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# A convenient synthesis of 1,2,4-trisubstituted azetidines by reductive cyclization of aza-Michael adducts of chalcones

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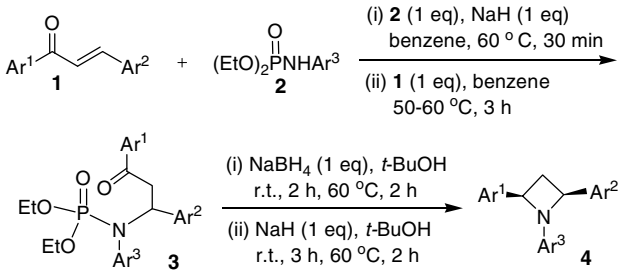
**Abstract**—Aza-Michael adducts of chalcones and diethyl *N*-arylphosphoramidates undergo reductive cyclization with sodium borohydride followed by sodium hydride to afford 1,2,4-trisubstituted azetidines diastereoselectively in a one-pot procedure and excellent yields.


Although azetidine was first prepared in 1888, this class of small ring heterocycles has not been extensively studied. The strain associated with four-membered rings leads to difficulties in the synthesis, substitutions and modifications of azetidines. The discovery of naturally occurring azetidine-2-carboxylic acid,[1] which has shown some unique and potentially useful biological activity,[2–4] has caused increased interest in the azetidine field. Some other compounds incorporating the azetidine system as structural motifs possess remarkable pharmacological properties. For example, they are markedly active against influenza A H2N2 virus,[5] and have anti-HIV-1, anti-HSV-1 and HSV-2 potential.[6] A major obstacle has been that the substituted azetidines have been difficult to prepare or synthetic routes provide inadequate quantities at reasonable cost.

Amongst the various methods available for the synthesis of azetidines, the most general involves cyclization of γ-amino alcohols or their derivatives.[7–10] Various syntheses of 1,2,4-trisubstituted azetidines via cyclization of γ-amino alcohol derivatives have been reported in the literature.[11–14] 1,3-Disubstituted and 1,2,3-trisubstituted azetidines have been recently synthesized from the corresponding γ-amino alcohols.[15,16] Very recently, β-amino alcohols have also been used for synthesizing azetidines.[17] The continued interest of synthetic chemists in azetidines and our ongoing efforts to devise new one-pot stereoselective cyclization processes[18–22] has encouraged us to develop a convenient route to 1,2,4-trisubstituted azetidines as outlined in Scheme 1.

On treatment with sodium hydride, diethyl *N*-aryl phosphoramidates **2** generated anions **5** *in situ* which underwent aza-Michael addition to chalcones **1** to afford




| 3,4 | $Ar^1$ | $Ar^2$ | $Ar^3$ | Yield(%)* | |
|---|---|---|---|---|---|
| | | | | 3 | 4 |
| **a** | Ph | Ph | Ph | 78 | 80 |
| **b** | Ph | Ph | 4-$FC_6H_4$ | 76 | 83 |
| **c** | Ph | Ph | 4-$MeOC_6H_4$ | 79 | 78 |
| **d** | Ph | 4-$ClC_6H_4$ | Ph | 81 | 81 |
| **e** | Ph | 4-$ClC_6H_4$ | 4-$FC_6H_4$ | 80 | 83 |
| **f** | Ph | 4-$ClC_6H_4$ | 4-$MeOC_6H_4$ | 86 | 81 |
| **g** | 4-$ClC_6H_4$ | Ph | Ph | 81 | 82 |
| **h** | 4-$ClC_6H_4$ | Ph | 4-$FC_6H_4$ | 78 | 84 |
| **i** | 4-$ClC_6H_4$ | Ph | 4-$MeOC_6H_4$ | 84 | 79 |
| **j** | 4-$ClC_6H_4$ | 4-$ClC_6H_4$ | Ph | 85 | 83 |
| **k** | 4-$ClC_6H_4$ | 4-$ClC_6H_4$ | 4-$FC_6H_4$ | 82 | 85 |
| **l** | 4-$ClC_6H_4$ | 4-$ClC_6H_4$ | 4-$MeOC_6H_4$ | 87 | 82 |

