ORGANIC LETTERS

2009
Vol. 11, No. 13
2840−2843

α-Aminoester-Derived Imidazoles by 1,5-Electrocyclization of Azavinyl Azomethine Ylides

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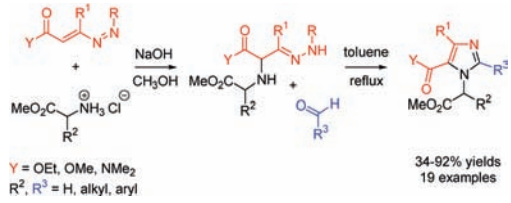
Received May 13, 2009

ABSTRACT



An efficient and practical method for the preparation of α-imidazol-1-yl esters from 1,2-diaza-1,3-dienes (DDs), α-amino esters, and aldehydes is described. The overall sequence features a Michael-type conjugate addition between the α-amino ester and the DD, followed by iminium ion formation via condensation with the aldehyde and 1,5-electrocyclization of the resulting thermally generated azavinyl azomethine ylide to afford eventually α-imidazol-1-yl esters. Such a protocol allows access to enantiomerically pure imidazoles from optically pure α-amino esters.

The reaction of azomethine ylides with π bonds is a powerful tool for the construction of a variety of N-containing heterocycles.[1] In fact, azomethine ylides behave as 1,3-dipoles and typically react with dipolarophiles via [3 + 2]-cycloaddition to afford five-membered heterocycles such as pyrrolidines or pyrrolines, where the ylide nitrogen atom is incorporated in the final ring product. Intramolecular cycloadditions of azomethine ylides are also possible, thus allowing the synthesis of complex heterocyclic architectures.[1f] When the azomethine ylide is conjugated with a double bond, a 1,5-electrocyclization pathway may occur.[2]

In the course of our painstaking research on the chemistry of 1,2-diaza-1,3-dienes[3] (DDs), we have disclosed a new access to highly decorated imidazoles via 1,5-electrocyclization of α-aziridinohydrazone-derived conjugated azavinyl azomethine ylides.[4] The reaction sequence hinged on the ease of DDs to undergo 1,4-conjugate addition with a most diverse range of nucleophiles,[3,5] including N-unsubstituted aziridines, which in turn are prone to thermal or photochemical electrocyclic ring opening at the C−C bond to generate azomethine ylides.[6] Unprecedentedly, incorporation of *two* nitrogen atoms of the conjugated azavinyl azomethine ylide into the 1,5-electrocyclization product was observed, and imidazoles

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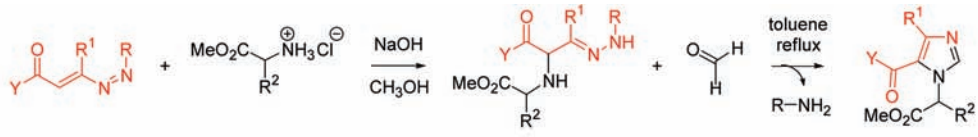
(1) For reviews on azomethine ylides, see: (a) Huisgen, R. *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 1, pp 1−177. (b) Tufariello, J. J. *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: Chichester, UK, 1984; Vol. 2, pp 83−168. (c) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863–909. (d) Harwood, L. M.; Vickers, R. J. *The Chemistry of Heterocyclic Compounds: Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; Wiley and Sons: New York, 2002; Vol. 59, pp 169−252. (e) Nájera, C.; Sansano, J. M. *Curr. Org. Chem.* **2003**, *7*, 1105–1150. (f) Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765–2809. (g) Bonin, M.; Chauveau, A.; Micouin, L. *Synlett* **2006**, 2349–2363. (h) Pandey, G.; Banerjee, P.; Gadre, S. R. *Chem. Rev.* **2006**, *106*, 4484–4517.

(2) Eberbach, W. *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; Padwa, A., Bellus, D., Eds.; Thieme Verlag: Stuttgart, 2004; Vol. 27, pp 441−498. For a specific review on conjugated azomethine ylides, see: Pinho e Melo, T. M. V. D. *Eur. J. Org. Chem.* **2006**, 2873–2888.

