Chalcones to Functionalized Azetidines via Anion-Induced Cyclization Using Task-Specific Ionic Liquids

Lal Dhar Singh Yadav,* Rajesh Patel, Vishnu Prabhakar Srivastava

Green Synthesis Lab, Department of Chemistry, University of Allahabad, Allahabad 211 002, India
Fax +91(532)2460533; E-mail: ldsyadav@hotmail.com

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Abstract: The first example of the application of task-specific ionic liquids (TSIL) to a new and practical synthesis of functionalized azetidines is reported. Aza-Michael addition of diethyl *N*-arylphosphoramidates to chalcones affords diethyl *N*-aryl-*N*-(1,3-diaryl-3-oxopropyl)phosphoramidates, which undergo cyclization to functionalized azetidines. The cyclization is induced by anions (NCS^-, PhS^-) of TSIL and gives excellent yields with high diastereoselectivity in a one-pot procedure. The use of KSCN or PhSNa instead of the corresponding TSIL, [bmim]SCN or [bmim]SPh, resulted in significantly lower yields of products. After isolation of the product, the ionic liquid could be recycled for further use.

Key words: azetidines, Michael addition, chalcones, ionic liquids, phosphoramidates

Azetidines constitute an important class of small-ring azaheterocycles with interesting pharmacological activities. Furthermore, some other compounds incorporating the azetidine structure have been reported to exhibit remarkable activity against influenza A H2N2 virus,[1] and to possess anti-HIV-1, anti-HSV-1, and anti-HSV-2 potential.[2] Whereas the strain associated with the azetidine ring system leads to difficulties in its synthesis, functionalizations, and modifications, it is advantageous for its synthetic applications involving ring-opening reactions. Over the past few years, several functionalized azetidines have been utilized as masked 1,4-dipoles for the construction of five- and six-membered azaheterocycles.[3–6]

Among the various general procedures available for the synthesis of azetidines, the most general involves cyclization of γ-amino alcohols or their derivatives.[7–13] Functionalized small-ring heterocycles play an important role in the drug discovery process.[14–17] De Kimpe and co-workers have reported elegant synthetic methods for functionalized azetidines that are based on the reaction of β-chloro or β-mesyloxy imines with nucleophiles such as hydride, cyanide, and alkoxides.[18–24] A very recently reported synthesis of 1,2,4-triarylazetidines involves reductive cyclization of *N*-aryl-*N*-(1,3-diaryl-3-oxopropyl)phosphoramidates.[25] To our knowledge, the literature does not report any direct synthetic method for the synthesis of *C*-sulfur-functionalized azetidines, i.e. the target molecules of the present synthesis.

Ionic liquids (IL) have gained considerable current interest as environmentally benign reaction media[26–29] and yet relatively little attention has been paid to their intrinsic reactivity. Besides their use as green reaction media, ionic liquids also play significant roles as catalysts,[29–31] and reagents,[32,33] and are easy to recycle.[32,33] A recent review[26] is focused on the reactivity of ionic liquids, as opposed to reactivity in ionic liquids, showing their ever-increasing importance.

The continued interest of synthetic chemists in azetidines and our ongoing efforts to devise new cyclization processes under environmentally benign conditions[34–38] has encouraged us to develop a practical synthesis of functionalized azetidines from chalcones using task-specific ionic liquids (TSIL) as outlined in Table 1. This is the first illustration of the application of TSIL to azetidine chemistry and the first example of a straightforward synthesis of *C*-sulfur-functionalized azetidines.

The strategy reported herein was successfully realized in two steps. In the initial step, diethyl *N*-arylphosphoramidates **2** were treated with sodium hydride in dry benzene to generate anions **6** in situ, which underwent aza-Michael addition to chalcones **1** to afford adducts **3** in 77–86% yields[39] (Scheme 1). The second step involved stirring of adduct **3** in 1.5 equivalents of TSIL **4** for 3–4 h at room temperature (for **4**, X = SCN) or at 60–65 °C (for **4**, X = PhS) to produce functionalized azetidines **5** in 76–89% yields.[40] The *cis*/*trans* relationships of substituents in azetidines **5** were confirmed by NOE experiments. The 17.6% NOE at 2-Ar^1/4-Ar^2 upon irradiation of 3-H_b (for example, at δ = 3.05 ppm for **5a**) combined with the absence of any measurable intensity enhancement at 2-Ar^1/4-Ar^2 upon irradiation of 3-H_a indicates that 3-H_b and 2-Ar^1/4-Ar^2 are located on the same face of the molecule, that is, azetidines **5** have 2,4-*cis* configuration with respect to the aryl groups.

