The preparation of N-acylbenzotriazoles from aldehydes

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Dedicated to our good friend Branko Stanovnik on his 65th birthday
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Abstract
N-Acyl- (3a–g) and N-alkyl-benzotriazoles (10a–c) were prepared from the corresponding aldehydes or alkanes, respectively, using a slight excess of N-chlorobenzotriazole in the presence of AIBN (2,2’-azobisisobutyronitrile) as an initiator.

Keywords: N-Chlorobenzotriazole, N-acylbenzotriazole, N-alkylbenzotriazole, AIBN

Introduction

N-Acylbenzotriazoles are versatile N- and C- acylating agents\(^1\)\(^-\)\(^3\) for the preparation of primary, secondary and tertiary amides\(^2\) including formamides\(^4\) and oxamides,\(^5\) cinnamoyl hydrazides,\(^6\) enamimines\(^3\) and for the conversion of ketone enolates into β-diketones.\(^7\)

Literature syntheses of N-acylbenzotriazoles (i) react acid chlorides with 1-(trimethylsilyl)benzotriazole,\(^8\) the sodium salt of benzotriazole,\(^9\) or benzotriazole\(^10,\)\(^11\); (ii) react carboxylic acids with 1-(methanesulfonyl)benzotriazole;\(^6\) or (iii) employ palladium catalyzed carbonylation of diaryliodonium salts in the presence of benzotriazole.\(^12\)

In cases where the aldehyde is more readily available than the corresponding carboxylic acid, it is convenient to carry out the conversion of aldehyde RCHO into an acylating agent RCOX. Indeed, a number of methods are available for the direct conversion of aldehydes to the corresponding acid halides: (i) by the treatment of aromatic aldehydes with SO\(_2\)Cl\(_2\) in the presence of a phosphonium catalyst;\(^13\) (ii) use of N-chlorosuccinimide;\(^14,\)\(^15\) (iii) carbon tetrahalides at high temperatures;\(^16\) (iv) vapor phase photochemical halogenation;\(^17\) and (v) iodobenzene dichloride.\(^18\)

N-Chlorobenzotriazole has been widely used as (i) a mild oxidant\(^19,\)\(^20\) for the preparation of aldehydes, ketones,\(^21\) azo-compounds,\(^21\) sulphoxides,\(^20\) sulphonimidoyl chlorides,\(^22\) nitrile oxides,\(^23\) (ii) a chlorinating agent\(^24,\)\(^25\) and (iii) for addition reactions to olefins\(^26\)\(^-\)\(^28\) and
isonitriles. Rees and Storr showed that the reactions of $N$-chlorobenzotriazole as an oxidant are radical in nature.

We now show that $N$-chlorobenzotriazole (2) conveniently converts aldehydes 1a–g into the corresponding $N$-acylbenzotriazoles 3a–g (Scheme 1). Alcohols 8a and 8h are also converted into acylbenzotriazoles (Scheme 4), while substituted toluenes give the corresponding $N$-alkylbenzotriazoles 10a–c. All these reactions take place in the presence of AIBN as a radical initiator.

**Results and Discussion**

**Preparation of $N$-acylbenzotriazoles 3a–g.** Refluxing aldehydes 1a–g with $N$-chlorobenzotriazole (2) in benzene for 0.5–4h in the presence of catalytic AIBN led to the $N$-acylbenzotriazole; yields in 53–83 % except for the furyl derivative 3g. (Scheme 1) This resembles the known reaction of aldehydes with $N$-bromosuccinimide to give the corresponding acid bromides using catalytic amount of AIBN as a radical initiator. Results are shown in Table 1. Known products were identified by m.p. and direct comparison of the NMR spectra. Compound 3e is novel and its structure is supported by elemental analysis and its spectra.