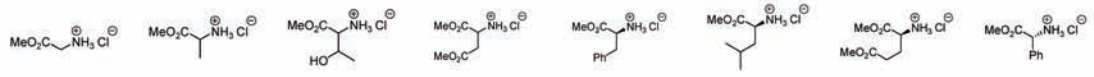
10.1021/ol901051z CCC: $40.75
Published on Web 06/10/2009

Table 1. Synthesis of α-Imidazol-1-yl Esters **5a**−**p**

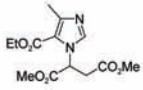
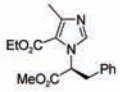
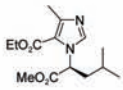
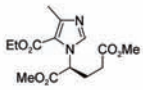
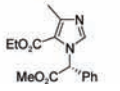
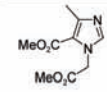
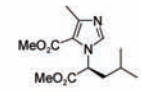
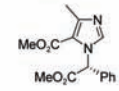
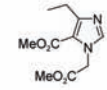
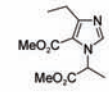
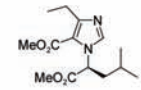
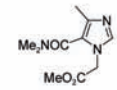
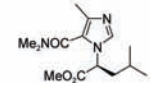


1a-d **2a-h** **3a-p** **4a** **5a-p**

1	Y	R^1	R
1a	OEt	Me	CO_2Et
1b	OMe	Me	CO_2Me
1c	OMe	Et	CO_2Me
1d	$N(Me)_2$	Me	CO_2t-Bu



2a	**2b**	**2c**	**2d**	**(*S*)-2e**	**(*S*)-2f**	**(*S*)-2g**	**(*R*)-2h**
Gly	(±)-Ala	(±)-Thr	(±)-Asp	L-Phe	L-Leu	L-Glu	D-Phg

entry	1	2	imidazole	5	yield[a] (%)	ee (%)
1	**1a**	**2a**		**5a**	59	–
2	**1a**	**2b**		**5b**	86	–
3	**1a**	**2c**		**5a**	69[b]	–
4	**1a**	**2d**		**5d**	62	–
5	**1a**	**(*S*)-2e**		**5e**	61	> 95
6	**1a**	**(*S*)-2f**		**5f**	77	> 95
7	**1a**	**(*S*)-2g**		**5g**	34	> 95
8	**1a**	**(*R*)-2h**		**5h**	70	30
9	**1b**	**2a**		**5i**	65	–
10	**1b**	**(*S*)-2f**		**5j**	78	> 95
11	**1b**	**(*R*)-2h**		**5k**	70	44
12	**1c**	**2a**		**5l**	75	–
13	**1c**	**2b**		**5m**	59	–
14	**1c**	**(*S*)-2f**		**5n**	72	> 95
15	**1d**	**2a**		**5o**	46	–
16	**1d**	**(*S*)-2f**		**5p**	92	> 95

[a] Isolated yield (after silica gel chromatography) based on DDs **1a**−**d**. [b] Under the reaction conditions, loss of the hydroxy ethyl side chain of threonine through a retro-aldol process occurred, and only the imidazole **5a** was isolated.

were ultimately obtained through an overall [3 + 2] annelation strategy whereby three atoms of the azo-ene system[7] and two atoms of the aziridine participated. Such an approach, however, required preliminary synthesis of the aziridine nucleophile, which clearly limited the range of available partners. Since azomethine ylides can also be formed by deprotonation of iminium ions,[1] we envisaged a much easier access to stabilized azavinyl azomethine ylides using DD-derived secondary α-aminoester hydrazones. In fact, these would be accessible by Michael-type addition of α-amino acid derivatives to DDs and are expected to undergo condensation with aldehydes to give an iminium ion which in turn is susceptible to deprotonation to generate conjugated azavinyl azomethine ylides.

Therefore, we wish to report a novel synthetic procedure which allows the straightforward conversion of α-ami-

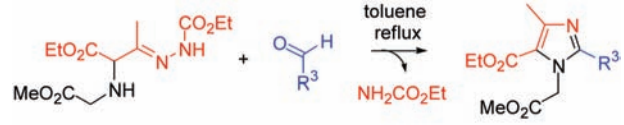
noesters into imidazoles through 1,5-electrocyclization of DD-derived azavinyl azomethine ylides.

α-Aminoester hydrazones **3a**−**p** were prepared by 1,4-conjugate addition of α-amino acid methyl esters **2a**−**h** to DDs **1a**−**d**.[8] The adducts **3a**−**p** did not require purification and were used as such for the following chemistry. Condensation of hydrazones **3a**−**p** with paraformaldehyde (**4a**) and subsequent heating in toluene under reflux afforded 2-unsubstituted imidazoles **5a**−**p** in moderate to excellent overall yields (Table 1).[9] Reaction of the adduct between threonine methyl ester and DD **1a** (Table 1, entry 3) was accompanied by loss of the hydroxy ethyl side chain through a retro-aldol process and resulted in imidazole **5a** in 69% yield. When adducts prepared from optically pure α-aminoesters (L-Phe, L-Leu, L-Glu) were used (Table 1, entries 5−7, 10, 14, and 16), enantiomerically pure imidazoles **5e**−**g**,**j**,**n**,**p** were recovered (ee > 95%).[10] Only in the case of D-phenylglycine (Table 1, entries 7 and 11), partial racemization was observed for the resulting imidazoles (**5h** and **5k**).

