A new methodology for the synthesis of N-acylbenzotriazoles

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Dedicated to the late Prof. Alan R Katritzky for his excellent contributions to benzotriazole chemistry

Abstract

A facile and economic path for an easy access of diverse N-acylbenzotriazoles from carboxylic acid has been devised using NBS/PPh₃ in anhydrous dichloromethane. High yield of product was obtained at room temperature in one hour reaction time under mild reaction conditions.

Keywords: N-acylbenzotriazole, benzotriazole, N-halosuccinimide, triphenylphosphine
Introduction

The interesting features of benzotriazole – its high solubility in organic solvents, stability in acidic as well as basic media, considerable compatibility with various organic reactions and easy introduction under standard reaction conditions, activation of numerous useful transformations and final elimination after the completion of a reaction sequence – make this moiety a favorable auxiliary for the synthesis of a wide range of compounds of great pharmacological and other interests.\(^1\)\(^-\)\(^9\) N-acylbenzotriazoles are one of the most useful benzotriazole-derivatives which have been successfully utilized to prepare numerous biologically relevant compounds under neutral and mild conditions by N-, C-, S-, and O-acylations.\(^10\)\(^-\)\(^24\) In recent years our group has been involved in exploration of the synthetic utility of N-acylbenzotriazoles to make sugar amides by N-acylation,\(^25\) benzoxazoles and N-phenylamides by benzotriazole ring cleavage\(^26,27\) and ureas, carbamates and thiocarbamates by the Curtius rearrangement.\(^28\)

The earlier synthetic methods for conversion of carboxylic acids to N-acyl benzotriazole i.e. path a, b, c and d (Scheme 1) comprise some drawbacks such as, bulk amount of BtH with toxic thionyl chloride is required in Path a, in Path b iodine is used which is highly toxic with base, in Path c requires much longer time to complete the reaction, where as in path d activation of carboxylic acids with tosyl chloride was utilized to afford good yields of N-acyl benzotriazoles under one-pot condition using a base.\(^11,29-31\)

\begin{equation}
\text{Previous methods:}
\begin{align*}
\text{Path a) } & \text{BtH/}\text{SOCl}_2 (4:1) \\
& \text{CH}_2\text{Cl}_2, 25^\circ \text{C} \\
\text{Path b) } & \text{I}_2, \text{PPh}_3 \\
& \text{BtH, Base, DCM} \\
\text{Path c) } & \text{BiSO}_2\text{R, Et}_3\text{N} \\
& \text{THF, reflux, overnight} \\
& \text{R= Me, 4-MeC}_6\text{H}_4 \\
\text{Path d) } & \text{TsCl, BtH, DMAP,} \\
& \text{Et}_3\text{N, DCM}
\end{align*}
\end{equation}

\begin{equation}
\text{This Work:}
\begin{align*}
& \text{OH} \\
& \text{NBS, PPh}_3 \\
& \text{BtH, CH}_2\text{Cl}_2
\end{align*}
\end{equation}

\begin{equation}
\begin{array}{c}
\text{alkyl, aryl, carbohydrate}
\end{array}
\end{equation}

Scheme 1. Comparative illustration of previous and present work.

Therefore, an improved method is considered necessary to make this transformation more facile, economical and of low toxicity. As we know that the reaction of an alcohol with BtH in the presence of NBS/PPh\(_3\) gives an alkylbenzotriazole, this idea can be applied to modify path b by using NBS in place of iodine. This leads to the introduction of a less toxic and cost-effective path to prepare N-acylbenzotriazoles, which we report in this manuscript.
**Results and Discussion**

A prototype reaction for the synthesis of \(N\)-acylbenzotriazole 2a was initiated with 1 equiv. \(\text{PPh}_3\) and 1 equiv. of NBS in dry dichloromethane. After a few minutes, 1.0 equiv. of benzoic acid was added and the mixture was stirred continuously at 0°C for 30 min followed by addition of 1\(H\)-benzotriazole and \(\text{Et}_3\text{N}\) at an interval of 10 minutes. The mixture was stirred for 1hr to afford \(N\)-benzoylbenzotriazole in 71% yield (Scheme 2).

