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2*H*-Azirines as dipolarophiles

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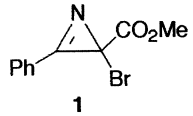
Abstract—2*H*-Azirine-3-carboxylates unsubstituted at C-2 act as dipolarophiles in the reaction with diazomethane giving new 4,5-dihydro-3*H*-pyrazole derivatives. The synthesis of a pyrimidine was also achieved via 1,3-dipolar cycloaddition of methyl 2-bromo-3-phenyl-2*H*-azirine-2-carboxylate with an azomethine ylide.

2H-Azirines represent a particular type of imine-based dipolarophiles. The strain inherent in the 2*H*-azirine ring system allows to overcome the low reactivity normally associated to *N*-alkylimines.[1] The reaction of diazomethane with 2-aryl-3-methyl-2*H*-azirines to give allyl azides was the first example reported of 1,3-dipolar cycloaddition of 2*H*-azirines acting as a 2π-component.[2] Subsequently, it has been demonstrated that 2*H*-azirines participate also in 1,3-dipolar cycloaddition with nitrile oxides and with azomethine ylides.[1] In this communication we report our studies aiming at extending the use of 2*H*-azirines as dipolarophiles.

The synthesis of 2-halo-*2H*-azirines starting from α-oxophosphorus ylides and the study of their reactivity is one of our current interests.[3] We became interested in exploiting the use of these 2-halo-2*H*-azirines as dipolarophiles.

Methyl 2-bromo-3-phenyl-2*H*-azirine-2-carboxylate **1** was prepared[3a] and attempts were made to carry out its reaction with diazomethane. However, complex mixtures were obtained, indicating that the cycloadduct generated from diazomethane and the 2-halo-2*H*-azirines can undergo ring opening by various competitive pathways in agreement with the work described by Storr et al.[4]



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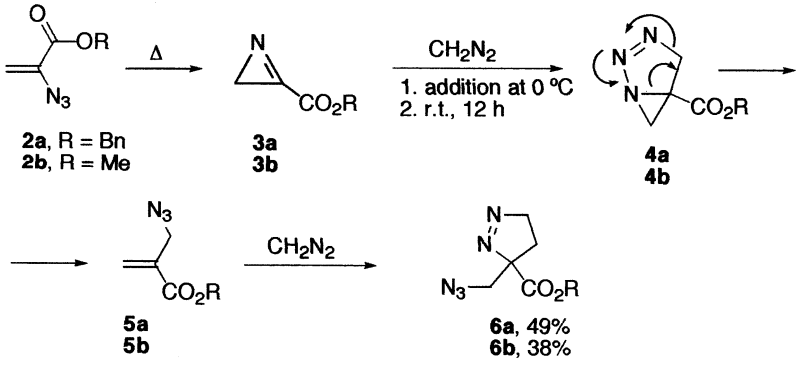

2a, R = Bn
2b, R = Me

3a
3b

4a
4b

5a
5b

6a, 49%
6b, 38%

Scheme 1.

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This result led us to study the reaction of diazomethane with a simpler C-2 unsubstituted 2*H*-azirine-3-carboxylate **3a** (Scheme 1). This 2*H*-azirine was generated from benzyl α-azidoacrylate **2a** by thermolysis, following a known synthetic procedure.[5]

Benzyl 2*H*-azirine-3-carboxylate **3a** was not isolated but instead freshly prepared 2*H*-azirine in toluene was used directly to react with diazomethane (Scheme 1).[6] The azirine solution was cooled at 0°C and diazomethane was added in excess. The reaction mixture was then left at room temperature for 12 h. One product (**6a**) was obtained in 49% yield. The process involves the reaction of 2*H*-azirine **3a** with diazomethane, leading to the cycloadduct **4a** which undergoes a rearrangement generating the allyl azide **5a**. This compound participates in a second 1,3-dipolar cycloaddition with diazomethane to give benzyl 3-azidomethyl-4,5-dihydro-3*H*-pyrazole-3-carboxylate **6a**.