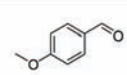
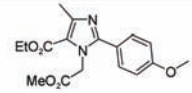
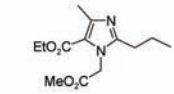
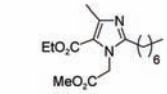
The adduct **3a** between glycine methyl ester and DD **1a** was also reacted with aromatic and aliphatic aldehydes, namely, *p*-anisaldehyde (**4b**), butanal (**4c**), and octanal (**4d**), under the same reaction conditions. α-Imidazol-1-yl esters **5q**−**s** were obtained in good to excellent yield (Table 2).

On the basis of these findings, the formation of α-imidazol-1-yl ester **5** can be rationalized as shown in Scheme 1. α-Aminoester hydrazone **3** arises from 1,4-conjugated addition of an α-aminoester to DD **1**.[5] Condensation of adduct **3** with aldehyde **4** leads to iminium ion **A** which upon heating may generate the conjugated azavinyl azomethine ylides **B** and **C**. Although the negative charge of both ylide species is stabilized by an adjacent electron-withdrawing carboxy group, ylide **C** benefits from additional stabilization by the DD-derived hydrazone moiety. Hence, 1,5-electrocyclization

Table 2. Synthesis of α-Imidazol-1-yl Esters **5q**−**s**

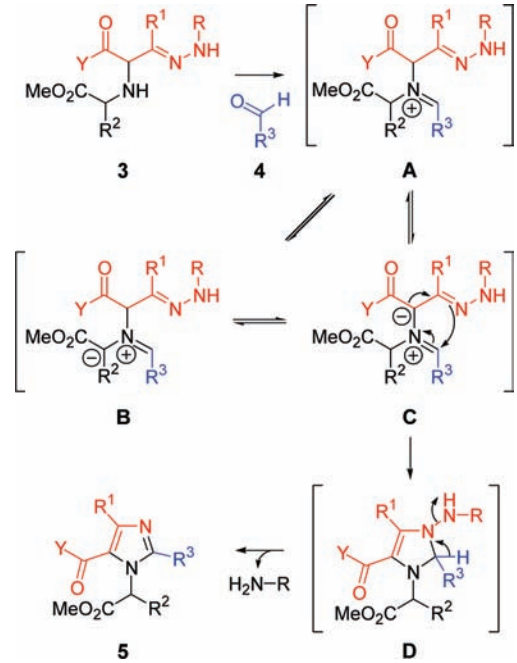


3a 4b-d 5q-s

entry	aldehyde	4	imidazole	5	yield[a] (%)
1		4b		5q	56
2		4c		5r	81
3		4d		5s	57

[a] Isolated yield (after silica gel chromatography) based on DD **1a**.

Scheme 1. Postulated Mechanism for the Formation of α-Imidazol-1-yl Esters **5** via 1,5-Electrocyclization of Azavinyl Azomethine Ylide **C**



(3) For reviews on the chemistry of DDs, see: (a) Attanasi, O. A.; De Crescentini, L.; Filippone, P.; Mantellini, F.; Santeusanio, S. *Arkivoc* **2002**, *xi*, 274–292. (b) Attanasi, O. A.; De Crescentini, L.; Favi, G.; Filippone, P.; Mantellini, F.; Perrulli, F. R.; Santeusanio, S. *Eur. J. Org. Chem.* **2009**, DOI: 10.1002/ejoc200900243. For selected articles, see: (c) Boeckman, R. K., Jr.; Ge, P.; Reed, J. E. *Org. Lett.* **2001**, *3*, 3651–3653. (d) Rossi, E.; Arcadi, A.; Abbiati, G.; Attanasi, O. A.; De Crescentini, L. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 1400–1402. (e) Yang, H.-T.; Wang, G.-W.; Xu, Y.; Huang, J.-C. *Tetrahedron Lett.* **2006**, *47*, 4129–4231. (f) Attanasi, O. A.; Favi, G.; Filippone, P.; Perrulli, F. R.; Santeusanio, S. *Org. Lett.* **2009**, *11*, 309–312. (g) Attanasi, O. A.; Berretta, S.; De Crescentini, L.; Favi, G.; Giorgi, G.; Mantellini, F. *Adv. Synth. Catal.* **2009**, *351*, 715–719. (h) Attanasi, O. A.; De Crescentini, L.; Favi, G.; Filippone, P.; Giorgi, G.; Mantellini, F.; Moscatelli, G.; Behalo, M. S. *Org. Lett.* **2009**, *11*, 2265–2268. (i) Attanasi, O. A.; Favi, G.; Giorgi, G.; Mantellini, F.; Karapetyan, V.; Langer, P. *Tetrahedron* **2009**, DOI: 10.1016/j.tet. 2009.04.018.

