Tetrahedron Letters 51 (2010) 843–845

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A new, one-step synthesis of 1-heteroaryl-2-alkylaminoethanols

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ARTICLE INFO

Article history:
Received 30 October 2009
Revised 28 November 2009
Accepted 4 December 2009
Available online 11 December 2009

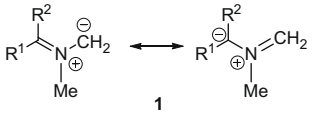
Keywords:
Azomethine ylides
Decarboxylation
β-Hydroxyamines
Aziridines
Ring-opening

ABSTRACT

Refluxing a mixture of a heteroarylcarboxaldehyde and an *N*-alkylamino acid in dry toluene, in the presence of 4 Å molecular sieves, results in the formation of β-hydroxyamines through the 1,3-electrocyclisation of an azomethine ylide and the subsequent ring-opening hydrolysis of an aziridine. The intermediacy of an azomethine ylide in this process is suggested by the isolation of oxazolidines from the cycloaddition of the azomethine ylides to their aldehyde precursors.

β-Hydroxyamines are an important class of β-blockers, with medicinal uses as bronchodilators and agents for the treatment of cardiac arrhythmias,[1] and this structural moiety is also a key component of many naturally occurring compounds.[2] As a consequence of their importance, many routes have been employed for the preparation of β-hydroxyamines, usually involving several steps via one of a range of intermediates, for example, dimethylaminoketones,[3] vicinal haloalcohols,[4,5] oxiranes,[5] oxazolidines[6] and α-ketoacetamides.[7] We describe here a new, one-step synthesis of 1-heteroaryl-2-alkylaminoethanols involving an azomethine ylide intermediate.

Azomethine ylides **1** can be used in the preparation of a range of heterocycles through 1,3-dipolar cycloadditions[8], 1,5-electrocyclisations[9] or 1,7-electrocyclisations,[10,11] and routes to these versatile intermediates include the decarboxylation of iminium salts,[12] the ring-opening of aziridines[13] and the 1,2-prototropy of α-imino esters.[14]



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Refluxing a mixture of a five-membered ring heteroaryl-2-carboxaldehydes **2a**–**e** and *N*-alkylamino acids **3a,b** in dry toluene, in the presence of 4 Å molecular sieves, resulted in a good yield of the corresponding β-hydroxyamines **7a**–**f** through the 1,3-electrocyclisation of the azomethine ylide **5**, formed by the decarboxylation of the iminium salt **4**, and subsequent ring-opening hydrolysis of the aziridine **6**, Scheme 1, Table 1. A simple work-up, consisting of filtration to remove any solid, and column chromatography of the residue obtained after evaporation of the solvent, gave the products in moderate, unoptimised yields.[15,16]

Such a 1,3-electrocyclisation of azomethine ylides, as depicted in Scheme 1, step 3 (**5**→**6**), is implicit in the cis/trans equilibration of aziridines[17] and has been detected using temperature shock–dilution conditions.[18] Perhaps the most surprising aspect of this one-step transformation, from the aldehydes **2** to the β-hydroxyamines **7**, is the ring-opening hydrolysis of the aziridine **6** to the β-hydroxyamines **7**, under such mild conditions as, in general, the ring-opening of aziridines which do not have an electron-withdrawing group on the nitrogen ('non-activated') requires either Lewis[19] or Brønsted acid catalysis.[20] The relatively mild conditions required for this aziridine ring-opening may be a result of it being facilitated by the electron-rich heterocycle, resulting in a two-step process via a zwitterionic intermediate **8**, Scheme 2.[21]

Evidence for the possible intermediacy of an azomethine ylide in this process was obtained by the isolation of a mixture of oxazolidines **11** (as an inseparable mixture of diastereoisomers) and **12** (again as a mixture of diastereoisomers), from the cycloaddition of the azomethine ylide **10** onto a second molecule of its precursor **9**, when 3,4-dibromothienyl-2-carboxaldehyde **9** was reacted with sarcosine (**3a**), Scheme 3. Inseparable mixtures of the diastereoisomers of the hexahydropyrrolo[2,1-*b*]oxazoles **14a**–**c** were also obtained when the heteroaryl-2-carboxaldehydes **2a,c,d** were reacted with L-proline (**3c**) to give the azomethine ylides **13**, which subsequently underwent cycloaddition to their aldehyde precursors **2**, Scheme 4.