Encouraged by this result we went on to study the reactivity of methyl 2*H*-azirine-3-carboxylate **3b** towards diazomethane. Methyl 2-azidoacrylate **2b** was prepared from the reaction of methyl 2,3-dibromopropionate with sodium azide using the procedure described for the ethyl ester.[7] The thermolysis of methyl 2-azidoacrylate **2b**, was carried out as described above for acrylate **2a** although it was found that the conversion into methyl 2*H*-azirine-3-carboxylate **2b** was complete after 2 hours. A solution of the 2*H*-azirine in toluene was treated with diazomethane, allowing the synthesis of methyl 3-azidomethyl-4,5-dihydro-3*H*-pyrazole-3-carboxylate **6b** in 38% yield (Scheme 1).

Gilchrist et al. reported the generation of methyl 2*H*-azirine-3-carboxylate **2b** although the reactivity of this heterocycle, described as highly unstable and volatile, was not studied.[8] The reaction of *tert*-butyl 2*H*-azirine-3-carboxylate, generated in situ from the corresponding α-azidoacrylate, with an azomethine ylide giving functionalized β-lactams has also been reported.[1e] The same authors indicate that a similar reaction can be promoted with methyl 2*H*-azirine-3-carboxylate **2b**.

The synthesis of 4,5-dihydro-3*H*-pyrazole-3-carboxylates (**6a** and **6b**) constitutes a new example of 1,3-dipolar cycloaddition of C-2 unsubstituted 2*H*-azirine-3-carboxylates.

Aziridines undergo thermal ring opening in a conrotatory manner to generate azomethine ylides which participate in cycloadditions with 2*H*-azirines giving bicyclic heterocycles.[1a,d] We decided to explore similar reactions using methyl 2-bromo-3-phenyl-2*H*-azirine-2-carboxylate **1** as dipolarophile.

Ethyl (3*S*,2*R*)-3-phenylaziridine-2-carboxylate **7** was prepared as described in the literature.[9] After heating a solution of this aziridine and 2*H*-azirine **1** in toluene for two hours the pyrimidine **11** was isolated in 12% yield. Thus, we could conclude that 2-bromo-2*H*-azirine **1** participated in the 1,3-dipolar cycloaddition with the azomethine ylide generated from **7** by thermal ring opening. The cycloadduct **9** underwent a ring opening reaction with elimination of HBr, leading to dihydropyrimidine **10** followed by the aromatisation to 2,5-diphenylpyrimidine-4,6-dicarboxylate **11**[10] (Scheme 2).

In conclusion, we have proved that C-2 unsubstituted 2*H*-azirine-3-carboxylates participate in 1,3-dipolar cycloadditions with diazomethane, leading to new 4,5-dihydro-3*H*-pyrazole derivatives. Methyl 2-bromo-3-phenyl-2*H*-azirine-2-carboxylate can also act as a dipolarophile and its reaction with an azomethine ylide gave 2,5-diphenylpyrimidine-4,6-dicarboxylate. This study has shown that 2*H*-azirines are an attractive system to be explored for the synthesis of new compounds via 1,3-dipolar cycloaddition.