The formation of azetidines **5** is best explained through attack of a nucleophile (NCS^- or PhS^-) on the carbonyl carbon of **3** followed by intramolecular attack of the alkoxide ion on the phosphorus atom (Scheme 1). A comparison with TSIL **4** was carried out by stirring phosphoramidates **3** in [bmim]BF_4 with 1.5 equivalents of KSCN or PhSNa for 3–4 hours at room temperature or at 60–65 °C, respectively. In this case, the anion-induced cyclization afforded the corresponding **5** in relatively lower yields (41–53%). This indicates that the nucleophilicty of SCN or PhS anion is considerably higher in [bmim]SCN or [bmim]SPh compared to that from KSCN or PhSNa. After isolation of products **5**, the residue was treated with concentrated HCl

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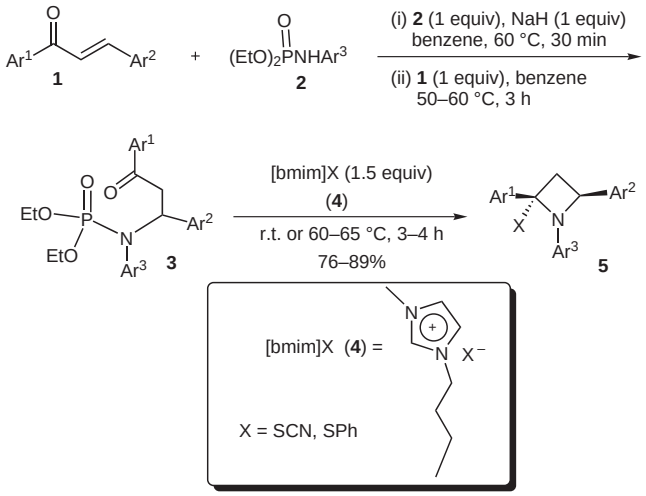
Table 1 Synthesis of Functionalized Azetidines **5**

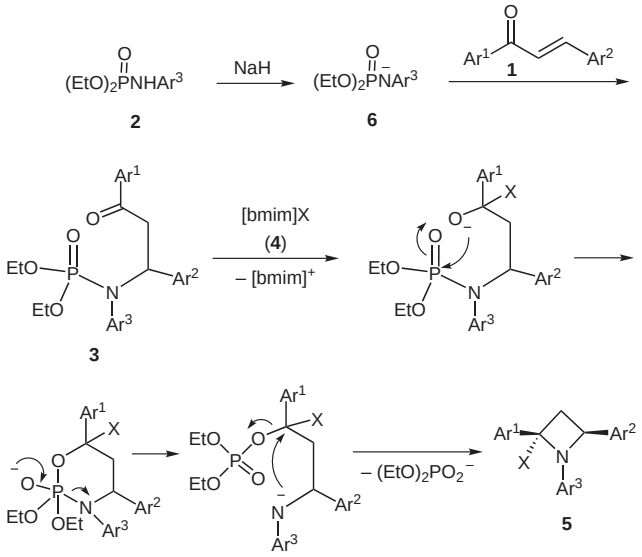


Product	Ar^1	Ar^2	Ar^3	X	Yield (%)[a]
3a	Ph	Ph	Ph	–	78
3b	Ph	4-ClC_6H_4	Ph	–	81
3c	Ph	Ph	4-$MeOC_6H_4$	–	79
3d	Ph	4-ClC_6H_4	4-$MeOC_6H_4$	–	86
3e	4-ClC_6H_4	Ph	Ph	–	81
3f	Ph	4-$MeOC_6H_4$	Ph	–	77
5a	Ph	Ph	Ph	SCN	81
5b	Ph	4-ClC_6H_4	Ph	SCN	76
5c	Ph	Ph	4-$MeOC_6H_4$	SCN	84
5d	Ph	4-ClC_6H_4	4-$MeOC_6H_4$	SCN	85
5e	4-ClC_6H_4	Ph	Ph	SCN	87
5f	Ph	4-$MeOC_6H_4$	Ph	SCN	83
5g	Ph	Ph	Ph	SPh	82
5h	Ph	4-ClC_6H_4	Ph	SPh	80
5i	Ph	Ph	4-$MeOC_6H_4$	SPh	85
5j	Ph	4-ClC_6H_4	4-$MeOC_6H_4$	SPh	87
5k	4-ClC_6H_4	Ph	Ph	SPh	89
5l	Ph	4-$MeOC_6H_4$	Ph	SPh	84

[a] Yields of isolated and purified product.

followed by stirring with KSCN or PhSNa at room temperature for 48 hours to obtain the corresponding recycled TSIL **4**.

In summary, we have developed a practical synthesis of functionalized azetidines by anion-induced cyclization of chalcone-derived phosphoramidates using task-specific ionic liquids in a one-pot procedure, which may be useful for the synthesis of this class of azetidines.