*Yields of isolated and purified product

**Scheme 1.** Formation of azetidines **4**.

*Keywords*: Azetidines; Michael addition; Phosphoramidates; Chalcones; Reduction; Cyclization reactions.
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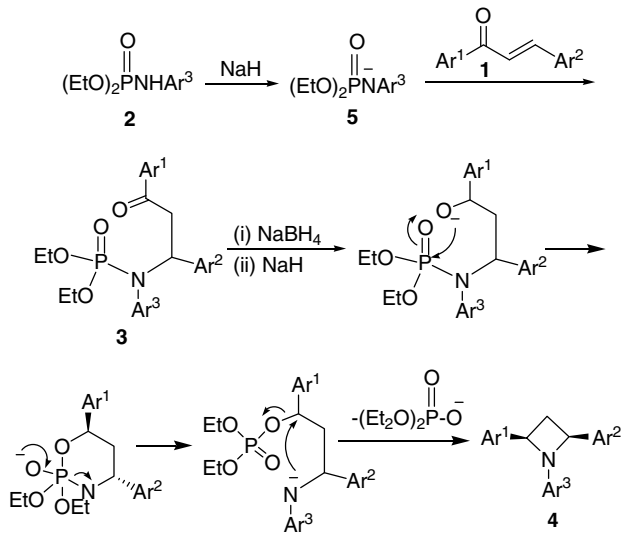


**Scheme 2.** Tentative mechanism for the reductive cyclization of aza-Michael adducts **3** to azetidines **4**.

adducts **3** in 76–87% yields (Scheme 2).[23] Conventional reduction of adducts **3** with sodium borohydride furnished the corresponding alcohols in addition to a small amount of azetidines **4**. Thus, adducts **3** were reduced with sodium borohydride in *t*-butanol followed by treatment with sodium hydride in the same vessel to produce the corresponding azetidines **4** in 78–85% yields.[24]

The cyclization of Michael adducts **3** to azetidines **4** was highly diastereoselective in favour of the 2,4-cis isomers. Diastereomeric ratios in the crude isolates were checked by $^1$H NMR to note any inadvertent alteration of these ratios during subsequent purification. The crude isolates of **4** were found to be diastereomeric mixtures containing 93–96% of the 2,4-cis isomer. The $^1$H NMR spectra of azetidines **4** show uncommon signals for 3-Ha/3-Hb resonances, which is a direct proof for their 2,4-cis configuration of **4**. If 1,2,4-trisubstituted azetidines **4** would have 2,4-trans stereochemistry, the 3-Ha/3-Hb resonances should appear as common signals. The 2,4-cis stereochemistry of azetidines **4** was further confirmed by NOE experiments. The 11.4% NOE at 2-H/4-H upon irradiation of Ha (at $\delta$ 2.65 for **4a**) combined with the absence of any measurable intensity enhancement at 2-H/4-H upon irradiation of Hb indicates that 3-Ha and 2-H/4-H are located on the same face of the molecule, that is, azetidines **4** have 2,4-cis configuration (Fig. 1).

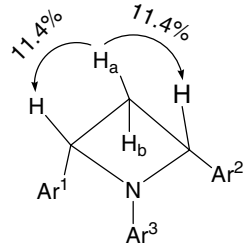


**Figure 1.** Determination of the stereochemistry of azetidines **4** by NOE.

The formation of azetidines **4** is best explained through intramolecular attack of the alkoxide ion on the phosphorus atom (Scheme 2). This assumption is supported by the exclusive formation of azetidines **4** on addition of a base, such as sodium hydride, to facilitate alkoxide ion formation.

In summary, we have developed a general method for a convenient synthesis of 1,2,4-trisubstituted azetidines by reductive cyclization of readily available aza-Michael adducts of chalcones and diethyl *N*-arylphosphoramidates in a one-pot procedure, which may find application in organic synthesis.

