Novel Synthesis of 5-Substituted-Tetrazoles

The AMPAC-GaTech Partnership fosters research aimed at opening and developing new avenues and compounds that fit the American Pacific Corporation (AMPAC)’s potential market. Under this umbrella, we are exploring advanced propellants technologies (ionic liquids, energetic polymers), azide chemistry, and applied polymers (agriculture, biomedical). The novel catalytic preparation of 5-aromatic substituted tetrazoles is one example to illustrate the collaborative research that Ampac and Georgia Tech have carried on for more than five years.

a. Introduction

The tetrazole moiety exhibits a wide and growing number of applications. This nitrogen-rich ring system is used in propellants, explosives, and pharmaceuticals. Although syntheses of tetrazoles have been reported since the mid-century, there is still a dearth of efficient processes. The [3+2] cycloaddition between hydrazoic acid and cyanide derivatives is a well known and one of the most efficient routes. Unfortunately, hydrazoic acid is highly explosive. Practically, the use of sodium azide as substrate in place of the hydrazoic acid would be convenient; however, the [3+2] cycloaddition energy barrier is significantly lower with hydrazoic acid than with azide ion. To overcome this energy limitation, syntheses have been designed either to control the hydrazoic acid formation or to use a large excess of azide ions in the presence of metal catalysts or strong Lewis Acids. Overall, these procedures are less than desirable due to the long reactions times, high temperatures, low yields, or non-recoverable catalysts. Also, the use of sensitive catalysts and excess amounts of sodium azide enhance the difficulty and inconvenience of these processes.

b. Results and Discussion

In the previous methods used for making tetrazoles, chemists typically used high boiling aprotic polar solvents to facilitate the reaction. In our preliminary experiments however, benzonitrile (BN) served as the reactant and solvent. Because BN is a liquid at room temperature, it provided the ability to run the reaction at lower temperatures than

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commonly reported as well as to ease the product isolation. Previous attempts illustrate the successful use of aromatic solvents in the synthesis of 5-substituted tetrazoles. The presence of the nitrile in excess also allowed for the azide to serve as the limiting reagent.

Initial experiments involved the reaction of sodium azide, BN, and a stoichiometric amount (relative to azide) of a tertiary amine hydrochloride to produce 5-phenyl-1H-tetrazole (2) as shown in Figure 1.

![Figure 1. Preparation of 5-phenyl-1H-tetrazole (2).](image)

The tertiary amine hydrochloride has as its role the transport of the sodium azide into the organic phase, but most importantly, also forms the reactive species 3 (Figure 2), which will then react with benzonitrile. As mentioned before, azide ions and cyanide derivatives do not undergo [3+2] cycloaddition without a sufficient energy input—which often results in poor yields due to competitive decomposition pathways—or the presence of a catalyst. The formation of the complex 3, however, sufficiently activates the azide ions to allow the [3+2] cycloaddition with benzonitrile to occur at mild conditions.

![Figure 2. Reactive complex 3.](image)

The initial proton source that we tested was triethylamine hydrochloride (1). After 16 hours at 50°C or 1h at 100°C, the reaction reached completion with a 97% isolated yield. After each reaction, a simple acidification with 6M HCl caused the product crystals to fall out of solution. The results at 50°C and 100°C with time variations are shown in Figure 3.

![Figure 3. Yields of 5-phenyl-1H-tetrazole (2) vs reaction time at 50°C & 100°C.](image)

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We altered the amount of amine hydrochloride added to the reaction, but at least a stoichiometric (relative to azide) amount produced quantitative yields. The triethylammonium hydrochloride is a phase transfer catalyst as well as a proton source, which allows the formation of the reactive species 3. Next we turned our attention to establishing efficient recycling strategies to regenerate/recycle the proton source.

The first strategy explored was a catalytic method that reduced the amount of proton source needed for the reaction up to 95%. We combined sodium azide with a 5-50 mol% of triethylamine hydrochloride (relative to azide) and a stoichiometric amount of benzyltriethylammonium chloride (11) in the presence of BN. Previously, researchers believed that the intermediate 9 (Figure 4) could not be recycled in the system because it is a very stable complex that discourages any ion exchange. The addition of 11, however, was expected to overcome this difficulty as seen in Figure 4 (below).

![Catalytic cycle with proton source as catalyst.](image)

The proposed catalytic cycle for this process starts with an initiation step in which 11 shuttles the azide anion (12) into the organic phase. The azide anion then displaces the chloride anion on 1 to reform 11 and the reactive complex 3. This complex then reacts with BN to produce the intermediate species 9. An ion exchange step between the product complex and 11 then takes place. This ion-exchange regenerates 1. Experiments have been carried out with variable amount of 1 and gave up to 88 % isolated yield as

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seen in Figure 5. Reactions involving less than a stoichiometric amount of 11 were limited by the ion exchange step and resulted in poor yields.