![Scheme 1](image-url)

**Table 1. Preparation of N-acylbenzotriazoles 3a–g**

<table>
<thead>
<tr>
<th></th>
<th>R$^1$</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>m.p. (°C)</th>
<th>Lit. m.p. (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>Ph</td>
<td>1.2</td>
<td>63</td>
<td>112–113</td>
<td>112–113$^{30-31}$</td>
</tr>
<tr>
<td>3b</td>
<td>C$_2$H$_5$</td>
<td>2.5</td>
<td>53$^a$</td>
<td>77–78</td>
<td>80–82$^{31}$</td>
</tr>
<tr>
<td>3c</td>
<td>4-ClC$_6$H$_4$</td>
<td>1.0</td>
<td>81</td>
<td>138–139</td>
<td>138–139$^2$</td>
</tr>
<tr>
<td>3d</td>
<td>C$_6$H$_5$(CH$_2$)$_2$</td>
<td>2.0</td>
<td>62</td>
<td>62–64</td>
<td>63–64$^2$</td>
</tr>
<tr>
<td>3e</td>
<td>3-thienyl</td>
<td>3.0</td>
<td>56</td>
<td>118–120</td>
<td>Novel</td>
</tr>
<tr>
<td>3f</td>
<td>(CH$_3$)$_2$CCH$_2$</td>
<td>1.5</td>
<td>83</td>
<td>56–57</td>
<td>56–57$^7$</td>
</tr>
<tr>
<td>3g</td>
<td>2-furyl</td>
<td>4.0</td>
<td>38</td>
<td>165–167</td>
<td>165–167$^{30}$</td>
</tr>
</tbody>
</table>

$^a$heating at 50–55 °C.
Treatment of 4-methoxynaphthaldehyde (4) using our standard conditions formed a mixture of two compounds, however using 2 equivalents of \( N \)-chlorobenzotriazole gave 1\( H \)-1,2,3-benzotriazol-1-yl-(3-chloro-4-methoxy-1-naphthyl)methanone (5). (Scheme 2) Boehlow et al. showed that ring halogenation takes place on the reaction of 4-methoxybenzaldehyde with \( N \)-bromosuccinimide\(^{32} \). Compound 5 was identified from its elemental analysis and spectral examination.

\[
\text{\begin{align*}
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{N} \\
\text{N} \\
\text{Cl} \\
\end{array}
\end{align*}} + \\
\text{\begin{align*}
\begin{array}{c}
\text{N} \\
\text{N} \\
\text{Cl} \\
\end{array}
\end{align*}} \\
\text{AIBN} \\
\text{\begin{align*}
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{Cl} \\
\end{array}
\end{align*}}
\]

Scheme 2

4-(Dimethylamino)-2-nitrobenzaldehyde (6), on treatment with 2 equiv of \( N \)-chlorobenzotriazole gave three ring halogenation products 7a–c (Scheme 3), which were separated by column chromatography. The structures of 7a–c were assigned on the basis of \( ^1\text{H} \) and \( ^{13}\text{C} \) NMR data and elemental analyses.

\[
\text{\begin{align*}
\begin{array}{c}
\text{N} \\
\text{N} \\
\text{Cl} \\
\end{array}
\end{align*}} + \\
\text{\begin{align*}
\begin{array}{c}
\text{N} \\
\text{N} \\
\text{Cl} \\
\end{array}
\end{align*}} \\
\text{AIBN} \\
\text{\begin{align*}
\begin{array}{c}
\text{N} \\
\text{N} \\
\text{Cl} \\
\text{Cl} \\
\text{Cl} \\
\end{array}
\end{align*}} \\
\text{\begin{align*}
\begin{array}{c}
\text{O} \\
\text{N} \\
\end{array}
\end{align*}} + \\
\text{\begin{align*}
\begin{array}{c}
\text{O} \\
\text{N} \\
\end{array}
\end{align*}} \\
\text{\begin{align*}
\begin{array}{c}
\text{O} \\
\text{N} \\
\end{array}
\end{align*}}
\]

