30%. When we screened other suitable bases in intramolecular cycloadditions, did not facilitate the intermolecular reaction. However, when 2.0 equivalents of t-BuOK were used as the base, the desired product was isolated in 38% yield, along with benzoaldehyde azine as a byproduct in a yield of 35% (entry 3). Encouraged by this result, and with the aim of restraining the formation of the benzoaldehyde azine byproduct, we increased the amount of t-BuOK to 3.0 equivalents, and this gave the desired product in an excellent yield of 90%. Cs₂CO₃ as a base gave a lower yield of 30%. When we screened other suitable bases in intramolecular cycloadditions, did not facilitate the intermolecular reaction. However, when 2.0 equivalents of t-BuOK were used as the base, the desired product was isolated in 38% yield, along with benzoaldehyde azine as a byproduct in a yield of 35% (entry 3). Encouraged by this result, and with the aim of restraining the formation of the benzoaldehyde azine byproduct, we increased the amount of t-BuOK to 3.0 equivalents, and this gave the desired product in an excellent yield of 90%. Cs₂CO₃ as a base gave a lower yield of 30%. When we screened other suitable bases in intramolecular cycloadditions, did not facilitate the intermolecular reaction. However, when 2.0 equivalents of t-BuOK were used as the base, the desired product was isolated in 38% yield, along with benzoaldehyde azine as a byproduct in a yield of 35% (entry 3). Encouraged by this result, and with the aim of restraining the formation of the benzoaldehyde azine byproduct, we increased the amount of t-BuOK to 3.0 equivalents, and this gave the desired product in an excellent yield of 90%. Cs₂CO₃ as a base gave a lower yield of 30%.
bases (see Supporting Information), we found that the use of t-BuOK as a strong base is critical in improving the efficiency of this intermolecular reaction.

Having increased the efficiency of the intermolecular reaction of the tosylhydrazone and nitrile, we turned our interest to the inhibition of the homocoupling of the tosylhydrazone. When the reaction of benzaldehyde tosylhydrazone (1a) and 4-methylbenzonitrile 2b was carried out, the 4,5-diphenyl-2H-1,2,3-triazole (3a) homocoupling byproduct could not be separated from the desired product 3b by flash column chromatography on silica gel. When DMF was used as the solvent, the isolated product contained 6.1% of the tosylhydrazone homocoupling product. When toluene or xylene was used, however, the proportion of 3a (as determined by HPLC) was significantly reduced, and xylene was found to give the best result in terms of the yield and the selectivity. We surmised that, in comparison with Cs₂CO₃, the greater basicity of t-BuOK is a critical factor in relation to the deprotonation of the tosylhydrazone to transfer anions or diazo compounds, thereby markedly inhibiting the homocoupling of the tosylhydrazone. Therefore the optimal reaction conditions are:

- tosylhydrazone (1.0 mmol), nitrile (1.2 mmol), t-BuOK (3.0 mmol) for four hours at 90 °C under an Ar atmosphere.

With these optimized conditions in hand, we extended the scope of the method to the reactions of 1a with various nitriles 2 (Scheme 2). The intermolecular cyclization reaction was found to tolerate various substituents on the aryl nitrile 2, and gave the desired products 3a-o in good to excellent yields. The yields of the cross-coupling products were calculated from the combined isolated yields of the mixtures of the homocoupled 1,2,3-triazole and the cross-coupled 1,2,3-triazole. The figures in parentheses are the purities of the cross-coupled 1,2,3-triazole, determined by reverse-phase HPLC.

**Scheme 3** Reaction scope of tosylhydrazones 1 with nitriles 2 under the optimized conditions. *Reaction conditions: 1a (1.0 mmol), 2 (1.2 mmol), xylene (6 mL), 90 °C, 4 h, under Ar. The yields of the cross-coupling products were calculated from the combined isolated yields of the mixtures of the homocoupled 1,2,3-triazole and the cross-coupled 1,2,3-triazole. The figures in parentheses are the purities of the cross-coupled 1,2,3-triazole, determined by reverse-phase HPLC.*

**Table 2** Optimization of the Inhibition of Homocoupling of the N-Tosylhydrazone

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yieldb of 3b (%)</th>
<th>3a/3b†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMF</td>
<td>90</td>
<td>6.1: 93.9</td>
</tr>
<tr>
<td>2</td>
<td>toluene</td>
<td>93</td>
<td>0.7: 99.3</td>
</tr>
<tr>
<td>3</td>
<td>xylene</td>
<td>93</td>
<td>0.5: 99.5</td>
</tr>
</tbody>
</table>