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23. *General procedure for the synthesis of diethyl N-aryl-N-(1,3-diaryl-3-oxopropyl)phosphoramidates* **3**: To a solution of diethyl *N*-arylphosphoramidate **2** (5 mmol) in dry benzene (5 mL) was added dropwise a solution of sodium hydride (120 mg, 5 mmol) in dry benzene (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 then cooled to rt. 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 water and recrystallized from *n*-hexane to afford an analytically pure sample of **3**. Physical data of representative compounds: compound **3a**: white crystals, yield 78%, mp 186–187 °C. IR (KBr) $\nu_{max}$ 3052, 2990, 1692, 1605, 1582, 1456 $cm^{-1}$. $^1H$ NMR (400 MHz; $CDCl_3$/TMS) $\delta$: 1.23 (t, 6H, $J = 7.5$ Hz, $2 \times$ Me), 3.06 (dd, 1H, $J = 12.9$, 8.5 Hz, 2-$H_a$), 3.38 (dd, 1H, $J = 12.9$, 3.5 Hz, 2-$H_b$), 4.16 (q, 4H, $J = 7.5$ Hz, $2 \times OCH_2$), 4.65 (dd, 1H, $J = 8.5$, 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) $\delta$: 16.3 (Me), 41.7 (*CH*Ph), 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 ($3 \times$ Ph), 193.2 (CO). EIMS (*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. **3j**: white crystals, yield 85%, mp 195–197 °C. IR (KBr) $\nu_{max}$ 3055, 2989, 1691, 1599, 1585, 1451 $cm^{-1}$. $^1H$ NMR (400 MHz; $CDCl_3$/TMS) $\delta$: 1.21 (t, 6H, $J = 7.5$ Hz, $2 \times$ Me), 3.05 (dd, 1H, $J = 12.9$, 8.5 Hz, 2-$H_a$), 3.41 (dd, 1H, $J = 12.9$, 3.5 Hz, 2-$H_b$), 4.13 (q, 4H, $J = 7.5$ Hz, $2 \times OCH_2$), 4.63 (dd, 1H, $J = 8.5$, 3.5 Hz, 3-H), 7.13–7.45 (m, 7$H_{arom}$), 7.83–8.03 (m, 6$H_{arom}$). $^{13}C$ NMR (100 MHz; $CDCl_3$/TMS) $\delta$: 16.5 (Me), 42.1 (*CH*Ph), 50.7 ($CH_2O$), 70.1 ($CH_2CO$), 126.7, 127.4, 128.5, 129.2, 131.1, 132.5, 133.1, 135.5 (Ph, $2 \times$ 4-$ClC_6H_4$), 193.5 (CO). EIMS (*m*/*z*): 505 ($M^+$). Anal. Calcd for $C_{25}H_{26}Cl_2NO_4P$: C, 59.30; H, 5.18; N, 2.77. Found: C, 59.66; H, 5.01; N, 2.92.
24. *General procedure for the synthesis of 1,2,4-triarylazetidines* **4**: A mixture of adduct **3** (5 mmol) and sodium borohydride (190 mg, 5 mmol) in dry *t*-butanol (25 mL) was stirred at rt for 2 h, then at 60 °C for 2 h. Sodium hydride (120 mg, 5 mmol) was added to the above reaction mixture at rt. Stirring was continued for 3 h at rt, then at 60 °C for 2 h. Water (30 mL) was added, the mixture was extracted with ether ($3 \times 50$ mL), dried over anhydrous magnesium sulfate, filtered and evaporated to dryness. The crude product **4** thus obtained was recrystallized twice from *n*-hexane to afford an analytically pure sample. Physical data of representative compounds: compound **4a**: white crystals, yield 80%, mp 92–93 °C. IR (KBr) $\nu_{max}$ 3081, 2966, 2892, 2811, 1601, 1495, 1453, 752, 700 $cm^{-1}$. $^1H$ NMR (400 MHz; $CDCl_3$/TMS) $\delta$: 2.65 (dt, 1H, $J = 11.6$, 8.9 Hz, $H_a$), 2.92 (dt, 1H, $J = 11.6$, 6.9 Hz, $H_b$), 5.23 (dd, 2H, $J = 8.9$, 6.9 Hz, 2-H, 4-H), 7.13–7.51 (m, 15$H_{arom}$). $^{13}C$ NMR (100 MHz; $CDCl_3$/TMS) $\delta$: 41.8 (3-C), 65.3 (2-C, 4-C), 126.5, 127.3, 128.5, 129.7, 130.7, 131.5, 133.2, 133.9, 134.8 ($3 \times$ Ph). EIMS (*m*/*z*): 285 ($M^+$). Anal. Calcd for $C_{21}H_{19}N$: C, 88.38; H, 6.71; N, 4.91. Found: C, 88.67; H, 6.49; N, 5.13. **4j**: white crystals, yield 83%, mp 118–119 °C. IR (KBr) $\nu_{max}$ 3083, 2969, 2891, 2815, 1602, 1499, 1455, 848, 755, 702 $cm^{-1}$. $^1H$ NMR (400 MHz; $CDCl_3$/TMS) $\delta$: 2.67 (dt, 1H, $J = 11.6$, 8.9 Hz, $H_a$), 2.93 (dt, 1H, $J = 11.6$, 6.9 Hz, $H_b$), 5.21 (dd, 2H, $J = 8.9$, 6.9 Hz, 2-H, 4-H), 7.09–7.49 (m, 9$H_{arom}$), 7.73–7.85 (m, 4$H_{arom}$). $^{13}C$ NMR (100 MHz; $CDCl_3$/TMS) $\delta$: 42.2 (3-C), 65.5 (2-C, 4-C), 126.7, 127.9, 128.6, 129.8, 130.7, 131.4, 133.0, 134.3 (Ph, $2 \times$ 4-$ClC_6H_4$). EIMS (*m*/*z*): 353 ($M^+$). Anal. Calcd for $C_{21}H_{17}Cl_2N$: C, 71.20; H, 4.84; N, 3.95. Found: C, 71.02; H, 4.48; N, 4.17.