Tetrahedron 70 (2014) 2054–2058

Contents lists available at ScienceDirect

Tetrahedron

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

Asymmetric synthesis of *syn* and *anti* methyl 2,3-diamino-3-phenylpropanoate derivatives from *N*-substituted imines and *Schöllkopf*'s bislactim ether

Giuseppe Cremonesi [†], Piero Dalla Croce, Maddalena Gallanti [‡], Concetta La Rosa [*]

Università degli Studi di Milano, DISFARM, Sezione di Chimica Generale e Organica "A. Marchesini", V. Venezian 21, I-20133 Milano, Italy

ARTICLE INFO

Article history:
Received 6 November 2013
Received in revised form 7 January 2014
Accepted 20 January 2014
Available online 5 February 2014

Keywords:
2,3-Diamino propanoates
α,β-Diamino acids
Imines
Schöllkopf bislactim ether

ABSTRACT

The reaction between differently *N*-substituted benzaldimines and (2*R*)-*Schöllkopf*'s bislactim ether was studied: the azaenolate addition to imines followed by hydrolysis of the resulting adducts gave *syn*-(2*S*,3*R*) and *anti*-(2*S*,3*S*)-methyl 2,3-diamino-3-phenylpropanoate derivatives in good yields. The configurations of the newly formed stereocenters of α,β-diamino acids were assigned on the basis of the ^{1}H NMR analysis and by comparison with known products. The diastereoisomeric ratios were explained taking into account the effect of the substituent present on the imine nitrogen on the transition state stability. This method represents a new approach for stereoselective synthesis of α,β-diamino acids.

1. Introduction

Non-proteinogenic, optically active 2,3-diamino acids are key structural units of numerous natural products, and they present important biological properties and can be versatile building blocks in organic synthesis. For example, (*S*)-2,3-diaminopropanoic acid is present in several natural antibiotic cyclopeptides,[1] and (2*S*,3*R*)-2,3-diamino-3-phenylpropanoic acid has been utilized as an analogue of the Taxol side chain improving the water solubility of this antitumour compound.[2] 2,3-Diamino acids have also been incorporated into peptides, which are used to modulate secondary and tertiary structural conformations.[3] For these reasons they have received a growing interest through the years.[4] Accordingly, the development of efficient and general methods in their preparation has received considerable attention, especially as regards the synthesis of enantiopure compounds.[5] Among the various methods of synthesis one of the most useful was the nucleophilic addition of chiral glycinate derivatives to imines.[6] *Schöllkopf*'s bislactim ether, (i.e., (2*R*)- or (2*S*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine),[7] is a particularly attractive chiral glycine equivalent because it has proved to be highly diastereoselective in aldol-type reactions and is commercially available in both (*R*) and (*S*)-forms. For many years our research group has studied the stereoselective synthesis of new α-amino acids by means of the reaction between the *Schöllkopf*'s bislactim ether and various electrophiles, such as alkyl halides,[8] heterocyclic-carbaldehydes,[9] or ketones.[10] In these two latter cases, β-hydroxy-α-amino acids were obtained, with an asymmetric, enantiomerically pure quaternary carbon in the β position when ketones were used.[10]

So we were interested in the possibility of obtaining enantiopure α,β-diamino acids derivatives by reacting *Schöllkopf*'s bislactim ether with the electrophilic carbon of imines. An analysis of the literature revealed that this reagent has been used with different types of electrophiles, especially aldehydes, but it had never been added to imines. Only in a publication of 1986, *Schöllkopf* reported that the anion of the (2*S*)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-methylpyrazine initially reacted with the azomethine double bond of 2-(benzylideneamino)ethylbromide affording, after an intramolecular cyclization, an aziridine compound.[11] The synthesis of 2,3-diamino acids by 'the bislactim ether method' was also accomplished in 1991 by Mittendorf reacting the lithium azaenolate of (2*S*)-5-alkyl-2,5-dihydro-3,6-dimethoxy-2-isopropyl-pyrazine with dibromomethane followed by nucleophilic substitution of bromide with sodium azide and final hydrolysis.[12]