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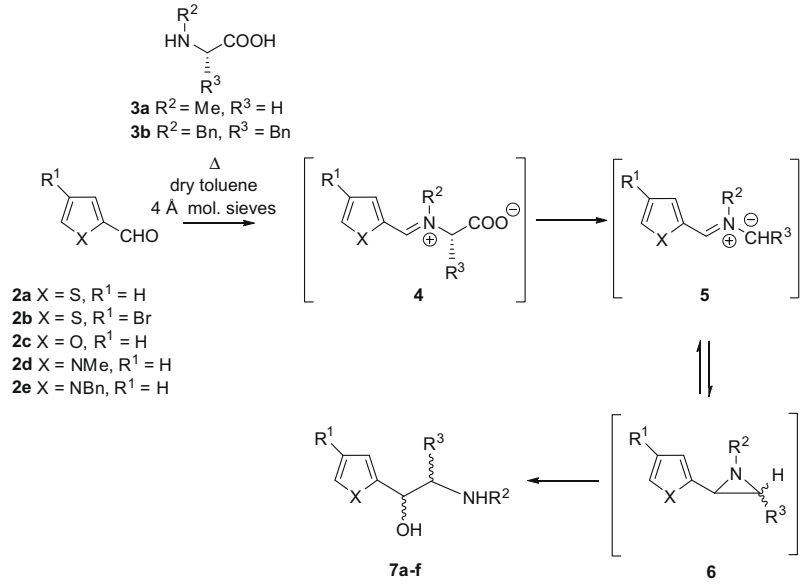
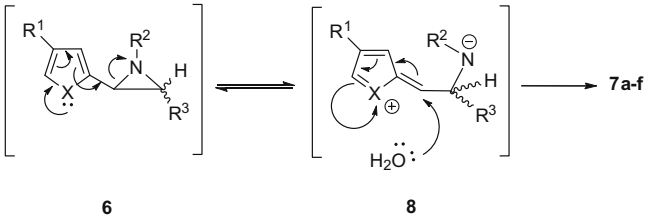
doi:10.1016/j.tetlet.2009.12.021



Scheme 1.

Table 1
Yields of β-hydroxyamines **7** from the reaction of an *N*-alkylamino acid **3** and an aldehyde **2**

Product	X	R^1	R^2	R^3	Yield (%)
7a	S	H	Me	H	43
7b	S	Br	Me	H	45
7c	S	H	Bn	Bn	44
7d	O	H	Me	H	44
7e	NMe	H	Me	H	46
7f	NBn	H	Me	H	64

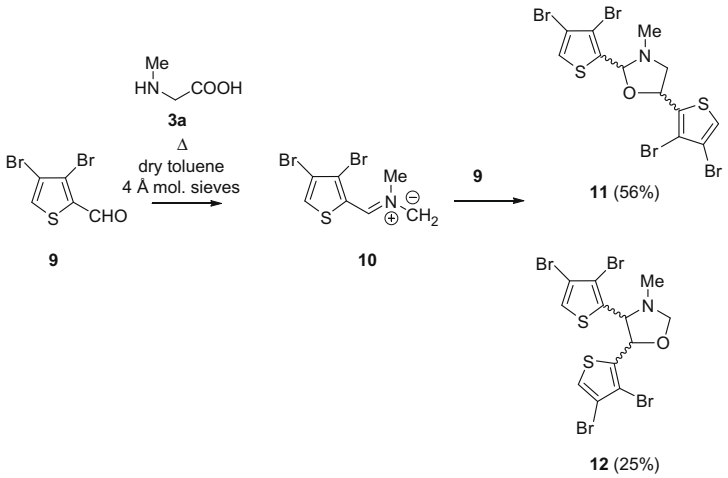


Scheme 2.