![Scheme 2. Prototype reaction for synthesis of \(N\)-acylbenzotriazoles.](image)

To optimize the reaction conditions for the better yield of resultant product, first of all we employed different types of \(N\)-halosuccinimide with 1.0 equiv. of \(\text{PPh}_3\) and 2.0 equiv. of triethylamine in dry dichloromethane (entries 1-3) and found best results with \(N\)-bromosuccinimide. After establishing the reagent of choice, we started varying the molar ratios of \(N\)-bromosuccinimide, \(\text{PPh}_3\) and triethylamine in dry dichloromethane (entries 3-8). It was found that reaction proceeds very smoothly even in the absence of base when we take 1.2 equiv. of both \(N\)-bromosuccinimide and \(\text{PPh}_3\) in dry dichloromethane at 0°C. Optimization results for solvent revealed that dry dichloromethane is the most suitable solvent for the reaction (entries 8-12, Table 1).

**Table 1. Reaction optimization study**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent (equiv)</th>
<th>(\text{PPh}_3) (equiv.)</th>
<th>Base (equiv.)</th>
<th>Solvent</th>
<th>Yield (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>NCS (1.2)</td>
<td>1.2</td>
<td>(\text{Et}_3\text{N}) (2.0)</td>
<td>DCM</td>
<td>59</td>
</tr>
<tr>
<td>2</td>
<td>NIS (1.2)</td>
<td>1.2</td>
<td>(\text{Et}_3\text{N}) (2.0)</td>
<td>DCM</td>
<td>53</td>
</tr>
<tr>
<td>3</td>
<td>NBS (1.0)</td>
<td>1.0</td>
<td>(\text{Et}_3\text{N}) (2.0)</td>
<td>DCM</td>
<td>71</td>
</tr>
<tr>
<td>4</td>
<td>NBS (0.5)</td>
<td>0.5</td>
<td>(\text{Et}_3\text{N}) (1.0)</td>
<td>DCM</td>
<td>26</td>
</tr>
<tr>
<td>5</td>
<td>NBS (1.2)</td>
<td>1.2</td>
<td>(\text{Et}_3\text{N}) (2.0)</td>
<td>DCM</td>
<td>87</td>
</tr>
<tr>
<td>6</td>
<td>NBS (2.0)</td>
<td>2.0</td>
<td>(\text{Et}_3\text{N}) (4.0)</td>
<td>DCM</td>
<td>86</td>
</tr>
<tr>
<td>7</td>
<td>NBS (1.2)</td>
<td>1.2</td>
<td>(\text{Et}_3\text{N}) (1.0)</td>
<td>DCM</td>
<td>87</td>
</tr>
<tr>
<td>8</td>
<td>NBS (1.2)</td>
<td>1.2</td>
<td>(\text{Et}_3\text{N}) (0.0)</td>
<td>DCM</td>
<td>89</td>
</tr>
<tr>
<td>9</td>
<td>NBS (1.2)</td>
<td>1.2</td>
<td>(\text{Et}_3\text{N}) (0.0)</td>
<td>Toluene</td>
<td>52</td>
</tr>
<tr>
<td>10</td>
<td>NBS (1.2)</td>
<td>1.2</td>
<td>(\text{Et}_3\text{N}) (0.0)</td>
<td>Chloroform</td>
<td>57</td>
</tr>
<tr>
<td>11</td>
<td>NBS (1.2)</td>
<td>1.2</td>
<td>(\text{Et}_3\text{N}) (0.0)</td>
<td>THF</td>
<td>49</td>
</tr>
<tr>
<td>12</td>
<td>NBS (1.2)</td>
<td>1.2</td>
<td>(\text{Et}_3\text{N}) (0.0)</td>
<td>DMF</td>
<td>22</td>
</tr>
</tbody>
</table>

