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**PAPER**

# Strategic applications of Baylis–Hillman adducts to general syntheses of 3-nitroazetidines†

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A novel one-pot highly diastereoselective synthesis of substituted 3-nitroazetidines *via* an anionic domino process is described. The synthesis involves a high yielding annulation of Baylis–Hillman alcohols and their aldehydes with either *N*-aryl/tosylphosphoramidates or *N*-aryl/tosylphosphoramidates in combination with a task-specific ionic liquid [bmim][X–Y] to afford the corresponding 1,2,3-tri- and 1,2,3,4-tetrasubstituted azetidines, respectively. Plausible mechanisms for the formation of various 3-nitroazetidines have been suggested.

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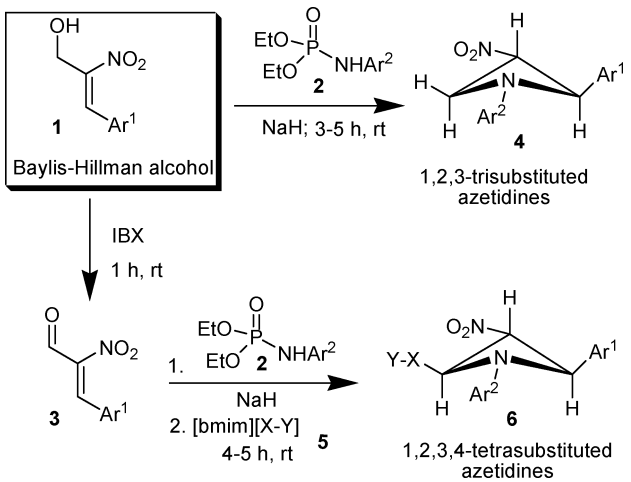
## Introduction

Azetidines are fascinating synthetic targets because of their remarkable chemical and biological properties.[1–3] The azetidine ring system prominently features in many medicinally important molecules some of which are markedly active against influenza A H2N2 virus,[4] and have anti-HIV-1, anti-HSV-1 and HSV-2 potential.[5] Although the inherent strain associated with the azetidine ring leads to difficulties in its construction, functionalisations and modifications, it is advantageous for its synthetic applications involving ring-opening reactions. For example, several functionalised azetidines have been used as masked 1,4-dipoles for the synthesis of five- and six-membered aza-heterocycles.[6] 3-Substituted azetidines are the most important constituent of various potential therapeutic moieties.[3] The literature records several reports on the synthesis of 3-substituted azetidines,[7,8] but the chemistry of 3-nitroazetidines has been scarcely investigated. Moreover, 3-nitroazetidines are of special interest because their nitro group can be served other functional groups such as to oximes, hydroxylamines, amines and ketones (Nef reaction).

Amongst various methods available for the synthesis of trisubstituted azetidines, the most general involves the cyclisation of γ-amino alcohols or their derivatives.[8a,9–12] De Kimpe and co-workers have reported elegant synthetic methods for functionalised azetidines that are based on the reaction of β-chloro or β-mesyloxy imines with nucleophiles such as hydride, cyanide, and alkoxides.[13] We have recently reported the synthesis of 1,2,4-triarylazetidines *via* a reductive cyclization of *N*-aryl-*N*-(1,3-diaryl-3-oxopropyl) phosphoramidates.[14]

The Baylis–Hillman (BH) reaction has attracted synthetic chemists because it is a highly economical carbon–carbon bond forming reaction which affords densely functionalised molecules in high yields.[15] The BH adducts have been a stimulus for developing art in organic synthesis *via* a multitude of functional group manipulations leading to their applications as versatile building blocks for various useful bioactive compounds and synthetic intermediates.[15]

The lack of a convenient synthetic method for 3-nitroazetidines and our ongoing efforts to devise new stereoselective cyclisation processes[14,16] prompted us to develop a general highly diastereoselective route to substituted 3-nitroazetidines **4** and **6** from BH adducts as depicted in Scheme 1. The present study would also widen the scope of synthetic applications of BH adducts.