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(6) *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, Germany, 2006.

(7) For recent [3 + 2] pyrrole syntheses that involve the C−C═N fragment of DDs, see: (a) Attanasi, O. A.; Favi, G.; Filippone, P.; Lillini, S.; Mantellini, F.; Spinelli, D.; Stenta, M. *Adv. Synth. Catal.* **2007**, *349*, 907–915. (b) Attanasi, O. A.; Favi, G.; Filippone, P.; Giorgi, G.; Mantellini, F.; Moscatelli, G.; Spinelli, D. *Org. Lett.* **2008**, *10*, 1983–1986. (c) Karapetyan, V.; Mkrtchyan, S.; Schmidt, A.; Attanasi, O. A.; Favi, G.; Mantellini, F.; Villinger, A.; Fischer, C.; Langer, P. *Adv. Synth. Catal.* **2008**, *350*, 1331–1336.

(8) 1,2-DDs **1a**−**d** were synthesized from the corresponding chlorohydrazones by treatment with base (see Supporting Information).

(9) The structure of imidazoles **5a**−**s** was confirmed by mono- (^{1}H, ^{13}C) and bidimensional (COSY, HSQC, and HMBC) NMR analysis and by mass spectroscopy (see Supporting Information).

(10) Enantiomeric excesses (ee) were determined either from ^{1}H NMR spectra recorded in the presence of the chiral solvating agent (*R*)-(−)-2,2,2-trifluoro-l-(9-anthryl)ethanol or by chiral HPLC analysis (see Supporting Information).

of conjugated ylide **C** to 2,3-dihydroimidazole **D**, followed by aromatization with concomitant loss of a carbamate residue through cleavage of the N−N bond,[11] results eventually in the formation of the imidazole **5** (Scheme 1). Such a reaction mechanism is corroborated by the isolation of enantiomerically pure imidazoles when adducts prepared from optically pure α-aminoesters were used, as formation of ylide **C** proceeds without affecting the stereogenic carbon atom. In the case of the D-Phg-derived adduct **3h**, however, additional stabilization of ylide **B** by the phenyl ring would account for the partial racemization that has been observed in imidazoles **5h** and **5k**. In this case, in fact, phenyl-stabilized ylide **B** is also generated, and the resulting imidazoles are ultimately formed through tautomeric equilibration of **B** to **C** and subsequent 1,5-electrocyclization. Further support to this view is lent by the fact that upon prolonged heating at 110 °C in toluene the ee value of D-Phg-based imidazole **5h** remained unchanged, thus ruling out that racemization occurred after the electrocyclization event.

In summary, we have reported a novel, efficient, and straightforward method for the synthesis of α-imidazol-1-yl ester from readily available starting material such as α-aminoesters and aldehydes.[12] The present approach is flexible and useful for the synthesis of a wide range of different substituted imidazoles. Furthermore, modulation of substituents at the C-2 and C-5 atoms of the final imidazole product is made possible by appropriate choice of the aldehyde and DD partners, respectively. Noteworthily, the amino group of the α-aminoester is incorporated into the resulting imidazole,[13] which may therefore be viewed as a rigid amino acid analogue bearing an aromatic heterocyclic scaffold that mimics an amide bond. Since a variety of aromatic heterocyclic rings such as pyrroles, tetrazoles, triazoles, pyrazoles, and imidazoles have been embodied in enzyme inhibitors as surrogates for replacement of the otherwise scissile peptide bond,[14,15] our synthetic approach may represent a versatile and attractive access to amino acid derived, heterocycle-based peptidomimetics. Further extension of this 1,5-electrocyclization pathway is currently being pursued in our laboratories and will be reported in due course.

Acknowledgment. This work was financially supported by the Ministero dell'Università, dell'Istruzione e della Ricerca (MIUR) - Rome, Università degli Studi di Urbino "Carlo Bo", and Università degli Studi di Modena e Reggio Emilia.

Supporting Information Available: Experimental procedures and full characterization for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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