Scheme 3

The oxidation of alcohols into the corresponding aldehydes by \( N \)-chlorobenzotriazole has been reported previously\(^{19} \). We now show that two equivalents of \( N \)-chlorobenzotriazole converted alcohols 8a,8h as expected into the corresponding \( N \)-acylbenzotriazoles 3a,8h (Scheme 4), which were purified by recrystallization. Known 3a was identical with the authentic sample, novel 3h was identified by elemental analysis and \( ^1\text{H} \) and \( ^{13}\text{C} \) NMR spectra.
Preparation of \( N \)-alkylbenzotriazoles \( 10a–c \). Reactions of \( N \)-chlorobenzotriazole (2) with substituted toluenes \( 9a–c \) in the presence of AIBN at 90–100 °C for 21–48 h led to the formation of corresponding \( N \)-alkylbenzotriazoles \( 10a–c \), similar to the radical bromination of the side chain of toluene previously observed by Slutter et al.\(^{33}\) on reaction with \( N \)-bromosuccinimide.

\[
\begin{array}{c|ccc}
\text{Time} & \text{Yield} & \text{R} \\
\text{(h)} & (%) & \\
3a & 1.0 & 60 & \text{Ph} \\
3h & 0.5 & 59 & \text{C}_6\text{H}_5\text{C}_6\text{H}_4
\end{array}
\]

Compounds \( 10a \) and \( 10b \) had singlets at \( \delta \) 5.84 and 5.82 identical with spectra previously published.\(^{34}\) Novel compound \( 10c \) was identified by elemental analysis and by its \(^1\text{H} \) and \(^{13}\text{C} \) NMR spectra.

\( N \)-Benzylbenzotriazoles are useful synthetically in many ways. Thus, lithiation with butyl lithium can be followed by the addition to aliphatic, aromatic, and \( \alpha,\beta \)-unsaturated aldehydes;\(^{35}\)
cyclic and acyclic ketones, carboxylic esters, enamines and imides, and leading to the formation of trans-alkenes, dienes, trienes and alkynes. 2-(Benzotriazol-1-yl)enamines (obtained from lithiated 1-(arylmethyl)benzotriazoles and nitriles) undergo rearrangement to give 2,2-diarylquinazolines. 1-Benzylbenzotriazoles act as a 1,3-dipole synthons in Michael addition–cyclization for the preparation of polysubstituted naphthalenes and phenanthrenes. Annulation of benzylbenzotriazole with 2-bromoacetaldehyde diethyl acetal followed by the treatment with BuLi and N-benzylideneaniline leads to the formation of 1,2,3-triarylpyrroles in one pot. [3+2] Cycloaddition of benzyl benzotriazole with alkenes leads to the formation of functionalised indans.

Literature methods to prepare N-benzylbenzotriazoles include reactions of the corresponding alkane or arene with 1-chloromethylbenzotriazole in the presence of aluminium halide; or from the corresponding arylmethyl halide with benzotriazole.

To summarize, we have developed one pot syntheses of N-acyl- and N-alkyl-benzotriazoles from the corresponding aldehydes/alcohols or toluenes respectively, utilizing N-chlorobenzotriazole in the presence of a radical initiator.

Experimental Section

General Procedures. Melting points were determined on a hot-stage apparatus and are uncorrected. NMR spectra were recorded in CDCl₃ with TMS as the internal standard for ¹H (300 MHz) or a solvent as the internal standard for ¹³C (75 MHz). Micro elemental analyses were performed on a Carlo Erba EA-1108 elemental analyzer.

Materials. 1-Chlorobenzotriazole (2) was synthesized according to the previously published procedure as white crystals mp 103–105 °C (103–105 °C). 4-(Dimethylamino)-2-nitrobenzaldehyde (6) was synthesized according to the published procedure by Baumann et al. and was confirmed by the NMR data and CHN analysis.

General procedure for the synthesis of N-acylbenzotriazole from the corresponding aldehydes (3a–g)
The mixture of corresponding aldehyde (11 mmol), N-chlorobenzotriazole (2.70 g, 17.6 mmol) and AIBN (0.1 g, 0.6 mmol) in benzene (80 mL) were refluxed for the specified time (Scheme 1). To the cooled reaction mixture ethyl acetate was added, and the organic layer was washed with saturated aqueous Na₂CO₃, brine, and dried over MgSO₄. The solvent was evaporated to give the crude product, which was purified by recrystallisation from the appropriate solvent to afford the pure compound.