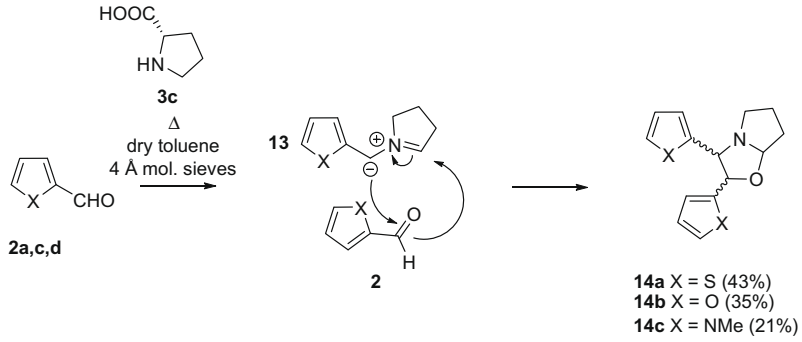
An identical transformation was observed when the heteroaryl-3-carboxaldehydes **15a–c** were employed as the precursors, with the β-hydroxyamines **18a–c** again being obtained in moderate to good yields via the azomethine ylides **16** and aziridines **17**, Scheme 5.

All the β-hydroxyamines were characterised by IR and ^{1}H, ^{13}C, HMQC and HMBC spectroscopy, and by high resolution mass spectrometry, with the ^{1}H NMR spectra for the products **7a,b,d–f** and **18** showing either an A_2X or an ABX spin system for the CH_2-CH protons.[15] Single crystal X-ray crystallography of the product of the reaction of thiophene-2-carboxaldehyde **2a** with sarcosine **3a** confirmed the structure of the hydroxylamine **7a**, Figure 1.[15]

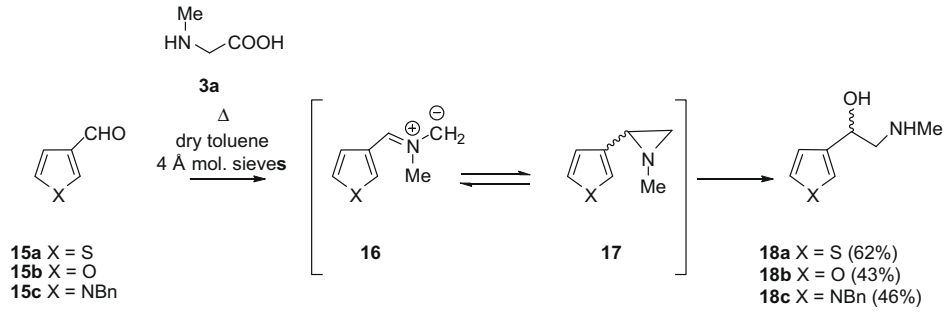
In conclusion, we have shown that a range of β-hydroxyamines **7** and **18** can be obtained in one-step via the 1,3-electrocyclisation of azomethine ylides **5** and **16**, formed by the reaction of an aldehyde **2** or **15** with *N*-alkylamino acids **3a,b** in refluxing toluene over 4 Å molecular sieves, followed by ring-opening hydrolysis of the resulting aziridines **6** and **17**.



Scheme 3.



Scheme 4.



Scheme 5.

