One-Step Synthesis of Sterically Hindered 1,5-Disubstituted Tetrazoles from Bulky Secondary N-Benzoyl Amides Using Triazidochlorosilane (TACS)

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ABSTRACT

In this paper, a one-step method is reported for the conversion of bulky secondary N-benzoyl amides to sterically hindered 1,5-disubstituted tetrazoles in 83%-88% yields using silicon tetrachloride in the presence of sodium azide (triazidochlorosilane) and acetonitrile as solvent. Triazidochlorosilane (TACS) was used as azide transfer reagent as it transformed the amides to imidoylazide intermediate and, then, by ring closing to tetrazole. The formation of hindered 1,5-disubstituted tetrazoles was confirmed by 1H, 13C, and 19F NMR, HRMS and FT-IR. A possible mechanism is described to clarify the effect of electron-withdrawing group on the conversion to tetrazole. In fact, substituent effect on nitrogen of amide group has key role in ring closing imidoylazide intermediate to tetrazole.

Keywords: Sterically hindered 1,5-Disubstituted tetrazoles, Triazidochlorosilane, Bulky secondary N-benzoyl amides, Imidoylazides.

INTRODUCTION

The tetrazole moiety and its derivatives are important in medicinal chemical research. The class of tetrazole compounds has been recently used both as anticancer and antimicrobial agents[1]. They have received increased attention due to their potential biological activity and industrial applications [2]. Furthermore, tetrazole fragment is a metabolically stable substitute for carboxy group and amide bond in the molecules of peptidomimetics [3]. The first report of amino acid derivatives containing a 5-tetrazolyl substituent were described by McManus and Herbst[4]. Later, Zabrocki et al proposed the use of tetrazole 1,5-diy1 fragment for the synthesis of peptidomimetics with cis-block peptide bond [5]. Growing demands for the synthesis of tetrazole containing peptides and peptidomimetics result in extensive studies aimed to developing effective methods for the preparation of amides derivatives containing a tetrazole moiety. Esikov and colleagues have synthesized the 1,5-dissubstituted tetrazoles [6]. They reported some intrinsic limitations to the azidating amides. Unlike N-acetyl derivatives of amino acids, N-benzoyl derivatives, almost do not react with tetrachlorosilane sodium azide which has been attributed to steric effect of the benzoyl substituent.

Duncia and coworkers reported synthesis of a sterically hindered ortho-tetrazole group by three different routes. However, their methods were only applied to prepare 5-substituted-1H-tetrazoles [7]. Katritzky and coworkers prepared 1,5-disubstituted tetrazoles with diverse substituents (aliphatic, aromatic, or heteroaromatic) on imidoylbenzotriazoles precursor[8]. Imidoylbenzotriazoles were prepared from corresponding secondary carboxamides and benzotriazoles by two methods: oxalyl chloride and pyridine or thionyl chloride under microwave (80 W/80 °C). However, these methods suffer from two disadvantages. Firstly, there is an added step in the preparation of imidoylbenzotriazoles using non-eco-friendly materials. Secondly, only para-substituted aromatic tetrazoles are obtained.

Schroeder and coworkers reported improved conditions for converting sterically hindered amides into their corresponding 1,5-disubstituted tetrazoles in good yield [9]. The optimum reaction conditions were applied by using disisopropyl azodicarboxylate (DIAD), diphenylphosphoryl azide (DPPA), and diphenyl-2-pyridyl phosphine in THF at 45°C. However, it should be mentioned that expensive, toxic and non-eco-
friendly materials were utilized in this method as well as applying just aliphatic amines.
Here, we wish to report synthesis of sterically hindered 1, 5-disubstituted tetrazoles from the bulky secondary N-benzoyl amides in one step using silicon tetrachloride in the presence of sodium azide (triazidochlorosilane) according to procedure reported by Esikov and co-workers. This method has been overcome the above mentioned disadvantages with high yield as well. In fact, anilines containing electron-withdrawing groups in ortho position gave satisfactory results and anilines containing electron-releasing groups such as 2-methyl, 2-ethyl, 2-sec-butyl and 2-methoxy anilines were unsuccessful. Furthermore, we propose a reasonable mechanism of how substituent affects on ring closing of imidoylazide intermediates and converting them to tetrazole.

MATERIALS AND METHODS

2-Trifluoromethyl aniline, 2-fluoro aniline, 2-chloro aniline, 2-methyl aniline, 2-ethyl aniline, 2-sec-butyl aniline, 2-methoxy aniline and benzoyl chloride were used for amides preparation and purchased from Merck. Sodium azide, tetrachlorosilane and acetonitrile were used for tetrazoles preparation and purchased from Merck. Ethyl acetate, acetonitrile and n-hexane were purchased from Merck and used as the organic solvents.

Amides 1a, 1b and 1c, as shown in Scheme 1, were prepared according to reported procedure by Ghosh and coworkers of benzoyl chloride and the corresponding anilines in solid-state [10].