**Scheme 1** Synthesis of 3-nitroazetidines **4** and **6**.

## Results and discussion

We herein report the first examples of the aza-Michael addition of *N*-aryl/tosylphosphoramidates to nitroalkene derived BH adducts and their aldehydes followed by anion induced

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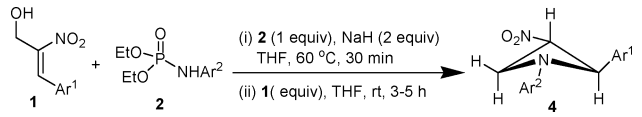
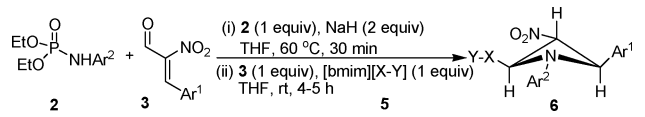
**Table 1** Synthesis of 1,2,3-trisubstituted azetidines **4**[a]




| Entry | $Ar^1$ | $Ar^2$ | Product | Time (h)[b] | Yield %[c,d] |
|---|---|---|---|---|---|
| 1 | Ph | Ph | **4a** | 3 | 85 |
| 2 | 4-$ClC_6H_4$ | Ph | **4b** | 3.5 | 92 |
| 3 | 2-$ClC_6H_4$ | Ph | **4c** | 4.5 | 90 |
| 4 | 4-$CH_3OC_6H_4$ | Ph | **4d** | 4 | 89 |
| 5 | Ph | 4-FPh | **4e** | 5 | 82 |
| 6 | 4-$ClC_6H_4$ | 4-FPh | **4f** | 3 | 91 |
| 7 | 2-$ClC_6H_4$ | 4-FPh | **4g** | 4.5 | 88 |
| 8 | 4-$CH_3OC_6H_4$ | 4-FPh | **4h** | 3.5 | 87 |
| 9 | Ph | Ts | **4i** | 3.5 | 91 |
| 10 | 3-Furyl | Ts | **4j** | 4 | 88 |

[a] Reaction conditions: **1** (5 mmol), **2** (5 mmol) and NaH (10 mmol) were used in dry THF (5 mL). [b] Time required for completion of step (ii). [c] Yield of isolated and purified product. [d] All compounds gave C, H and N analyses within ±0.37% and satisfactory spectral (IR, $^1$H NMR, $^{13}$C NMR and EIMS) data.