Scheme 1 Plausible mechanism for the formation of azetidines **5**

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(39) **General Procedure for the Synthesis of Diethyl *N*-Aryl-*N*-(1,3-diaryl-3-oxopropyl)phosphoramidates 3**[25]
To a solution of diethyl *N*-arylphosphoramidate **2** (5 mmol) in dry benzene (5 mL) was added dropwise a solution of NaH (120 mg, 5 mmol) in dry benzene (10 mL) with stirring at r.t. 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 then cooled to r.t. Next, a solution of chalcone **1** (5 mmol) in dry benzene (5 mL) was added and the reaction mixture was stirred at 50–60 °C for 3 h. The solvent was evaporated under reduced pressure, the residue washed with H_2O and recrystallized from *n*-hexane to afford an analytically pure sample of **3**.
Physical Data of a Representative Compound
Compound **3a**: white crystals yield 87%, mp 186–187 °C. IR (KBr): ν_{max} = 3052, 2990, 1692, 1605, 1582, 1456 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$/TMS): d = 1.23 (t, 6 H, *J* = 7.5 Hz, 2 ´ Me), 3.06 (dd, 1 H, *J* = 12.9, 8.5 Hz, 2-H_a), 3.38 (dd, 1 H, *J* = 12.9, 3.5 Hz, 2-H_b), 4.16 (q, 4 H, *J* = 7.5 Hz, 2 ´ OCH_2), 4.65 (dd, 1 H, *J* = 8.5, 3.5 Hz, 3-H), 7.08–7.43 (m, 13 H_{arom}), 7.81–7.89 (m, 2 H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$/TMS): d = 16.3 (Me), 41.7 (CHPh), 50.3 (CH_2O), 69.9 (CH_2CO), 126.5, 127.5, 128.3, 129.4, 131.4, 132.7, 133.4, 134.2, 135.5 (3 ´ Ph), 193.2 (CO). MS (EI): *m/z* = 437 [M^+]. Anal. Calcd (%) for $C_{25}H_{28}NO_4P$: C, 68.64; H, 6.45; N, 3.20. Found: C, 68.92; H, 6.74; N, 3.07.
(40) **General Procedure for the Synthesis of Functionalized Azetidines 5**
A mixture of adduct **3** (5 mmol) and [bmim]SCN or [bmim]SPh (**4**, 7.5 mmol) with a few drops of distilled H_2O was taken in a 50 mL round-bottomed flask and stirred for 3–4 h at r.t. (for [bmim]SCN) or at 60–65 °C (for [bmim]SPh). After completion of the reaction as indicated by TLC, the product was extracted with Et_2O (3 × 20 mL), dried over anhyd $MgSO_4$, filtered, and evaporated to dryness. The crude product **5** thus obtained was recrystallized twice from *n*-hexane to afford an analytically pure sample.
Physical Data of Representative Compounds
Compound **5a**: white crystals, yield 81%, mp 98–99 °C. IR (KBr): ν_{max} = 3082, 2965, 2892, 2813, 2132, 1604, 1495, 1451, 753, 706 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 2.75 (dd, 1 H, *J* = 11.3, 8.7 Hz, 3-H_a), 3.05 (dd, 1 H, *J* = 11.3, 6.6 Hz, 3-H_b), 4.90 (dd, 1 H, *J* = 8.7, 6.6 Hz, 4-H), 7.11–7.43 (m, 15 H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 41.1 (3-C), 55.7, 78.5 (2-C, 4-C), 111.7 (SCN), 123.6, 124.5, 125.3, 126.7, 129.8, 130.7, 131.6, 132.4, 133.5, 134.3, 139.0, 141.7 (3 × Ph). MS (EI): *m/z* = 342 [M^+]. Anal. Calcd (%) for $C_{22}H_{18}N_2S$: C, 77.16; H, 5.30; N, 8.18. Found: C, 76.81; H, 5.53; N, 8.39.
Compound **5g**: white crystals, yield 82%, mp 58–59 °C. IR (KBr): ν_{max} = 3073, 2968, 2896, 2818, 1600, 1492, 1456, 758, 696 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 2.79 (dd, 1 H, *J* = 11.3, 8.7 Hz, 3-H_a), 3.10 (dd, 1 H, *J* = 11.3, 6.6 Hz, 3-H_b), 4.92 (dd, 1 H, *J* = 8.7, 6.6 Hz, 4-H), 7.01–7.53 (m, 20 H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 41.2 (3-C), 55.9, 79.0 (2-C, 4-C), 123.5, 124.6, 125.3, 126.3, 127.2, 128.0, 129.8, 130.6, 131.5, 132.6, 133.4, 134.5, 135.8, 138.2, 139.7, 141.3 (4 × Ph). MS (EI): *m/z* = 393 [M^+]. Anal. Calcd (%) for $C_{27}H_{23}NS$: C, 82.40; H, 5.89; N, 3.56. Found: C, 82.76; H, 5.52; N, 3.85.