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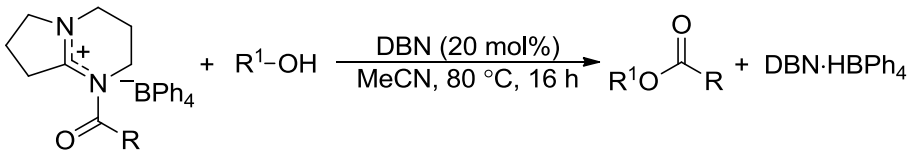

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N-Acyl 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) tetraphenylborate salts as *O*-acylating agents

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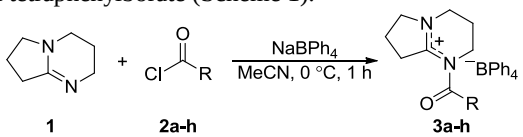
ABSTRACT

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·BPh_4 salts have been shown to acylate regioselectively their primary alcohol functionality in the presence of a secondary alcohol. The DBN hydrotetraphenylborate side product can be readily removed by filtration, providing the ester products without the need for further purification.

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.[1] 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.[2]

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.[2,3] Various other alternative acyl sources have also been developed for carrying out *O*-acylation reactions.[4,5] For example, Katritzky and co-workers have developed an extensive range of *N*-acyl benzotriazoles as stoichiometric acylating agents.[6] Some of these *N*-acyl benzotriazoles have been used as *O*-acylating reagents for trifluoroacetylations, the preparation of fluorescently labeled carbohydrates, and recently for the formation of depsipeptides and oligoesters.[7] 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 pyrroles and indoles.[8,9] 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·BPh_4 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).[10,11]



1 **2a-h** **3a-h**

3a R = Me, 97%; **3b** R = Ph, 93%; **3c** R = *o*-Tol, 98%;
3d R = CH_2CH_2Ph, 73%; **3e** R = ^{t}Bu, 98%; **3f** R = OEt, 95%

Scheme 1. Synthesis of *N*-acyl DBN·BPh_4 salts **3a-h** from DBN (**1**) and acyl chlorides **2a-h**.

N-Acyl DBN·BPh_4 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 sulfonamides (Scheme 2b) to form their corresponding *N*-acylated products in high yields. It was found that the DBN hydrotetraphenylborate side-product could be readily removed by filtration, providing *N*-acylated products without the need for

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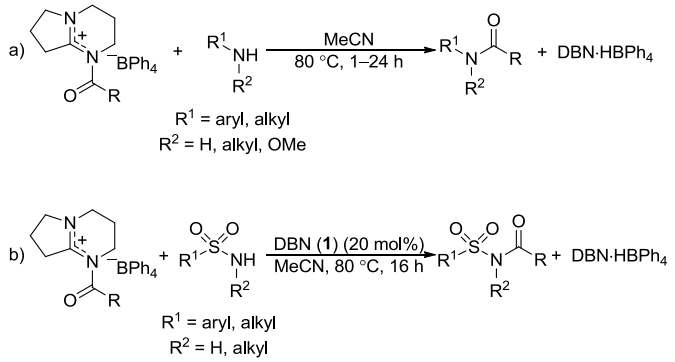
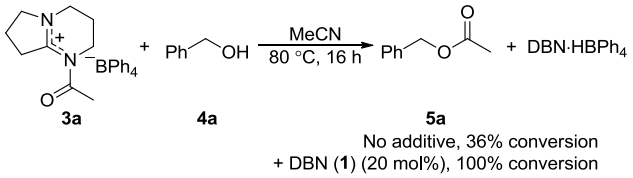
further purification. These *N*-acyl DBN·BPh_4 salts are attractive alternatives to acyl halides and acid anhydrides as they can be stored in air without decomposition, avoid the production of free acid during acylation reactions, and can be used under forcing thermal conditions.[10]



Scheme 2. *N*-Acyl DBN·BPh_4 salts as *N*-acylating agents for a) anilines, primary amines, and secondary amines, and b) for sulfonamides.

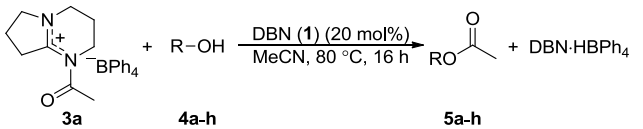
Consequently, it was decided to investigate whether the *N*-acetyl DBN·BPh_4 salt (**3a**) could be applied to the *O*-acetylation of alcohols to form esters. Initially, benzyl alcohol (**4a**) and 1.3 equivalents of *N*-acetyl DBN·BPh_4 (**3a**) were heated in acetonitrile at 80 °C for 16 hours, in accordance with the optimal conditions developed for the *N*-acylation of amines. However, ^{1}H 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 *N*-acylation using *N*-acyl DBN·BPh_4 salts. Pleasingly, this resulted in complete conversion of benzyl alcohol (**4a**) into benzyl acetate (**5a**) within 16 hours. The crude product could be readily purified by dissolving the reaction mixture in chloroform and filtering off the insoluble salts, which were a mixture of unreacted *N*-acetyl DBN·BPh_4 (**3a**) and DBN·$HBPh_4$. The filtrate was then washed with NH_4Cl and brine to remove the DBN (**1**) catalyst, providing pure benzyl acetate (**5a**) in 88% yield without the need for chromatographic purificiation.[12]



Scheme 3. *O*-Acetylation of benzyl alcohol (**4a**) using *N*-acetyl DBN·BPh_4 (**3a**).