**Table 2** Synthesis of 1,2,3,4-tetrasubstituted azetidines **6**[a]



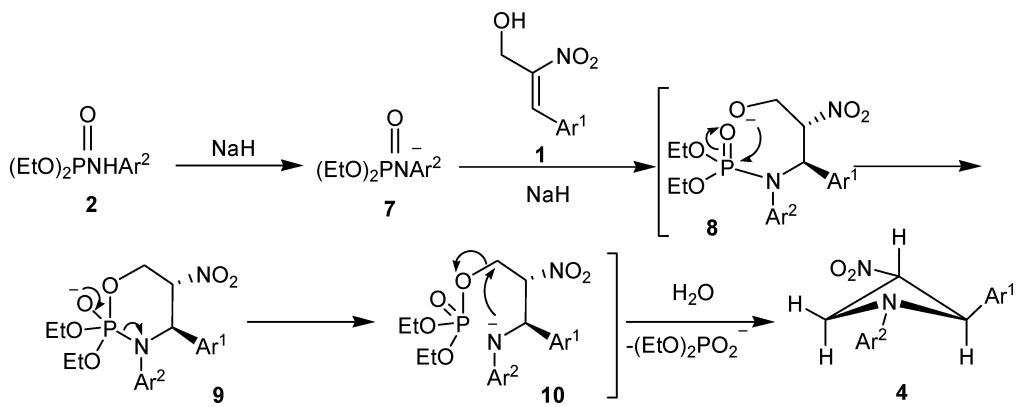

| Entry | $Ar^1$ | $Ar^2$ | X–Y | Product | Time (h)[b] | Yield %[c,d] |
|---|---|---|---|---|---|---|
| 1 | Ph | Ph | SCN | **6a** | 4 | 87 |
| 2 | 4-$ClC_6H_4$ | Ph | SCN | **6b** | 4.5 | 94 |
| 3 | 2-$ClC_6H_4$ | Ph | SCN | **6c** | 5 | 88 |
| 4 | 4-$CH_3OC_6H_4$ | Ph | SCN | **6d** | 5 | 91 |
| 5 | Ph | Ph | SPh | **6e** | 5 | 84 |
| 6 | 4-$ClC_6H_4$ | Ph | SPh | **6f** | 5 | 93 |
| 7 | 2-$ClC_6H_4$ | Ph | SPh | **6g** | 4.5 | 87 |
| 8 | 4-$CH_3OC_6H_4$ | Ph | SPh | **6h** | 4.5 | 90 |
| 9 | Ph | Ts | $NO_3$ | **6i** | 4 | 84 |
| 10 | Ph | Ts | TfO | **6j** | 4.5 | 89 |
| 11 | 3-Furyl | Ts | SCN | **6k** | 4.5 | 92 |
| 12 | 3-Furyl | Ph | SCN | **6l** | 5 | 91 |

[a] Reaction conditions: **2** (5 mmol), **3** (5 mmol), NaH (10 mmol) and [bmim][X–Y] were used in dry THF (5 mL). [b] Time required for completion of step (ii). [c] Yield of isolated and purified product. [d] All compounds gave C, H and N analyses within ±0.37% and satisfactory spectral (IR, $^1$H NMR, $^{13}$C NMR and EIMS) data.

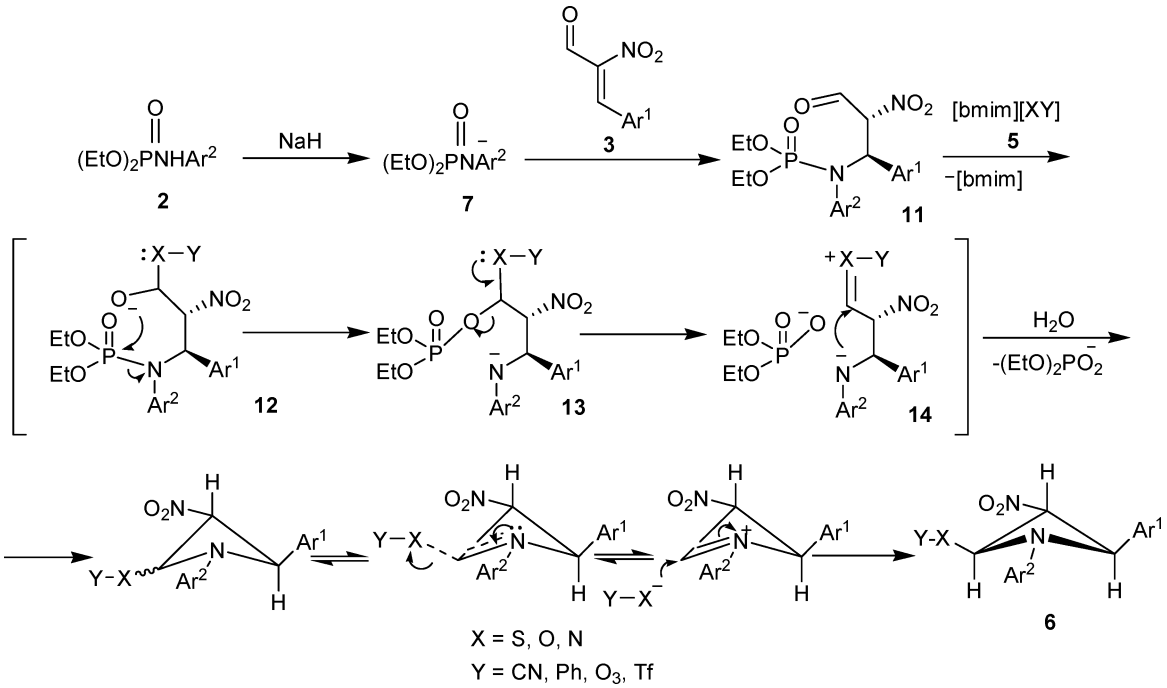
cyclisation to afford 3-nitroazetidines in excellent yields with high diastereoselectivity. This divergent route can be used to produce skeletally diverse azetidine scaffolds from the same precursor.