1H-1,2,3-Benzotriazol-1-yl-(phenyl)methanone (3a). White needles from 2-propanol (63 %), mp 112–113 °C (112–113 °C); ¹H NMR δ 7.53–7.61 (m, 3H), 7.68–7.74 (m, 2H), 8.16–8.23 (m, 3H), 8.40 (d, J = 8.2 Hz, 1H); ¹³C NMR δ 114.8, 120.2, 126.3, 128.4, 130.4, 131.5, 131.7, 132.3, 133.7, 145.7, 166.7.
1- (1H-1,2,3-Benzotriazol-1-yl)-1-propanone (3b). White prisms from 2-propanol (53 %), mp 77–78 °C (80– 82 °C), 1H NMR δ 1.43 (t, J = 7.3 Hz, 3H), 3.47 (q, J = 7.4 Hz, 2H), 7.51 (t, J = 8.0 Hz, 1H), 7.66 (t, J = 8.1 Hz, 1H), 8.12 (d, J = 8.2 Hz, 1H), 8.30 (d, J = 8.2 Hz, 1H); 13C NMR δ 8.3, 29.1, 114.4, 120.1, 126.0, 130.3, 131.1, 146.1, 173.3. Anal. Calcd for C9H9N3O: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.77; H, 5.22; N, 24.12.

1H-1,2,3-Benzotriazol-1-yl-(4-chlorophenyl)methanone (3c). White needles from 2-propanol (81 %), mp 138–139 °C (138–139 °C), 1H NMR δ 7.54–7.59 (m, 3H), 7.72 (t, J = 8.1 Hz, 1H), 8.16–8.22 (m, 3H), 8.38 (d, J = 8.2 Hz, 1H); 13C NMR δ 114.8, 120.2, 126.5, 128.8, 129.7, 130.5, 132.2, 133.2, 140.4, 145.7, 165.6.

1-(1H-1,2,3-Benzotriazol-1-yl)-3-phenyl-1-propanone (3d). White prisms from benzene at 5–10 °C overnight (62 %), mp 62–64 °C (63–64 °C), 1H NMR δ 3.23 (t, J = 7.8 Hz, 2H), 3.77 (t, J = 7.6 Hz, 2H), 7.19–7.32 (m, 5H), 7.47–7.52 (m, 1H), 7.61–7.67 (m, 1H), 8.11 (d, J = 8.2 Hz, 1H), 8.28 (d, J = 8.2 Hz, 1H); 13C NMR δ 30.1, 37.1, 114.4, 120.1, 126.1, 126.5, 128.4, 128.6, 130.3, 131.0, 139.8, 146.1, 171.6.

1H-1,2,3-Benzotriazol-1-yl(3-thienyl)methanone (3e). Brownish microcrystals from 2-propanol (56 %), mp 118–120 °C; 1H NMR (DMSO) δ 7.65 (t, J = 7.7 Hz, 1H), 7.79–7.84 (m, 2H), 7.90 (d, J = 4.9 Hz, 1H), 8.28–8.34 (m, 1H), 8.98 (br s, 1H); 13C NMR (DMSO) δ 114.4, 120.0, 126.5, 127.3, 129.4, 130.7, 131.7, 132.5, 138.6, 145.0, 160.1. Anal. Calcd for C11H7N3OS: C, 57.63; H, 3.08; N, 18.33. Found: C, 57.55; H, 2.92; N, 18.44.

1H-1,2,3-Benzotriazol-1-yl (2-furyl)methanone (3g). White microcrystals from 2-propanol (38 %); mp 165–167 °C (165–167 °C), 1H NMR δ 6.74 (dd, J = 3.7, 1.6 Hz, 1H), 7.52–7.57 (m, 1H), 7.63–7.68 (m, 1H), 8.12 (d, J = 8.4 Hz, 1H), 8.34 (d, J = 8.2 Hz, 1H); 13C NMR δ 29.8, 32.0, 47.1, 114.6, 120.1, 126.0, 130.2, 146.1, 171.3.