\(a\) Molar ratio: carboxylic acid (1.0 mmol). \(b\) dry solvents. \(c\) Yields reported after purification by column chromatography (SiO\(_2\)).
After optimization of the reaction conditions, we attempted to generalize the reaction by applying it to different class of carboxylic acids including aryl, substituted aryl, fused aryl, aliphatic and glycosylated carboxylic acids where in all cases the reaction was found to be smooth and the corresponding N-acylbenzotriazole products were obtained in good to excellent yields. It was observed that variation of functional groups around the aromatic ring of the acid slightly affected the yield of product and a small decrease in yield was obtained with electron withdrawing groups. In the case of aliphatic acids, variation in length of carbon chain did not show any notable change in product yield. This reaction protocol also goes well with sugar acids and gives excellent product yields. The crude reaction product was purified by flash column chromatography (SiO$_2$) using a gradient of ethyl acetate/n-hexane, and the corresponding N-acylbenzotriazoles 2a-o were obtained in good yield (Figure 1). All the synthesized compounds have been characterized by standard spectroscopic techniques including mass, IR, $^1$H and $^{13}$C NMR studies.

Figure 1. Synthesis of N-acylbenzotriazoles 2a-o from acids using NBS/PPh$_3$. Molar ratios: carboxylic acids (1a-o) (1.0 equiv.), NBS (1.2 equiv), PPh$_3$ (1.2 equiv), benzotriazole (1.2 equiv). Yields reported after purification by column chromatography (SiO$_2$).
Synthesis of N-Acylbenzotriazole: reaction in gram scale

A scale-up reaction was carried out for quantitative generalization of the method starting with 10 g of benzoic acid. The reaction was found to go well in gram scale also and produced N-Benzoyl benzotriazole 2a in 87% yield. This suggested that the method is equally applicable to milligram and gram scales and yield is not much affected by quantitative scale of reaction.

Scheme 3. Synthesis of N-acylbenzotriazole 2a reaction in gram scale.

Mechanism

The reaction possibly begins with the formation of intermediate (A) generated by the reaction of PPh₃ and NBS. The intermediate (A) reacts with carboxylic acid to form acyloxyphosphonium ion with the loss of succinimide. This acyloxyphosphonium ion (B) further reacts with BtH to form the final product N-acylbenzotriazole 2.

Scheme 4. Possible mechanism for synthesis of N-acylbenzotriazole 2.

Conclusions

In summary, we have developed a low-toxic, economical and efficient method for synthesis of N-acylbenzotriazole from carboxylic acid. The developed synthetic path was successfully employed for a variety of substrates and furnished good yields at 0 °C with simple purification methods. The method was found equally facile for milligram to gram scales.
Experimental Section

General. All reagents and solvents were of pure analytical grade. Thin-layer chromatography (TLC) was performed on 60 F254 silica gel, pre-coated on aluminium plates and revealed with either a UV lamp (λ max = 254 nm) or a specific colour reagent (Dragendorff’s reagent or iodine vapour) or by spraying with methanolic H2SO4 solution and subsequent charring by heating at 100 °C (for a carbohydrate derivative only). Solvents were evaporated under reduced pressure at temperature < 50 °C. Column chromatography was carried out on silica gel (230-400 mesh, Merck). Distilled n-hexane and ethyl acetate were used for the column chromatography. 1H and 13C NMR were recorded at 500 and 125 MHz, respectively. Chemical shifts given in ppm downfield from internal TMS; J values in Hz. Infrared spectra recorded as Nujol mulls in KBr pellets.

Typical experimental procedure for synthesis of N-acylbenzotriazoles

Compound 1a (1.0 g, 8.19 mmol) was added to a RB flask containing stirring solution of NBS (1.7 g, 9.83 mmol) and PPh3 (2.5 g, 9.83 mmol) in Dry dichloromethane (30.0 mL) and temperature was maintained at 0 °C. Benzotriazole (1.2 g, 9.83 mmol) was added portion wise. After complete addition, the reaction mixture was stirred for 1 hour at room temperature. After completion of reaction (monitored by TLC), the reaction mass was evaporated under reduced pressure at temperature < 50 °C. White crystalline solid, 1.7 g, yield 97%; Rf = 0.6 (5% ethyl acetate/n-hexane).

