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A novel diastereoselective α-functionalization of proline with benzaldehydes: synthesis of α-(α-hydroxybenzyl)prolines

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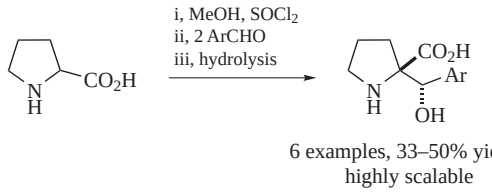
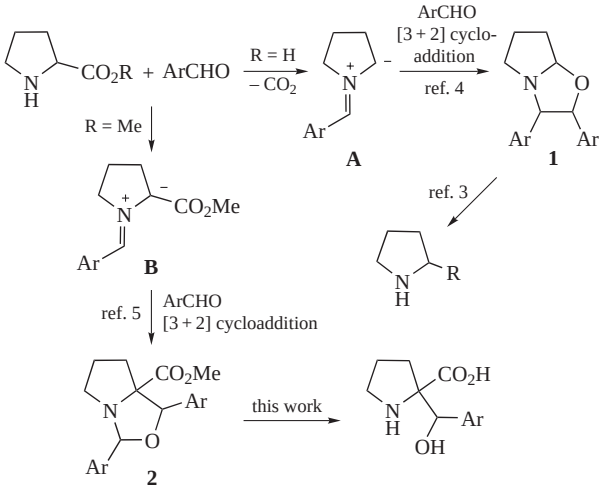
2-Oxapyrrolizidines formed in reactions of methyl prolinate with two molecules of aromatic aldehyde upon gradual hydrolysis give α-(α-hydroxybenzyl)prolines. The products are preferentially formed as one diastereomer (91–100%) in overall yield 33–50% (five stages starting from proline).



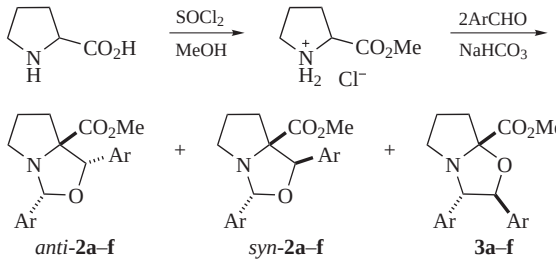
6 examples, 33–50% yields, highly scalable

The [3+2] cycloaddition of azomethine ylides is among the most convenient methods for synthesizing complex nitrogen-containing heterocycles.[1] In particular, reactions of carbonyl compounds with azomethine ylides afford oxazolidines possessing good synthetic potential as their structure incorporates an electrophilic semiaminal moiety.[2] Recently, we reported[3] on transformation of proline into 2-substituted pyrrolidines, involving the preparation of 1-oxapyrrolizidines **1**[4] containing an oxazolidine moiety with required reactivity from non-stabilized azomethine ylide **A** as the key stage (Scheme 1). A similar reaction of methyl prolinate occurs *via* the formation of azomethine ylide **B** stabilized by a methoxycarbonyl group. This ylide reacts with a second aldehyde molecule, mainly to give 2-oxapyrrolizidines **2**.[5] The latter compounds were used in this study to access α-functionalized prolines bearing α-hydroxybenzyl substituents (see Scheme 1). Note that some related examples of application of azomethine ylides for incorporation of functional groups to carbonyl compounds are available in literature.[6–9]



Scheme 1

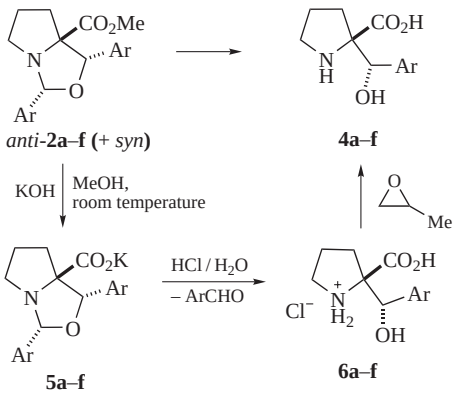
Here, we repeated the reaction of methyl prolinate with benzaldehyde (Scheme 2) and elaborated a procedure for synthesizing isomeric mixture of 1- and 2-oxapyrrolizidines with considerable predomination of 2-oxapyrrolizidine *anti*-**2a** (2 h refluxing in a hexane–toluene mixture with a Dean–Stark trap afforded 80% content of adduct *anti*-**2a**). To verify the scope of the procedure, a series of new 2-oxapyrrolizidines *anti*-**2b–f** with 69–80% content in the crude reaction mixture (NMR data) were obtained. Since the reaction proceeded through planar azomethine ylide **B** (see Scheme 1), the enantiomeric purity of the starting proline did not matter and the cycloaddition adducts **2**, **3** were formed as racemates (see Scheme 2).



a Ar = Ph
b Ar = 4-MeC_6H_4
c Ar = 4-ClC_6H_4
d Ar = 4-BrC_6H_4
e Ar = 4-$MeOC_6H_4$
f Ar = 3,4-$(MeO)_2C_6H_3$