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·BPh_4 (**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 octanol (**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·BPh_4 (**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·BPh_4 (**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

Table 1. *O*-Acetylation of alcohols **4a-h** using *N*-acetyl DBN·BPh_4 (**3a**) to afford esters **5a-h**.[a]



Entry	Alcohol	Ester	Conversion (%)[b, c]
1	**4a**	**5a**	100 (88)
2	**4b**	**5b**	100 (80)
3	**4c**	**5c**	100 (74)
4[d]	**4d**	**5d**	100 (84)
5	**4e**	**5e**	100 (79)
6	**4f**	**5f**	100 (63)
7	**4g**	**5g**	100 (70)
8	**4h**	–	0 (–)

[a]Reactions performed on a 0.5 mmol scale using 0.65 mmol *N*-acetyl DBN·BPh_4 (**3a**) and 20 mol% DBN (**1**).
[b]Determined by ^{1}H NMR spectroscopic analysis.
[c]Isolated yields in parentheses.
[d]No DBN (**1**) required.

secondary alcohol, 1-indanol (**4g**) was also successfully acetylated using *N*-acetyl DBN·BPh_4 (**3a**), providing the corresponding acetate **5g** in 70% isolated yield (Table 1, entry 7). However, reaction of *N*-acetyl DBN·BPh_4 (**3a**) with the tertiary alcohol *tert*-butanol (**4h**) was unsuccessful, with ^{1}H NMR spectroscopic analysis of the crude material showing no evidence of any *O*-acetylation 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*-acetylation observed in either case.

The successful *O*-acetylation protocol using *N*-acetyl DBN·BPh_4 (**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·BPh_4 (**3a**) was used, rather than the 1.3 equivalents used for the previous acetylations. After the standard work-up procedure, ^{1}H NMR spectroscopic analysis revealed that the reaction had proceeded to 84% conversion, with 76% of the converted material being 2-hydroxy-2-phenethyl acetate (**7a**) obtained from acetylation of the primary alcohol. However, the

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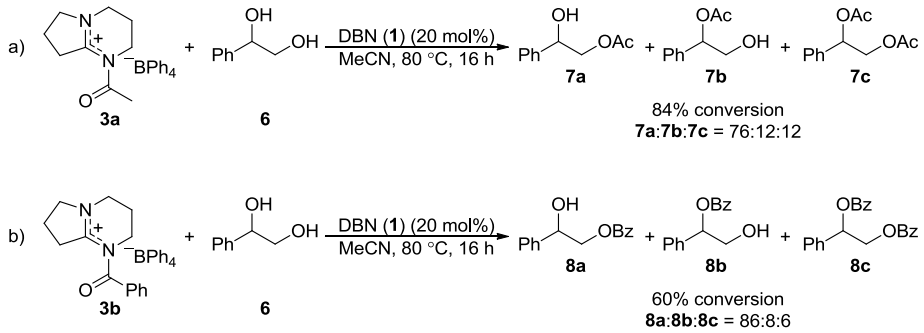

Scheme 4. Acylation of 1-phenyl-1,2-ethanediol (**6**) using a) *N*-acetyl DBN·BPh_4 (**3a**) and b) *N*-benzoyl DBN·BPh_4 (**3b**).

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·BPh_4 (**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·BPh_4 salt (**3a**) has been shown to be an efficient *O*-acetylating 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·BPh_4 (**3a**) and *N*-benzoyl DBN·BPh_4 (**3b**) have also been shown to acylate regioselectively the primary alcohol functionality of diols that also contain a secondary alcohol group.

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11. **General procedure for the synthesis of *N*-Acyl DBN·BPh_4 salts (3a-f):** $NaBPh_4$ (1 equiv.) was added to a round-bottom flask and purged with nitrogen. Dry MeCN (to make a 0.2 M solution of $NaBPh_4$) 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*-acyl DBN·BPh_4 salt purified by recrystallization from CH_2Cl_2 and hexane.
12. **General procedure for the *O*-acetylation of alcohols using *N*-acetyl DBN·BPh_4 (3a):** *N*-acetyl DBN·BPh_4 (**3a**) (1.3 equiv., 0.65 mmol) was added to a carousel tube and purged with nitrogen. Dry MeCN (2 mL), the appropriate alcohol (1 equiv., 0.5 mmol), and 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 $CHCl_3$ and allowed to cool before filtering off the insoluble salts. The filtrate was washed with $NH_4Cl_{(aq)}$ and brine before being dried over $MgSO_4$, filtered, and concentrated under reduced pressure.