Our interest in the stereoselective synthesis of enantiopure α-amino acids, led us to report a novel and efficient method to obtain enantiopure α,β-diamino acids by means of the reaction between

* Corresponding author. Tel.: +39 02 503 14473; fax: +39 02 503 14476; e-mail address: concetta.larosa@unimi.it (C. La Rosa).
† Present address: Sifavitor S.r.l., Via Livelli 1, I-26852 Mairano di Casaletto Lodigiano (LO), Italy.
‡ Present address: Abcam Biochemicals, Unit 3 Victoria Rd, Bristol BS11 9DB, United Kingdom.

0040-4020/$ – see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2014.01.040

the lithium enolate of (2*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine **1** and *N*-substituted imines. In order to obtain differently *N*-protected diamino acids and also to evaluate the steric and electronic effects of the nitrogen substituent on the diastereoselectivity of the addition, we decided to conduct our investigation using variously *N*-substituted benzaldimines (*E*)-**2a**–**f**, bearing both electron withdrawing and electron donating groups. This should enable us to obtain, after acid hydrolysis, differently N_β-protected α,β-diamino acids (Fig. 1).

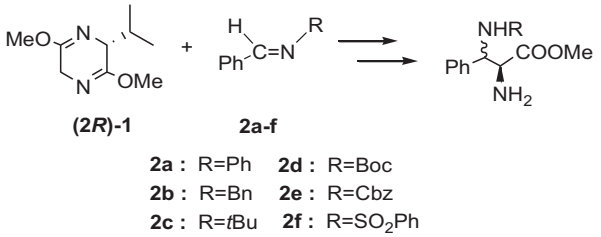


Fig. 1. Synthetic pathway for N_β-protected α,β-diamino acids.

2. Results and discussion

Various experimental conditions and counter-ions were examined to optimize yields and evaluate the diastereoselectivity of the reaction. In these experiments imine **2a** was taken as reference. A THF solution of imine was added to the anion of the bislactim ether (2*R*)-**1** generated by the addition of *n*BuLi in THF at *T*=−78 °C. The reaction mixture was then maintained at variable temperatures and times (representative conditions are listed in Table 1, entries 1–4). In all cases the reaction gave mixtures of two diastereoisomeric adducts **3a**/**4a** whose ratio was determined from integration of the H-2 (4.35/4.56 δ) or H-5 (3.59/3.10 δ) signals in the ^{1}H NMR spectra of the crude reaction mixtures (Scheme 1).

The observed diastereoselectivity was generally poor, similarly to that found in the case of ketones.[10] Under experimental conditions providing the best yield, the two adducts were formed in almost the same amount (Table 1, entry 1). It was observed that when conducted at higher temperatures (*T*=−20 °C or +4 °C rather than −78 °C) the ratio between the two diastereoisomers was inverted and the yield decreased (Table 1, entries 2–4). This was not due to the reversibility of the addition as the two adducts were found to be stable under the reaction conditions. In fact, after having separated them, they were treated with *n*BuLi at temperatures between −78 and +4 °C for 24 h but they were recovered unaffected. Generally, the observed diastereoselectivity could also be influenced by the nature of the counter-ion. To assess this, the lithium azaenolate was treated with $ZnCl_2$, $TiCl(O^iPr)_3$[13] or $SnCl_4$ to give the corresponding transmetalated azaenolates before the addition of the imine (Table 1, entries 5–7): only in the last case did the reaction afforded a mixture of **3a**/**4a** at almost the same ratio but in a lower yield.

