Graphical Abstract

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\[ N\text{-Acyl } 1,5\text{-diazabicyclo[4.3.0]non-5-ene (DBN) tetraphenylborate salts as } O\text{-acylating agents} \]

James E. Taylor, Jonathan M. J. Williams, Steven D. Bull*

\[
\begin{align*}
\text{N} & \text{Acyl} & 1,5 \text{-diazabicyclo[4.3.0]non-5-ene (DBN) tetraphenylborate salts as } O\text{-acylating agents} \\
\text{James E. Taylor, Jonathan M. J. Williams, Steven D. Bull*} \\
\text{\textbf{A}} & \text{\textbf{B}} & \text{\textbf{C}} \\
\text{\textbf{D}} & \text{\textbf{E}} & \text{\textbf{F}} \\
\text{\textbf{G}} & \text{\textbf{H}} & \text{\textbf{I}} \\
\end{align*}
\]
Acyl chlorides and acid anhydrides are currently the most commonly used acyl sources in acylation reactions of alcohols. However, there are some limitations to the use of acyl chlorides and acid anhydrides in synthesis. For example, the acylation reactions of heteroatoms using acyl chlorides and acid anhydrides can be highly exothermic. These processes also release acids, which can cause problems with any acid-sensitive functionality present within the reacting substrate. In addition, acyl chlorides of complex substrates can be difficult to prepare, whilst simpler acyl chlorides are often air-sensitive and volatile, which makes them practically difficult to use. Base or Lewis acid catalysed O-acylation reactions of alcohols using acyl chlorides or acid anhydrides can also suffer from poor regioselectivity between primary and secondary alcohols.

The O-acylation of alcohols using carboxylic acids as sacrificial acyl donors is also widely used, although forcing conditions are often required to drive the equilibrium towards formation of ester products. Transesterification reactions are also commonly used, with a number of different esters having been employed as sacrificial acyl donors. Various other alternative acyl sources have also been developed for carrying out O-acylation reactions. For example, Katritzky and co-workers have developed an extensive range of N-acyl benzoazoles as stoichiometric acylating agents. Some of these N-acyl benzoazoles have been used as O-acylating reagents for trifluoroacetylations, the preparation of fluorescently labeled carbohydrates, and recently for the formation of depsipeptides and oligoesters. Herein, we report the application of a new bench-stable and crystalline acyl source for the O-acylation of alcohols.

We previously reported that the bicyclic amidine 1,5-diazabicyclo[4.3.0]non-5-ene (DBN, 1) can be used to catalyse the Friedel-Crafts acylation reaction of N-protected pyroles and indoles. Whilst investigating the mechanism of this process, the X-ray crystal structure of an N-acyl DBN tetraphenylborate salt was obtained, providing structural information on the proposed intermediates in these reactions. Subsequently, we found that a number of air-stable and highly crystalline N-acyl DBN-BPh₄ salts 3a-h could be prepared in high yields by reacting DBN (1) with the corresponding acyl chloride 2a-h in the presence of sodium tetraphenylborate (Scheme 1).

![Scheme 1. Synthesis of N-acyl DBN-BPh₄ salts 3a-h from DBN (1) and acyl chlorides 2a-h.](image)

N-Acyl DBN-BPh₄ salts 3a-h were found to be highly efficient N-acylating agents, reacting with a wide variety of anilines, primary amines, and secondary amines (Scheme 2a), as well as sultanomides (Scheme 2b) to form their corresponding N-acylated products in high yields. It was found that the DBN hydrotetrathyphenylborate side-product could be readily removed by filtration, providing N-acylated products without the need for further purification.

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**ARTICLE INFO**

**ABSTRACT**

Air stable and crystalline N-Acyl DBN tetraphenylborate salts have been shown to be effective O-acylating agents, reacting with both primary and secondary alcohols to give the corresponding esters in good yields. In the case of diols, the N-acyl DBN-BPh₄ salts have been shown to acylate regioselectively their primary alcohol functionality in the presence of a secondary alcohol. The DBN hydrotetrathyphenylborate side product can be readily removed by filtration, providing the ester products without the need for further purification.
further purification. These N-acetyl DBN-BPh₄ salts are attractive alternatives to acyl halides and acid anhydrides as they can be stored in air without decomposition, avoid the production of free acid during acylation reactions, and can be used under forcing thermal conditions.¹⁰

Scheme 2. N-Acetyl DBN-BPh₄ salts as N-acylating agents for a) anilines, primary amines, and secondary amines, and b) for sulfonamides.