Physical data of developed compounds (2a-o)

(1H-1,2,3-Benzotriazol-1-yl)(phenyl)methanone (2a).28 White crystalline solid, 1.62 g, yield 89%; Rf = 0.6 (10% ethyl acetate/n-hexane); m.p. 110-114 °C (lit. m.p. 112 °C); IR (KBr):νmax 3109, 3094, 2925, 1712, 1711, 1599, 1488, 1451, 1379, 1379, 1047, 942, 838, 751 cm⁻¹; 1H NMR (500 MHz, CDCl3): δ 8.27 (d, J = 8.5 Hz, 1H), 8.11 (d, J = 7.5 Hz, 2H), 8.05 (d, J = 8.5 Hz, 1H), 7.59-7.56 (m, 2H), 7.48-7.41 (m, 3H); 13C NMR (125 MHz, CDCl3): δ 166.6, 145.6, 133.5, 132.2, 131.6, 131.3, 130.2, 128.3, 126.2, 126.0 and 114.7 ppm.

(1H-1,2,3-Benzotriazol-1-yl)(p-tolyl)methanone (2b).28 White crystalline solid, 1.7 g, yield 97%; Rf = 0.6 (5% ethyl acetate/n-hexane); m.p. 122-124 °C (lit. m.p. 123 °C); 1H NMR (500 MHz, CDCl3): δ 8.27 (d, J = 8.5 Hz, 1H), 8.11-8.09 (m, 3H), 7.63 (t, J = 7.5Hz, 1H), 7.48 (t, J = 7.5Hz, 1H), 7.32 (d, J = 7.5Hz, 2H), 2.43 (s, 3H); 13C NMR (125 MHz, CDCl3): δ 166.5, 145.7, 144.8, 132.4, 132.0 (2C), 130.3, 129.2 (2C), 128.6, 126.2, 126.1, 114.8 and 21.8 ppm.

(1H-1,2,3-Benzotriazol-1-yl)(m-tolyl)methanone (2c).28 White crystalline solid, 1.5 g, yield 87%; Rf = 0.6 (5% ethyl acetate/n-hexane); m.p. 206-210 °C (lit. m.p. 205 °C); 1H NMR (500 MHz, CDCl3): δ 8.37 (d, J = 8.1Hz, 1H), 8.35 (d, J = 8.5Hz, 1H), 8.13 (d, J = 8.5Hz, 1H), 8.99 (d, J = 1.4Hz, 1H), 7.66 (t, J = 7.5Hz, 1H), 7.52-7.41 (m, 3H), 2.44 (s, 3H); 13C NMR (125 MHz, CDCl3): δ 166.9, 145.8, 138.3, 134.5, 132.4, 132.1, 131.5, 130.2, 129.0, 128.3, 126.3, 120.2, 114.8 and 21.4 ppm.

(1H-1,2,3-Benzotriazol-1-yl)(o-tolyl)methanone (2d).28 White crystalline solid, 1.6 g, yield 92%; Rf = 0.5 (5% ethyl acetate/n-hexane); m.p. 86-90°C; 1H NMR (500 MHz, CDCl3): δ 8.28 (d, J = 8.5Hz, 1H), 8.03 (d, J = 8.5Hz, 1H), 7.58 (t, J = 7.5Hz, 1H), 7.52 (d, J = 7.5Hz, 1H), 7.43-7.37 (m, 2H), 7.25-7.21 (m, 2H), 2.32 (s, 3H); 13C NMR (125 MHz, CDCl3): δ 168.1, 146.0, 137.8, 132.1, 131.7, 131.6, 130.9, 130.3, 129.9, 126.2, 125.3, 120.1, 114.4 and 19.9 ppm.