![Graph showing yield of 5-phenyl-1H-tetrazole (2) vs Mol% of triethylamine (proton source).](image)

**Figure 5. Yield of 5-phenyl-1H-tetrazole (2) vs Mol% of triethylamine (proton source).**

This unique system successfully limits the amount of proton source—triethylamine hydrochloride salt—as well as minimizes potentially explosive hydrazoic acid formation. Nonetheless, a stoichiometric amount of benzyltriethylammonium chloride (11) remains necessary.

The second strategy focused on regenerating the recycling the proton source. If the reaction mixture was treated with gaseous HCl, the product could be precipitated and filtered while the proton source remains active and soluble in the benzonitrile and derivatives. Then, only the addition of sodium azide to the solvent would be needed to continue the reaction. First, a range of tertiary amines have been tested to understand the structure/activity relationship of the amine as proton source. In addition to triethylamine hydrochloride, we tested a wide range of tertiary amines hydrochloride salts. The amine hydrochlorides with longer alkyl chains such as trioctylamine were soluble in BN, but produced no product. Clearly, the steric hindrance around the nitrogen plays a critical role in the formation and/or reactivity of the complex 3. Therefore, we focused on asymmetrical amines with shorter alkyl chains, and consequently minimized the steric hindrance around the nitrogen, but with sufficient organic character to remain soluble in BN. As expected the yields were high and reached up to 91% with the triethylamine hydrochloride as the proton source.

Besides benzonitrile (BN), 4’-methyl-2-biphenylcarbonitrile has also been tested to yield the 5-(4’-methyl-2-biphenyl)-1H-tetrazole. The 4’-methyl-2-biphenylcarbonitrile is liquid above 50°C; therefore the reaction was carried out with toluene; this has little effect on the reaction or on the recycling of the proton source. In all of the reactions, we used gaseous HCl to precipitate the tetrazole product. After filtering and washing the
product with the aromatic nitrile or toluene, we added more NaN₃ directly to the filtrate and repeated the procedure. The results from these recycled experiments were very successful since the yields were the same at the first and the second cycles (Figure 6).

![Graph](image)

**Figure 6. Results from Gaseous HCl Recycled Reactions**

In the case of the preparation of the 5-(4’-methyl-2-biphenyl)-1H-tetrazole using triethylamine as proton source, the isolated yield was 44% after 24h at 100°C. The second cycle yields 46% of 5-(4’-methyl-2-biphenyl)-1H-tetrazole confirming that the proton source is again recycled efficiently. To address the issue of stoichiometric addition, we tested several reactions with a 2:1 proton source addition (relative to azide). While the ability to recycle the amine hydrochloride made this method economically sustainable, the excess addition had little effect on the isolated yields. The reactions run with triethylamine 4 displayed an insignificant (1-4%) increase in yield when a 2:1 ratio of amine hydrochloride to sodium azide was present. Overall, 4 clearly provided the best results with the gaseous workup. However, headspace analysis of the reaction with 4 showed that 4-5% of the NaN₃ converted to hydrazoic acid during the course of the reaction. On the other hand, tributylamine 7 did not produce any hydrazoic acid regardless of the temperature of the reaction.

The 5-phenyl-2-triphenylmethyltetrazole (10) is a potential pharmaceutical intermediate and has been prepared by using triethylamine hydrochloride salt as a recyclable proton source. The tetrazole moiety is commonly protected in pharmaceutical research by deprotonating the tetrazole and reacting it with triphenylchloromethane (TPCM). Instead of aqueous or gaseous HCl, we added TPCM to the solution containing the deprotonated intermediate 9. This procedure produced 5-phenyl-2-triphenylmethyltetrazole (10) in very competitive yields (81%) as shown in Figure 7.

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Table 2. Results From Trityl Protected Tetrazoles*

<table>
<thead>
<tr>
<th>Temp. of Reaction During Addition (°C)</th>
<th>Time TPCM Reacted (Hours)</th>
<th>Temperature (°C)</th>
<th>Yield of 10 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3</td>
<td>100</td>
<td>77</td>
</tr>
<tr>
<td>100</td>
<td>3</td>
<td>100</td>
<td>81</td>
</tr>
</tbody>
</table>

*All of these reactions used TEAHCl for the first step

c. Conclusion

By forming a reactive complex from sodium azide and tertiary amine hydrochlorides, we have been able to prepare tetrazole derivatives under mild conditions. High yields have been obtained without the need of a toxic and/or expensive metal catalyst or a high boiling point polar solvent. In addition, a minimal amount of hydrazoic acid—if any—was formed, enhancing dramatically the previous processes. Finally, the tertiary amines—proton source—can be efficiently recycled. A unique catalytic system has been optimized as well as an original regeneration/recycling sequence, and provides a novel, efficient and safer techniques to prepare tetrazole-substituted derivatives.