At the outset, we synthesised 1,2,3-trisubstituted azetidines **4** by a novel one-pot procedure. Thus, diethyl *N*-aryl/tosylphosphoramidates **2** were treated with sodium hydride in dry THF to the generate anion **7**, which *in situ* underwent aza-Michael addition to BH adducts **1** followed by cyclisation to afford azetidines **4** in 82–92% yields (Table 1). The formation of azetidines **4** is best explained through an anionic domino process as outlined in (Scheme 2). This presumption is supported by the isolation of representative alkoxide **8a** as its parent alcohol **9a** in 42% yield and its easy conversion to azetidine **4a** 96% yield under the same reaction conditions. In order to enhance the generality and scope of the method and introduce further functionalities into the azetidine ring, we undertook for the first time the oxidation of BH alcohols **1** to their aldehydes employing IBX in DMSO[17] as it is a mild oxidant, and a variety of functional groups are compatible with its use. The aldehydes **3** underwent aza-Michael addition with *N*-aryl/tosylphosphoramidates **2** followed by anion-induced cyclisation with a task-specific ionic liquid (TSIL) [bmim][X–Y] to afford azetidines **6** in 84–94% yields (Table 2) as depicted in Scheme 3.

The reaction can be best explained through the attack of a nucleophile ($^-$X–Y) on the carbonyl carbon followed by the intramolecular attack of the alkoxide ion **12** on the phosphorus atom. Then the lone pair of X forms a bond with carbon, and carbon-oxygen bond breaks leading to the formation of products **6** through **13** and **14** (Scheme 3). Furthermore, during the formation of products **6** an iminium ion comes into play which sets equilibrium to furnish the more favourable *trans-trans* product as depicted in Scheme 3. A comparison of [bmim]SCN/SPh with KSCN/PhSNa for the synthesis of **6** was carried out under similar conditions by stirring Baylis–Hillman adduct[15a] **1** and *in situ* generated phosphoramidate anion **7** with 1.5 equivalents of KSCN or PhSNa in THF for 4–5 h at room temperature. In the case of KSCN/PhSNa, the anion induced cyclisation afforded the corresponding **6** in relatively lower yields (41–53%). This indicates that the nucleophilicity of SCN or PhS anion from [bmim]SCN or [bmim]SPh is considerably higher compared to that from KSCN or PhSNa. After isolation of products **6**, the




**Scheme 2** A plausible mechanism for the formation of 3-nitroazetidines **4**.




**Scheme 3** A plausible mechanism for the formation of 3-nitroazetidines **6**.

residue was treated with concentrated HCl followed by stirring with KSCN or PhSNa at room temperature for 48 h to obtain the corresponding recycled task-specific ionic liquid (TSIL). The high affinity of phosphorus for oxygen is the main driving force for both of the present cyclisation reactions depicted in Schemes 2 and 3. Furthermore, in order to improve the utility of this synthetic method, an additional experiment to remove tosyl group from azetidine ring nitrogen was also performed. Azetidines can be easily detosylated using $SmI_2$ in a refluxing mixture of THF and DMPU (*N*,*N*′-dimethylpropyleneurea) employing the method of Vedejs and Lin.[18]