Consequently, it was decided to investigate whether the N-acetyl DBN-BPh₄ salt (3a) could be applied to the O-acylation of alcohols to form esters. Initially, benzyl alcohol (4a) and 1.3 equivalents of N-acetyl DBN-BPh₄ (3a) were heated in acetonitrile at 80 °C for 16 hours, in accordance with the optimal conditions developed for the N-acylation of amines. However, ¹H NMR spectroscopic analysis of the crude reaction mixture showed only 36% conversion into benzyl acetate (5a), with the remainder being unreacted starting material (Scheme 3). In an attempt to improve the conversion, the reaction was repeated using 20 mol% DBN (1) as a catalyst, as this had previously been shown to increase the rate of sulfonamide O-acylation reactions, and can be used under forcing thermal conditions. However, reaction of N-acetyl DBN-BPh₄ (3a) with the tert-butyl alcohol tert-butanol (4h) was unsuccessful, with ¹H NMR spectroscopic analysis of the crude material showing no evidence of any O-acylation having occurred (Table 1, entry 8). Attempts to promote the reaction by using an excess of alcohol, or using tert-butanol (4h) as solvent were also unsuccessful, with no O-acylation observed in either case.

The successful O-acylation protocol using 20 mol% DBN (1) was then applied to a range of alcohols 4b-h, with the results summarized in Table 1. The reaction of N-acetyl DBN-BPh₄ (3a) with 2-phenethyl alcohol (4b) proceeded with complete conversion, enabling 2-phenethyl acetate (5b) to be isolated in 80% yield (Table 1, entry 2). Acetylation of octan-1-ol (4c) also worked well, providing octyl acetate (5c) in 74% yield after the standard work-up procedure (Table 1, entry 3). It was found that phenol (4d) was sufficiently acidic to be acylated using N-acetyl DBN-BPh₄ (3a) without the DBN (1) catalyst, giving phenyl acetate (5d) in 84% isolated yield (Table 1, entry 4). Secondary alcohols could also be acylated using N-acetyl DBN-BPh₄ (3a) and 20 mol% DBN (1), with the reactions of both 1-phenyl-1-propanol (4e) and unsaturated 1-octen-3-ol (4f) giving complete conversion into their corresponding esters 5e and 5f in 79% and 63% yields respectively (Table 1, entries 5 and 6). The cyclic secondary alcohol, 1-indanol (4g) was also successfully acylated using N-acetyl DBN-BPh₄ (3a), providing the corresponding acetate 5g in 70% isolated yield (Table 1, entry 7). However, reaction of N-acetyl DBN-BPh₄ (3a) with the tertiary alcohol tert-butanol (4h) was unsuccessful, with ¹H NMR spectroscopic analysis of the crude material showing no evidence of any O-acylation having occurred (Table 1, entry 8). Attempts to promote the reaction by using an excess of alcohol, or using tert-butanol (4h) as solvent were also unsuccessful, with no O-acylation observed in either case.

The successful O-acylation protocol using N-acetyl DBN-BPh₄ (3a) and 20 mol% DBN (1) was then applied to 1-phenyl-1,2-ethanediol (6) to investigate whether its primary alcohol functionality could be acetylated regioselectively in the presence of a secondary alcohol. In this case, one equivalent of N-acetyl DBN-BPh₄ (3a) was used, rather than the 1.3 equivalents used for the previous acylations. After the standard work-up procedure, ¹H NMR spectroscopic analysis revealed that the reaction had proceeded to 84% conversion, with 76% of the converted material being 2-hydroxy-2-phenylacetate (7a) obtained from acetylation of the primary alcohol. However, the

Table 1. O-Acetylation of alcohols 4a-h using N-acetyl DBN-BPh₄ (3a) to afford esters 5a-h.³