*a Reaction conditions: 1a (1.0 mmol), 2b (1.2 mmol), solvent (6 mL), 4 h, under Ar.
*Based on the isolated mixture of 3a and 3b.
† Determined by HPLC.
cellent yields of 68–98%; however, the methoxycarbonyl-substituted product 3p was obtained in only 40% yield. Only small amounts of the corresponding homocoupling products of the tosylhydrazones were formed, and the cross-coupling products of the tosylhydrazone with the nitrile were formed in high ratios. The yields were little affected by the presence of electron-withdrawing or electron-donating groups on the nitriles. Moreover, the presence of steric hindrance at the ortho-position had little effect on the yields in this transformation (3h, 3j, and 3k). However, an aryl nitrile bearing two methyl groups at the two ortho-positions gave the corresponding 1,2,3-triazole 3m in a lower yield and a lower cross-coupling ratio. Heterocyclic aryl nitrile-bearing two methyl groups at the two ortho-positions also worked well under optimized conditions, and gave good yields of corresponding 1,2,3-triazoles 3n and 3o with a high cross-coupling ratio. Unfortunately, when a hydroxy or amino group was present in the benzonitrile, the desired product was not obtained and the unreacted nitrile was recovered by column chromatography (3p, 3q, 3r). Nonaromatic nitriles 2s and 2t also failed to give the desired products 3s and 3t. When phenylacetonitrile was used, the benzaldehyde azine was isolated.

To further expand the scope of this reaction, a series of tosylhydrazones were explored in reactions with various nitriles under the optimized conditions (Scheme 3). Generally, the corresponding 1,2,3-triazoles were obtained in good to excellent yields with high purities. The cyclization was highly tolerant of various functional groups on the benzene rings. When electron-rich or electron-deficient phenyl tosylhydrazones reacted with benzonitrile, the 1,2,3-triazoles 4a–d were obtained in excellent yields and high purities. The reaction also permitted the use of other substituted benzoaldehydehydrazones with substituted benzonitriles (4e–z). Additionally, hetaryl aldehyde tosylhydrazones were also well tolerated, affording corresponding 1,2,3-triazoles 4aa–ac in good yields.

To demonstrate the synthetic utility of this reaction, we performed a gram-scale reaction (Scheme 4). When 1a and 2b were used as substrates, the corresponding product 3b was isolated by column chromatography in 85% yield and a purity of 98.4%.

In summary, an intermolecular reaction of tosylhydrazones with nitriles is described.20 This reaction proceeded smoothly when promoted by potassium tert-butoxide in xylene; these conditions were beneficial to intermolecular cyclization and inhibited the homocoupling of the tosylhydrazone. The reaction provides an efficient and convenient method for the synthesis of NH-1,2,3-triazoles, and a wide range of 4,5-diaryl-2H-1,2,3-triazoles were obtained in good to excellent yields.

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References and Notes


(19) Sha, Q.; Wei, Y. Tetrahedron 2013, 69, 3820.

(20) 4,5-Diaryl-1,2,3-triazoles 3a–t, 4a–ag; General Procedure
A mixture of the appropriate tosylhydrazone 1 (1.0 mmol), nitrile 2 (1.2 mmol), and tBuOK (3.0 mmol) in xylene (6 ml) was stirred at 90 °C for 4 h under Ar. The mixture was then cooled to r.t. and diluted with EtOAc (40 ml). The organic layer was washed with water (3 × 40 ml) and brine (30 ml), then dried (Na2SO4) and filtered. The filtrate was concentrated in vacuum, and the crude product was purified by column chromatography (silica gel, PE–EtOAc).

4,5-Bis(4-methoxyphenyl)-1,2,3-triazole (4x)
White solid; yield: 261.3 mg (93%); mp 121.9–124.9 °C. 1H NMR (400 MHz, CDCl3): δ = 7.41 (d, J = 8.8 Hz, 4 H), 6.79 (d, J = 8.9 Hz, 4 H), 3.74 (s, 6 H). 13C NMR (100 MHz, CDCl3): δ = 159.5, 140.6, 129.3, 122.2, 113.9, 55.0.

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