Procedure for the synthesis of 1H-1,2,3-benzotriazol-1-yl (3-chloro-4-methoxy-1-naphthyl)methanone (5)
The mixture of 4-methoxy-1-naphthaldehyde (0.45 g, 2.4 mmol), N-chlorobenzotriazole (0.70 g, 4.6 mmol) and AIBN (0.1 g, 0.6 mmol) in benzene (80 mL) were refluxed for 4.0 h, then stirred at room temperature overnight. To the reaction mixture, ethyl acetate was added (50 ml), and the organic layer was washed with saturated aqueous Na2CO3, brine and dried over MgSO4. The solvent was evaporated to give the crude product, which was purified by column chromatography (CH2Cl2: Hexanes = 1:1) to afford the pure product. White microcrystals from 2-propanol (38 %); mp 165–167 °C (165–167 °C), 1H NMR δ 6.74 (dd, J = 3.7, 1.6 Hz, 1H), 7.52–7.57 (m, 1H), 7.63–7.68 (m, 1H), 8.12 (d, J = 8.4 Hz, 1H), 8.34 (d, J = 8.2 Hz, 1H); 13C NMR δ 113.0, 114.7, 120.2, 124.8, 126.3, 130.5, 132.2, 144.6, 145.6, 148.9, 155.1.
131.4, 132.0, 132.4, 146.2, 155.7, 166.0. Anal. Calcd for C₁₈H₁₂ClN₃O₂: C, 64.01; H, 3.58; N, 12.44. Found: C, 64.30; H, 3.46; N, 12.42.

**General procedure for the synthesis of substituted 4-(dimethylamino)-6-nitrobenzaldehyde (7a–c)**
The mixture of 4-(dimethylamino)-2-nitrobenzaldehyde (0.97 g, 5.0 mmol), N-chlorobenzotriazole (1.44 g, 9.4 mmol) and AIBN (0.1 g, 0.6 mmol) in benzene (80 mL) were refluxed for 3.0 h, then stirred at room temperature overnight. To the reaction mixture, ethyl acetate was added, and the organic layer was washed with saturated aqueous Na₂CO₃, brine, and dried over MgSO₄. The solvent was evaporated to give the crude product, which was purified by column chromatography (CH₂Cl₂:Hexanes = 6:4) to give 7a–c.

**5-Chloro-4-(dimethylamino)-2-nitrobenzaldehyde (7a).** Orange microcrystals (17 %), mp 92–94 °C; ¹H NMR δ 3.07 (s, 6H), 7.52 (s, 1H), 7.95 (s, 1H), 10.25 (s, 1H); ¹³C NMR δ 42.8, 113.7, 122.5, 129.7, 132.4, 149.1, 154.1, 186.0. Anal. Calcd for C₉H₉ClN₂O₃: C, 47.28; H, 3.97; N, 12.25. Found: C, 47.23; H, 3.82; N, 12.49.

**3-Chloro-4-(dimethylamino)-2-nitrobenzaldehyde (7b).** Orange microcrystals (4%), mp 95–97 °C; ¹H NMR δ 3.07 (s, 6H), 7.09 (d, J = 8.7 Hz, 1H), 7.93 (d, J = 8.7 Hz, 1H), 9.72 (s, 1H); ¹³C NMR δ 43.0, 116.0, 118.6, 119.8, 129.9, 130.3, 155.7, 184.8. Anal. Calcd for C₉H₉ClN₂O₃: C, 47.28; H, 3.97; N, 12.25. Found: C, 46.94; H, 3.77; N, 12.24.

**3,5-Dichloro-4-(dimethylamino)-6-nitrobenzaldehyde (7c).** Yellow needles (43%), mp 63–64 °C; ¹H NMR δ 3.07 (s, 6H), 7.83 (s, 1H), 9.73 (s, 1H); ¹³C NMR δ 42.9, 100.2, 122.3, 124.3, 131.3, 134.0, 152.7, 183.9. Anal. Calcd for C₉H₈Cl₂N₂O₃: C, 41.09; H, 3.07; N, 10.65. Found: C, 41.17; H, 2.96; N, 10.47.