The annulation of BH alcohols **1** and their aldehydes **3** to functionalised azetidines was entirely diastereoselective and afforded exclusively the *trans* isomers. The configurational assignment of azetidines **4** and **6** was made on the basis of $^1$H NMR coupling constants $J_{trans\ H/H}$ of 2-H, 3-H, and 3-H, 4-H of the heterocycle which are in the range of 6.5–7.7 Hz as already reported for tri- and tetrasubstituted azetidines.[19] The relative configuration was further confirmed by NOE experiments as shown in Fig. 1. The absence of any measurable NOE between 2-H and 3-H, and the presence of measurable NOE between 3-H and aryl protons at C-2, indicates that 2-H and 3-H protons are on opposite faces of the molecule, confirming the *trans* and *trans-trans* stereochemistry of **4** and **6**, respectively. However, the NOE between 1-H(Ar$^2$) and 2-H or between 1-H(Ar$^2$) and 4-H were not so significant and conclusive (hence not shown in the Fig. 1) as observed in the case of 2-H(Ar$^1$) and 3-H. The exclusive formation of *trans* isomer **4** is understandable in view of most of the Michael additions which usually give *anti*/*trans* products. The formation of the most stable *trans-trans* isomers **6** with complete diastereoselectivity indicates that the reaction is under thermodynamic control and a Y–X$^-$ addition/elimination equilibrium is at play through an iminium ion (Scheme 3). The intermediacy of the iminium ion was proved by placing compound **6a** in the presence of PhSNa under the reaction conditions and stirring for 5 h, which led to the isolation compound **6e** as well. This rationalizes the complete *trans-trans* diastereoselectivity in the formation of **6**.

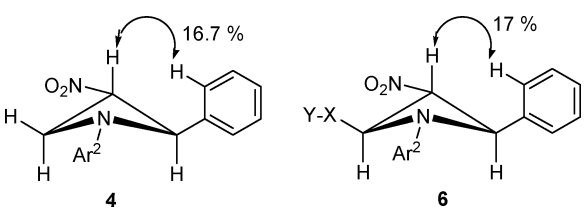



**Fig. 1** NOE for 3-nitroazetidines.

## Conclusions

In summary, we have developed a novel one-pot procedure for a highly diastereoselective synthesis of 1,2,3-tri- and 1,2,3,4-tetrasubstituted azetidines from BH alcohols and their aldehydes, respectively. The synthetic protocol presents the first application of BH alcohols and their aldehydes to the synthesis of nitroazetidines *via* an anionic domino process, thereby it also widens the scope of synthetic utility of BH adducts.

## Experimental

### General procedure for the synthesis of of 1,2,3-trisubstituted azetidines 4 and 1,2,3,4-tetrasubstituted azetidines 6

To a solution of diethyl *N*-arylphosphoramidate **2** (5 mmol) in dry THF (5 mL) was added dropwise a suspension of NaH (240 mg, 10 mmol) in dry THF (10 mL) with stirring at rt. After the addition was complete and evolution of hydrogen gas (effervescence) had ceased, the reaction mixture was stirred at 60 °C for 30 min and

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then cooled to rt. Next, a solution of Baylis Hillman alcohol **1** (5 mmol) in dry THF (5 mL) was added, and the reaction mixture was stirred at rt for 3–5 h. Water (20 mL) was added, the mixture was extracted with ether (3 × 30 mL), the combined organic layers were dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The crude product thus obtained was purified by silica gel column chromatography (hexane/EtOAc, 95 : 5) to afford an analytically pure sample of **4**.

Similarly, **6** were synthesised using aldehydes **3** instead of alcohols **1** followed by TSILs **5**. The structure of the products **4** and **6** were confirmed by their elemental and spectral analyses (see ESI†).

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