(1H-1,2,3-Benzotriazol-1-yl)(4-chlorophenyl)methanone (2e).28 White crystalline solid, 1.3 g, yield 82%; Rf = 0.5 (10% ethyl acetate/n-hexane); m.p. 136-140°C; IR (KBr):νmax 3118, 3094, 2925, 1707, 1591, 1481, 1450, 1380, 1047, 942, 838, 751 cm⁻¹; 1H NMR (500 MHz, CDCl3): δ 8.25 (d, J = 7.5Hz, 1H), 8.10–8.04 (m, 3H), 7.61-7.58 (m, 1H), 7.45-7.43 (m, 3H); 13C NMR (125 MHz, CDCl3): δ 165.6, 145.7, 140.4, 133.2, 132.3, 130.6, 129.8, 128.9, 126.5, 120.3 and 114.8 ppm.
(1H,1,2,3-Benzotriazol-1-yl)(3-(trifluoromethyl) phenyl)methanone (2f).\(^{27}\) White crystalline solid, 0.87g, yield 57%; \(R_f = 0.7\) (10% ethyl acetate/n-hexane); m.p. 51-52°C; \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 8.41 (1H), 8.37 (d, \(J = 7.5\) Hz, 1H), 8.32 (d, \(J = 8.5\) Hz, 1H), 8.11 (d, \(J = 8.5\) Hz, 1H), 7.87 (d, \(J = 7.5\) Hz, 1H), 7.68-7.64 (m, 2H), 7.50 (t, \(J = 7.5\) Hz, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 165.4, 145.8, 134.9, 132.4, 132.2 130.8, 130.2, 130.1, 129.1, 128.7, 128.6, 126.8, 120.4 and 114.8 ppm.

(1H-1,2,3-Benzotriazol-1-yl)(3-methoxynaphthalen-2-yl)methanone (2n).\(^{28}\) White solid, yield 85%; \(R_f = 0.6\) (15% ethyl acetate/n-hexane); m.p. 118-120°C; \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 8.73 (s, 1H), 8.31 (d, \(J = 7.5\) Hz, 1H), 8.10-8.06 (m, 2H), 7.90-7.88 (m, 2H), 7.86-7.81 (m, 1H), 7.79-7.59 (m, 1H), 7.57-7.53 (m, 1H), 7.51-7.42 (m, 1H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 165.9, 145.7, 131.0, 130.6, 126.4, 114.1, 112.8, 106.0, 84.7, 84.6, 82.3, 82.2, 81.5 (d), 68.6, 37.7, 27.2, 26.5, 24.0, 22.2 and 21.0 ppm.

**References:**

NMR (125 MHz, CDCl₃): δ 166.7, 145.8, 135.7, 134.4, 132.5, 132.2, 130.4, 129.9, 129.2, 128.5, 128.3, 127.8, 127.1, 126.6, 126.4, 120.2 and 114.9 ppm.

(1H-1,2,3-Benzotriazol-1-yl)(2-Bromophenyl)methanone (2o).²⁸ Solid, Rᵢ = 0.7 (5% ethyl acetate/n-hexane); ¹H NMR (300 MHz, CDCl₃): δ 8.28 (d, J = 8.0 Hz, 1H), 8.03 (d, J = 8.5 Hz, 1H), 7.61 - 7.47 (m, 3H), 7.43 - 7.32 (m, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 166.5, 146.3, 135.1, 133.3, 132.6, 131.3, 130.8, 130.2, 127.3, 126.8, 120.6, 120.4 and 114.5 ppm.

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Supplementary Material

Characterization data (for all the developed acyl benzotriazoles) including copies of ¹H and ¹³C NMR spectra associated with this paper can be found in the online version.

References

   http://dx.doi.org/10.1081/SCC-120021983
   http://dx.doi.org/10.1021/jo026796x.
   http://dx.doi.org/10.1021/jo026636l.
   http://dx.doi.org/10.1021/jo026636l.
   http://dx.doi.org/10.1021/jo026636l.
   http://dx.doi.org/10.1021/jo070162e.
   http://dx.doi.org/10.1021/ol701599v.
   http://dx.doi.org/10.1080/00397910903531615.
   http://dx.doi.org/10.1016/j.tetlet.2011.07.057
   https://dx.doi.org/10.2174/157017810903531615.
   http://dx.doi.org/10.1002/slct.201601116.
   http://dx.doi.org/10.1002/slct.201601830.
   http://dx.doi.org/10.1039/C6RA14131E.
   http://dx.doi.org/10.1002/ejoc.201403076.
   http://dx.doi.org/10.3998/ark.5550190.p009.459
   http://dx.doi.org/10.1080/00397919708006100.
   http://dx.doi.org/10.1039/C5RA03184B.