The best experimental conditions reported in Table 1 entry 1, were then applied to the reaction of (2*R*)-**1** with imines **2b**–**f**. In the case of imines **2b**, **c** the reaction led to unreacted reagents and traces of products (Table 1, entries 8, 9). In particular, the treatment of imine **2b** with the anion of (2*R*)-**1**, produced an intense pink colour due to the deprotonation of the benzylic carbon[14] and extensive delocalization of the corresponding anion prevented the addition.[15] In the case of imine **1c**, failure to obtain the products has been attributed to the steric hindrance generated by the bulky *tert*-butyl group, as already observed.[16] On the contrary, the reaction of the imines **2d**, **e** afforded mixtures of the two diastereoisomeric adducts **3d**/**4d** and **3e**/**4e** in good yields and, with imine **2e**, also with a better diastereoselectivity (Table 1, entries 10, 11). Only with imine **2f** the formation of all the four possible diastereoisomers was observed but with a preference for adduct **4f** (Table 1, entry 12).

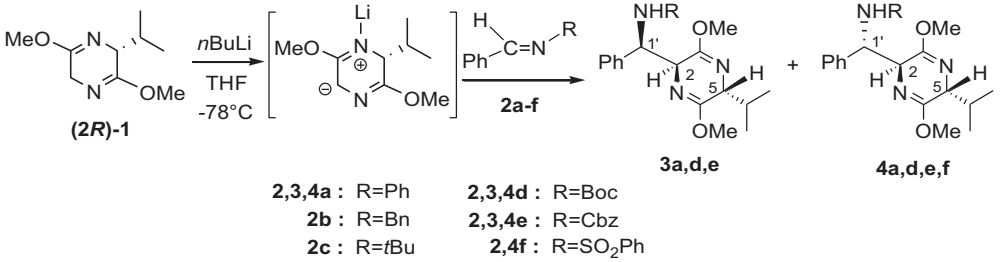
Diastereoisomers **3a**, **d**, **e** and **4a**, **d**–**f** were easily isolated by means of flash chromatography on silica gel, and their structures were confirmed on the basis of analytical and spectroscopic data (HSQC, COSY and NOESY experiments). The (2*S*)-configuration was established using the $^5J_{H2/H5}$ coupling constant value of approximately 3.5 Hz, which corresponds to a *trans* relationship between the H-2 and H-5 protons of the pyrazine ring.[17] The (*R*)- and (*S*)-configuration were assigned to the C-1′ of the adducts **3** and 4, respectively, by means of comparison with each other and using the data reported in the literature for the corresponding α,β-diamino acids obtained after hydrolysis (see below).

The reactions of (2*R*)-**1** with aldehydes[9,7b] or ketones[10,18] always afforded mixtures of the two (2*S*)-epimers arising from the attack of the azaenolate–pyrazine from the less hindered side opposite the isopropyl group, according to the *Zimmerman–Traxler* six-membered ring model,[19] and our present results confirm the 2,5-*trans*-relationship in the adducts **3**/**4**.

Table 1
Total yields and ratios of compounds **3**/**4**

Entry	Imine	R	Counter-ion	*T* (°C)	*t* (h)	Total yield (%)	**3** (%)	**4** (%)
1	**2a**	Ph	Li^+	−78	8	72	53	47
2	**2a**	Ph	Li^+	−20	6	56	45	55
3	**2a**	Ph	Li^+	+4	4	51	33	67
4	**2a**	Ph	Li^+	+4	16	55	42	58
5	**2a**	Ph	Zn^{2+}	−20	6	—	—	—
6	**2a**	Ph	Ti^{4+}	−20	6	—	—	—
7	**2a**	Ph	Sn^{4+}	−20	6	34	40	60
8	**2b**	Bn	Li^+	−78	8	Trace	—	—
9	**2c**	^{t}Bu	Li^+	−78	8	Trace	—	—
10	**2d**	Boc	Li^+	−78	8	65	41	59
11	**2e**	Cbz	Li^+[a]	−78	8	75	13	87
12	**2f**	SO_2Ph	Li^+	−78	8	70	38[b]	62

[a] The reported results were obtained using 2 equiv of LDA as base.
[b] Total ratio of three inseparable diastereoisomers.



Scheme 1.