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alcohol</th>
<th>Ester</th>
<th>Conversion (%)³⁻⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhOH</td>
<td>PhOAc</td>
<td>100 (88)</td>
</tr>
<tr>
<td>2</td>
<td>PhOH</td>
<td>PhOAc</td>
<td>100 (80)</td>
</tr>
<tr>
<td>3</td>
<td>H₂O</td>
<td>H₂O</td>
<td>100 (74)</td>
</tr>
<tr>
<td>4</td>
<td>PhOH</td>
<td>PhOAc</td>
<td>100 (84)</td>
</tr>
<tr>
<td>5</td>
<td>EtOH</td>
<td>EtOAc</td>
<td>100 (79)</td>
</tr>
<tr>
<td>6</td>
<td>PhOH</td>
<td>PhOAc</td>
<td>100 (63)</td>
</tr>
<tr>
<td>7</td>
<td>4g</td>
<td>5g</td>
<td>100 (70)</td>
</tr>
<tr>
<td>8</td>
<td>4h</td>
<td>–</td>
<td>0 (–)</td>
</tr>
</tbody>
</table>

³Reactions performed on a 0.5 mmol scale using 0.65 mmol N-acetyl DBN-BPh₄ (3a) and 20 mol% DBN (1).
⁴Determined by ¹H NMR spectroscopic analysis.
⁵Isolated yields in parentheses.
⁶No DBN (1) required.

Tetrahedron Letters

Scheme 3. O-Acetylation of benzyl alcohol (4a) using N-acetyl DBN-BPh₄ (3a).
Scheme 4. Acylation of 1-phenyl-1,2-ethanediol (6) using a) N-acetyl DBN-BPh₄ (3a) and b) N-benzoyl DBN-BPh₄ (3b).

reaction was not completely regioselective, as 12% of the secondary ester 7b and 12% of the bis-acylated ester 7c were also observed (Scheme 4a). It was found that using more sterically demanding N-benzoyl DBN-BPh₄ (3b) as the acyl source improved the regioselectivity of the acylation, with the primary ester 8a, secondary ester 8b, and bis-benzoylated product 8c being formed in an 86:8:6 ratio, although the overall conversion was reduced to 60% (Scheme 4b).

In conclusion, the bench-stable and highly crystalline N-acetyl DBN-BPh₄ salt (3a) has been shown to be an efficient O-acylating agent for a range of primary and secondary alcohols. The ester products can be isolated via a simple work-up procedure, without the need for further purification by column chromatography. N-Acetyl DBN-BPh₄ (3a) and N-benzoyl DBN-BPh₄ (3b) have also been shown to acylate regioselectively the primary alcohol functionality of diols that also contain a secondary alcohol group.

Acknowledgement

J.E.T. gratefully acknowledges the University of Bath for the award of a Ph.D. scholarship.

References and notes


11. General procedure for the synthesis of N-Acyl DBN-BPh₄ salts (3a-f): NaBPh₄ (1 equiv.) was added to a round-bottom flask and purged with nitrogen. Dry MeCN (to make a 0.2 M solution of NaBPh₄) and the appropriate acyl chloride (1.04 equiv.) were added and the resulting solution cooled to 0 °C. DBN (1) (1 equiv.) was added dropwise and a precipitate of NaCl began to form. The reaction was left to stir for 1 h before being warmed to room temperature and filtered through a pad of Celite®, washing thoroughly with MeCN. The filtrate was then concentrated under reduced pressure and the resulting N-acetyl DBN-BPh₄ salt purified by recrystallization from CHCl₃ and hexane.

12. General procedure for the O-acylation of alcohols using N-acetyl DBN-BPh₄ salts (3a-f): NaBPh₄ (1.3 equiv., 0.65 mmol) was added to a carousel tube and purged with nitrogen. Dry MeCN (to make a 0.2 M solution of NaBPh₄) and the appropriate acyl chloride (1.04 equiv.) were added and the resulting solution cooled to 0 °C. DBN (1) (20 mol%), 0.1 mmol) were added and the resulting solution heated at 80 °C for 16 h. After being cooled to room temperature, the mixture was filtered and concentrated under reduced pressure. The crude product was suspended in a minimum amount of hot CH₂Cl₂ and allowed to cool before filtering off the insoluble salts. The filtrate was washed with NH₄Cl (aq) and brine before being dried over MgSO₄, filtered, and concentrated under reduced pressure.