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amide</th>
<th>Time (hr.)</th>
<th>Tetrazole</th>
<th>m.p. (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>42</td>
<td>5a</td>
<td>101-102</td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>42</td>
<td>5b</td>
<td>105-106</td>
<td>83</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>54</td>
<td>5c</td>
<td>103-104</td>
<td>88</td>
</tr>
</tbody>
</table>

Scheme 1

Instrumentation

The obtained tetrazoles were characterized by 1H-, 13C- and 19F-NMR spectra recorded on a Bruker Avance DRX 500 (500 MHz) using the solvent signal as reference (CDCl₃). The FT-IR spectra were obtained on a Shimadzu-470 (potassium bromide tablet). The progress of the reaction and purity of the products were monitored by TLC on Kieselgel 60 F₂₅₄ plates (Merck). The eluent user petroleum ether-ethyl acetate 95:5, spots were visualized by UV irradiation. Melting points were recorded by an Electro
Preparation of Hindered 1,5-Disubstituted Tetrazoles 5a-5c

Tetrazoles 5a, 5b and 5c were synthesized according to reported procedure by Esikov and co-workers. As typical procedure for 5a 1-(2-trifluoromethyl phenyl)-5-phenyl-1H-tetrazole] from amide 1a; a mixture of 1a (4 mmol), sodium azide (8 mmol) and tetrachlorosilane (8 mmol) in dry acetone (16 ml) were refluxed and stirred with exclusion of moisture (Scheme 1). In order to determine the end of the reaction, TLC test was used to check the reaction every 6 hours. After each TLC test, 1 mmol sodium azide and 2 mmol tetrachlorosilane were added to the mixture of the reaction. The last TLC test showed the pure hindered 1,5-disubstituted tetrazole clearly. After the completion of reaction, the mixture was poured into the saturated solution of Na₂CO₃ (pH ~ 7). Then the precipitate of silica was filtered. The pure products were obtained by extracting the mixture with ethyl acetate. The organic solvents (ethyl acetate and acetonitrile) were evaporated under the vacuum. The final products were kept at room temperature for more characterization.

RESULTS AND DISCUSSION

To confirm the formation of hindered 1,5-disubstituted tetrazoles, characterizations such as ¹H-, ¹³C- and ¹⁹F-NMR, HRMS and FT-IR were used. TLC was utilized to monitor the progress of the reaction and purity of the products. Melting point was used to verify the purity of the products.

The reaction of secondary amides 1a-1c with triazidochlorosilane (TACS) is shown in Table. Triazidochlorosilane (TACS) was used as azide transfer reagent. It transforms amides to nitriles or acid azides(imidoylazides) however ketones are transformed with rearrangement into their corresponding tetrazoles [12] and the spread of general synthetic achieves for chemo selective formation of tetrazole derivatives.

The main question that comes in mind is that why reaction was successful with anilines containing electron-withdrawing groups in ortho position and unsuccessful with anilines containing electron-releasing groups such as 2-methyl, 2-ethyl, 2-sec-butyl and 2-methoxy anilines. Our suggested mechanism has been showed in Scheme 2. According to the mechanism the rate-determining step (slow step) is the isomerisation of the initially formed Z-isomer of the imidoylazide 3Z to its E-isomer 3E (via imine nitrogen inversion or rotation about C=N bond). Then, tetrazole ring is formed by fast step of ring closing of 3E.

We have recently demonstrated a very high energy barrier for the interconversion of nitrogen about the C=N bond in imidoyl azides and other similar compounds [13]. In principle, the effect of structure on the rate process of E/Z isomerisation about the C=N bond is discussed in relation to the bond-rotation and
nitrogen-inversion mechanisms or by a mixture of the mechanisms. Nature of the substituent attached to the imine nitrogen has significant effect on energy barrier of E/Z isomerisation [13]. Indeed, electron-withdrawing groups decrease energy barrier and (vice versa) electron-releasing groups increase energy barrier due to bond rotation mechanism. These results confirm our mechanism. Hegarty and coworkers also reported the similar results [14]. They found that reaction of N-alkyl- and N-trifluoroalkylbenzimidoyl chlorides in the presence of either acetae or azide ion leads initially to the formation of the corresponding isoimides (Z form) and imidoyl azides (Z form). Subsequently these imidoyl acetates and azides rearrange to the more stable imides or tetrazoles. These rearrangements indicated that the rate-determining step is the isomerisation of the initially formed Z-isomer of the imine to the E-isomer (imine nitrogen inversion) rather than the subsequent transfer or cyclisation. Thus, this mechanism shows well why Esikov and co-workers could not obtain 1,5-disubstituted tetrazoles from N-benzoyl derivatives of amides (from amino acids). Indeed, their amide contains aliphatic amines, that is, there is electron-releasing group on nitrogen. Further studies are in progress.

\[ \text{Scheme 2} \]

CONCLUSIONS
In this paper, a one-step method is reported for synthesis of sterically hindered 1,5-disubstituted tetrazoles from bulky secondary N-benzoyl amides in 83%-88% yields by Esikov and co-workers method using silicon tetrachloride in the presence of sodium azide (triazidochlorosilane) and acetonitrile as a solvent. A proposed mechanism is described to justify why anilines containing electron-withdrawing groups in ring can be converted to tetrazole. According to this mechanism the rate-determining step (slow) is the isomerisation of the initially formed Z-isomer of the imidoylazide 3Z to its E-isomer 3E. Then, tetrazole ring is formed by fast step of ring closing of 3E. This mechanism shows well why Esikov and co-workers could not obtain 1,5-disubstituted tetrazoles from N-benzoyl derivatives of amides (from amino acids). Infact, their amides contain aliphatic amines which is electron-releasing group.
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REFERENCES

**CITATION OF THIS PAPER**