2H-Azirines as dipolarophiles

Teresa M. V. D. Pinho e Melo,* Ana L. Cardoso, Clara S. B. Gomes and António M. d’A. Rocha Gonsalves

Departamento de Química, Faculdade de Ciências e Tecnologia, Universidade de Coimbra, 3004-535 Coimbra, Portugal

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

2H-Azirines represent a particular type of imine-based dipolarophiles. The strain inherent in the 2H-azirine ring system allows to overcome the low reactivity normally associated to N′-alkylimines.1 The reaction of diazomethane with 2-aryl-3-methyl-2H-azirines to give allyl azides was the first example reported of 1,3-dipolar cycloaddition of 2H-azirines acting as a 2π-component.2 Subsequently, it has been demonstrated that 2H-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 exploiting the use of these 2-halo-2H-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

Scheme 1.

Keywords: 2H-azirines; 1,3-dipolar cycloaddition; 3H-pyrazole; pyrimidine.

* Corresponding author. Fax: +351 239 826068; e-mail: tmelo@ci.uc.pt

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

Benzyl 2H-azirine-3-carboxylate 3a was not isolated but instead freshly prepared 2H-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 2H-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-3H-pyrazole-3-carboxylate 6a.

Encouraged by this result we went on to study the reactivity of methyl 2H-azirine-3-carboxylate 3b towards diazomethane. Methyl 2-azidocaproate 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-azidocaproate 2b, was carried out as described above for acrylate 2a although it was found that the conversion into methyl 2H-azirine-3-carboxylate 2b was complete after 2 hours. A solution of the 2H-azirine in toluene was treated with diazomethane, allowing the synthesis of methyl 3-azidomethyl-4,5-dihydro-3H-pyrazole-3-carboxylate 6b in 38% yield (Scheme 1).

Gilchrist et al. reported the generation of methyl 2H-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 2H-azirine-3-carboxylate, generated in situ from the corresponding α-azidocaproate, 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 2H-azirine-3-carboxylate 2b.

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

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

Ethyl (3S,2R)-3-phenylaziridine-2-carboxylate 7 was prepared as described in the literature.9 After heating a solution of this aziridine and 2H-azirine 1 in toluene for two hours the pyrimidine 11 was isolated in 12% yield. Thus, we could conclude that 2-bromo-2H-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 1110 (Scheme 2).

In conclusion, we have proved that C-2 unsubstituted 2H-azirine-3-carboxylates participate in 1,3-dipolar cycloadditions with diazomethane, leading to new 4,5-dihydro-3H-pyrazole derivatives. Methyl 2-bromo-3-phenyl-2H-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 2H-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.
References

6. Benzy1 3-azidomethyl-4,5-dihydro-3H-pyrazole-3-carboxylate 6a. A solution of benzyl 2-azidoacrylate 2a (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 (ν = 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%). νₘₐₓ (film) 2108, 1737 cm⁻¹; δₑₑ (CDCl₃, 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); δₑₑ (CDCl₃, 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+NH₄]⁺ (58%) and 260 [MH⁺]⁺ (86).
10. 2,5-Diphenylpyrimidine-4,6-dicarboxylic acid 4-ethyl ester 6-methyl ester 11. A solution of ethyl (3S,2R)-3-phenylaziridine-2-carboxylate 11° (0.1 g, 0.55 mmol) and methyl 2-bromo-3-phenyl-2H-azirine-2-carboxylate 11° (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%). δₑₑ (CDCl₃, 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); δₑₑ (CDCl₃, 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).