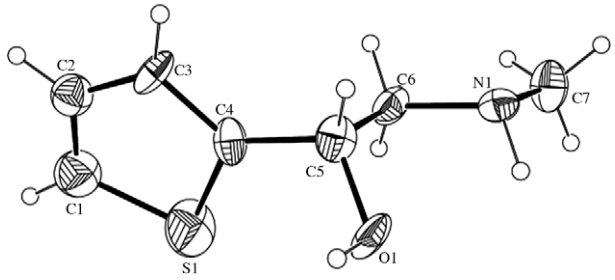


Figure 1. ORTEP representation of the single crystal X-ray structure of hydroxylamine **7a**.[22]

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15. Examples of the experimental method and spectroscopic data;
N-Methyl-1-(2-thienyl)-2-aminoethanol **7a**;[4] A mixture of thiophene-2-carboxaldehyde **2a** (0.45 g, 4 mmol), *N*-methylglycine **3a** (0.75 g, 8.4 mmol) and 4 Å molecular sieves (2.0 g), in anhydrous toluene (20 ml), was heated at reflux, under dry argon, overnight. After cooling to room temperature, the mixture was filtered to remove any solid. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel, eluting with EtOAc/MeOH (4:1), to give *N-methyl-1-(2-thienyl)-2-aminoethanol* **7a** as a yellow resin (0.27 g, 43%) which solidified upon standing, mp 41–43 °C (from EtOAc); (Found: MH^+, 158.0643. Calcd for $C_7H_{12}NOS$: MH^+ 158.0634); ν_{max} (KBr)/cm^{-1} 3310 (NH), 2889 (broad, OH), 1474 (C=C), 1439 (C=C); δ_H (300 MHz, $CDCl_3$) 2.35 (3H, s, *N*Me), 2.77–2.80 (2H, m H-$2^{A,B}$), 3.10 (2H, br s, OH, NH), 4.95 (1H, dd, J = 6.6, 6.0 Hz, H-1), 6.87–6.90 (2H, m, ArH), 7.15 (1H, m, ArH); δ_C (75.5 MHz, $CDCl_3$) 35.8 (*N*Me), 59.0 (CH_2, C-2), 67.8 (CH, C-1), 123.5 (CH), 124.4 (CH), 126.7 (CH), 146.8 (quat., C-2′).
N-Methyl-1-(3-furyl)-2-aminoethanol **18b**; Furan-3-carboxaldehyde **15b** (0.50 g, 5.2 mmol) was reacted with *N*-methylglycine (0.70 g, 7.9 mmol) and 4 Å molecular sieves (2.0 g), in anhydrous toluene (20 ml), as described above. Removal of the solid, by filtration, and the solvent, by evaporation under reduced pressure, and purification, by column chromatography on silica gel, eluting with EtOAc/MeOH (10:3), gave *N-methyl-1-(3-furyl)-aminoethanol* **18b** as a colourless oil (0.30 g, 43%); (Found: MH^+, 142.0867. Calcd for $C_7H_{12}NO_2$: MH^+ 142.0863); ν_{max} (liquid film)/cm^{-1} 3317 (NH), 2944 (br, OH), 1501 (C=C), 1452 (C=C); δ_H (300 MHz, $CDCl_3$) 2.44 (3H, s, *N*Me), 2.77 (2H, d, J = 6.3 Hz, H-2), 2.90 (2H, br s, OH, NH), 4.72 (1H, t, J = 6.3 Hz, H-1), 6.38 (1H, dd, J = 1.8, 0.8 Hz, H-4′), 7.38 (1H, t, J = 1.8 Hz, H-5′), 7.40 (1H, dd, J = 1.8, 0.8 Hz, H-2′); δ_C (75.5 MHz, $CDCl_3$) 35.9 (*N*Me), 57.9 (CH_2, C-2), 64.7 (CH, C-1), 108.5 (CH, C-4′), 127.3 (quat., C-3′), 139.2 (CH, C-2′), 143.2 (CH, C-5′).
16. The relative stereochemistry of the product **7c** from the reaction of thiophene-2-carboxaldehyde **2a** and *N*-benzyl-L-phenylalanine **3b** was not determined.
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21. We are grateful to a referee for suggesting this mechanism.
22. CCDC 755745 contains the supplementary crystallographic data for this Letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.