**General procedure for the synthesis of N-acylbenzotriazole (3a, 3h) from the corresponding alcohols**
The mixture of alcohol (8 mmol) and N-chlorobenzotriazole (1.78 g, 11.6 mmol) in benzene (100 mL) were refluxed for 2 h, then AIBN (0.1 g, 0.6 mmol) and the next portion of N-chlorobenzotriazole (1.70 g, 11.1 mmol) were added. The solution was kept at 80 °C for the specified time (Scheme 1), then stirred at room temperature overnight. To the reaction mixture, ethyl acetate was added and the organic layer was washed with saturated aqueous Na₂CO₃, brine and dried over anhyd. MgSO₄. The solvent was evaporated to give the crude product, which was purified by recrystallisation from the appropriate solvent to afford the pure compound.

**1H-1,2,3-Benzotriazol-1-yl (phenyl)methanone (3a).** White needles from 2-propanol (60 %), mp 112–113 °C (112–113 °C ⁰). The spectrum is identical with that for compound 3a prepared from benzaldehyde above.

**1H-1,2,3-Benzotriazol-1-yl ([1,1'-biphenyl]-4-yl)methanone (3h).** White prisms from 2-propanol (59 %), mp 165–167 °C; ¹H NMR (DMSO) δ 7.45–7.58 (m, 3H), 7.67 (t, J = 7.7 Hz, 1H), 7.82–7.88 (m, 3H), 7.96 (d, J = 8.4 Hz, A part of AB system, 2H), 8.24 (d, J = 8.4 Hz, B part of AB system, 2H), 8.30–8.37 (m, 2H); ¹³C NMR (DMSO) δ 114.5, 120.0, 126.5, 126.6,

**General procedure for the synthesis of $N$-alkyl- and $N$-aryl-benzotriazoles (10a–c)**

The mixture of $N$-chlorobenzotriazole (2.30 g, 15.0 mmol) and AIBN (0.1 g, 0.6 mmol) in excess of corresponding toluene as a reagent as well as solvent (126.8 mmol) were heated at 105–110 °C for the specified time (Scheme 3). To the cooled reaction mixture, ethyl acetate was added, and the organic layer was washed with saturated aqueous Na_{2}CO_{3}, brine and dried over anhyd. MgSO_{4}. The solvent was evaporated under reduced pressure to give the crude product, which was purified by recrystallization from the appropriate solvent to give the pure compound.

**1-Benzyl-1H-1,2,3-benzotriazole (10a).** White microcrystals form 2-propanol (69 %), mp 115–116 °C (115–116 °C); $^{1}$H NMR δ 5.84 (s, 2H), 7.25–7.39 (m, 8H), 8.06 (d, $J = 7.83$ Hz, 1H); $^{13}$C NMR δ 52.2, 109.7, 120.0, 123.8, 127.3, 127.5, 128.4, 128.9, 132.7, 134.7, 146.3.

**1-(4-Chlorobenzyl)-1H-1,2,3-benzotriazole (10b).** White microcrystals from 2-propanol (55 %), mp 98–99 °C (101–102 °C); $^{1}$H NMR δ 5.82 (s, 2H), 7.21 (d, $J = 8.2$ Hz, A part of the AB system, 2H), 7.29–7.46 (m, 5H), 8.08 (d, $J = 8.8$ Hz, 1H); $^{13}$C NMR δ 51.4, 109.4, 120.2, 124.0, 127.6, 128.9, 129.2, 132.6, 133.2, 134.4, 146.3. Anal. Calcd for C_{13}H_{10}ClN_{3}: C, 64.07; H, 4.14; N, 17.24. Found: C, 64.01; H, 3.95; N, 17.31.

**4-(1H-1,2,3-Benzotriazol-1-ylmethyl)benzonitrile (10c).** White prisms from 2-propanol (64 %), mp 164–166 °C; $^{1}$H NMR δ 5.91 (s, 2H), 7.33–7.49 (m, 5H), 7.63 (d, $J = 8.4$ Hz, A part of the AB system, 2H), 8.10 (d, $J = 8.2$ Hz, 1H); $^{13}$C NMR δ 51.3, 109.1, 112.5, 118.1, 120.3, 124.2, 27.9, 128.0, 132.6, 132.7, 139.9, 146.2. Anal. Calcd for C_{14}H_{10}N_{4}: C, 71.78; H, 4.30; N, 23.92. Found: C, 71.50; H, 4.30; N, 23.67.

**References**