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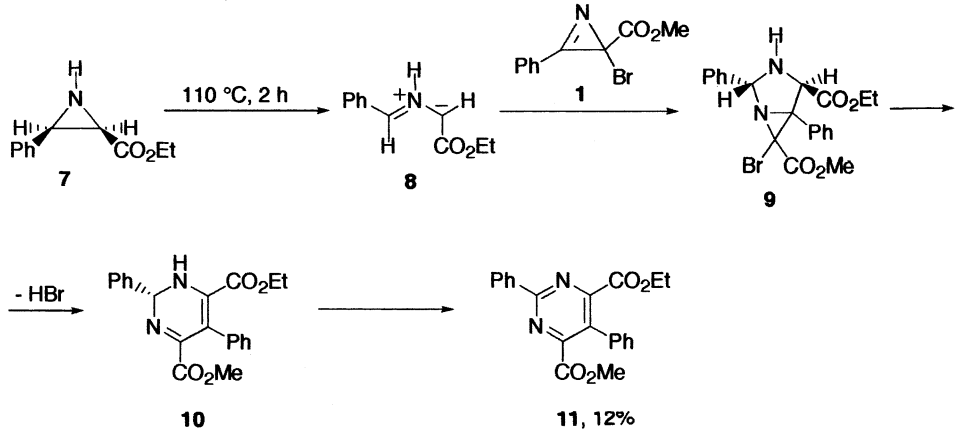

Scheme 2.

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6. *Benzyl 3-azidomethyl-4,5-dihydro-3H-pyrazole-3-carboxylate* ***6a***. A solution of benzyl 2-azidoacrylate **2a**[5] (0.34 g, 1.7 mmol) in dry toluene (40 mL) was heated at reflux for 5 h. The reaction was followed by TLC and IR by monitoring the disappearance of the band corresponding to the azido group ($\nu = 2113$ cm^{-1}) of the starting azidoalkene. The solution was cooled to 0°C and freshly prepared diazomethane solution was added in excess. The reaction mixture was left at room temperature for 12 h and the solvent was evaporated off. The crude product was purified by flash chromatography [hexane–ethyl acetate (2:1)] giving compound **6a** as an oil (49%). ν_{max} (film) 2108, 1737 cm^{-1}; δ_H ($CDCl_3$, 300 MHz) 1.70 (1H, ddd, *J* 13.0, 9.4 and 6.7 Hz), 2.03 (1H, ddd, *J* 13.0, 9.4 and 5.7 Hz), 3.91 (1H, d, *J* 12.9 Hz), 4.11 (1H, d, *J* 12.9 Hz), 4.66 (1H, ddd, *J* 18.2, 9.4 and 6.7 Hz), 4.78 (1H, ddd, *J* 18.2, 9.4 and 5.7 Hz), 7.30–7.39 (5H, m, Ar–H); δ_C ($CDCl_3$, 75.5 MHz) 23.4, 53.9, 68.2, 79.6, 98.3, 128.9, 129.1, 135.3 and 168.4; *m*/*z* (CI) 277 $[M+NH_4]^+$ (58%) and 260 $[MH^+]$ (86).
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10. *2,5-Diphenylpyrimidine-4,6-dicarboxylic acid 4-ethyl ester 6-methyl ester* **11**. A solution of ethyl (3*S*,2*R*)-3-phenylaziridine-2-carboxylate **11**[9] (0.1 g, 0.55 mmol) and methyl 2-bromo-3-phenyl-2*H*-azirine-2-carboxylate **1**[3a] (0.14 g, 0.55 mmol) in dry toluene (15 mL) was heated at reflux for 2 hours. The solvent was evaporated off and the crude product was purified by flash chromatography [hexane–ethyl acetate (3:1), hexane–ethyl acetate (2:1), hexane–ethyl acetate (1:1)] giving compound **11** as an oil (12%). δ_H ($CDCl_3$, 300 MHz) 1.16 (3H, t, *J* 7 Hz), 3.85 (3H, s), 4.31 (2H, q, *J* 7 Hz), 7.47–7.49 (6H, m, Ar–H) and 7.71–7.74 (4H, m, Ar–H); δ_C ($CDCl_3$, 75.5 MHz) 13.7, 53.1, 62.4, 128.6, 128.7, 128.7, 129.9, 130.0, 135.9. 144.2, 144.9, 149.7, 149.8, 166.0 and 166.4; *m*/*z* 362 (M^+, 70%), 290 (100), 273 (24), 231 (42), 129 (23), 105 (35) and 77 (27).