Scheme 2

As we had gram amounts of 2-oxapyrrolizidine *anti*-**2a** in a mixture with small amounts of minor isomers (*anti*-**2a**, 80%; *syn*-**2a**, 7%; **3a**, 13%), we anticipated to hydrolyze this mixture, purify the final product from minor components, and thus develop a diastereoselective synthesis of functionalized proline **4a** (Scheme 3). However, attempted hydrolysis of the ester group in **2a** by heating with dilute hydrochloric acid or potassium hydroxide in methanol followed by acid opening of the oxazolidine ring gave a large amount of proline and a mixture of α-(α-hydroxybenzyl)-proline **4a** with its diastereomer in nearly equal amounts, which indicated the instability of compound **4a** in the presence of benzaldehyde in a strongly acidic or strongly basic medium at temperatures above 80 °C. This was likely due to a retro-aldol process, while the change in the diastereomer ratio allows us to assume that either *anti*-**2a** → *syn*-**2a** isomerization through cycloreversion–cycloaddition occurs, or the retro-aldol reaction rate is higher for one of the isomers.



	Ar	Yield of **4** (%)
a	Ph	45
b	4-MeC_6H_4	48
c	4-ClC_6H_4	44
d	4-BrC_6H_4	44
e	4-$MeOC_6H_4$	50
f	3,4-$(MeO)_2C_6H_3$	33

Scheme 3

A technique we developed for conversion of compound *anti*-**2a** to proline **4a** involved the saponification of the ester group with KOH in methanol at room temperature (see Scheme 3). The subsequent acidic opening of the oxalizidine moiety in salt **5a** gave the hydrochloride of acid **6a** in a two-phase system to remove the benzaldehyde formed. Final treatment with propylene oxide (HCl scavenger) afforded neutral amino acid **4a**.† In this case, α-(α-hydroxybenzyl)proline **4a** is formed as a pure *RS*,*SR*-diastereomer in 45% overall yield with respect to the starting proline. The similar processing of other 2-oxapyrrolizidines *anti*-**2b–f** afforded a series of *RS*,*SR*-acids **4b–f** in overall yields of 33–50% based on the starting proline upon five stages (Scheme 3).‡

The ^{1}H NMR spectra of amino acids **4a–f** in D_2O contain downfield singlets of benzyl protons in the narrow range of δ 5.15–5.18, as well as multiplets of six signals from diastereotopic methylene protons of the pyrrolidine ring at δ 1.64–3.42. The stereochemistry of the simplest 2-oxapyrrolizidine *anti*-**2a** was strictly proved previously using a NOE NMR experiment.[5] Since hydrolysis of adducts **2** does not involve the bond between the benzyl carbon atom and the C-2 atom of the pyrrolidine ring, the stereo configuration of these chiral centers does not change and products **4** are formed as a racemic mixture of *RS*,*SR*-diastereomers.

The suggested method is experimentally simple and easily scalable, which allowed us to obtain gram amounts of hitherto unknown prolines **4a–f** with high diastereoselectivity (no more than 9% of the second isomer was detected). Apart from the synthetic value of these compounds as structural fragments for further functionalization, they may be expected to have important pharmaceutical properties, since their structures are similar to well known pharmaceuticals such as Methyldopa and Droxidopa, modulators of arterial pressure used to increase or decrease it, respectively.[10]

In conclusion, we were the first to introduce α-hydroxybenzyl substituent to the α-position of proline. The reaction sequence is a diastereoselective aldol functionalization of proline that offers a wide range of new α-substituted prolines promising for their potential biological activity and possible further modification.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2017.11.031.

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† *Methyl prolinate hydrochloride*. Thionyl chloride (29.2 ml, 0.403 mol) was added dropwise in 1 h with stirring and cooling on an ice bath to L-proline (23.2 g, 0.202 mol) in MeOH (140 ml), and the mixture was additionally stirred at room temperature for 2 h. After concentrating *in vacuo* at 60 °C, the viscous colourless product crystallized in quantitative yield.

Compounds **2** (+**3**). Sodium bicarbonate (0.53 g, 6.3 mmol) was added to methyl prolinate hydrochloride (1 g, 6 mmol), then PhMe (12 ml), hexane (8 ml) and water (1 ml) were added. The two-phase mixture was stirred until CO_2 evolution ceased (~10–20 min). The corresponding aldehyde (12 mmol) was added and the mixture was refluxed on stirring with a Dean–Stark trap for 2 h. The NaCl precipitate was filtered off and the filtrate was concentrated *in vacuo* at 50 °C to give a viscous yellow oily product.

Products **4**. The obtained mixture of compounds **2** and **3** was dissolved in MeOH (7 ml). Separately, KOH (0.50 g, 9 mmol, 1.5 equiv. with respect to methyl prolinate) was dissolved in MeOH (7 ml). The solutions were mixed, kept at room temperature for 24 h, and then concentrated *in vacuo* at 35 °C. Water (7 ml) and toluene (10 ml) were added to the residue and a solution of concentrated HCl (1.4 ml, 2.7 equiv. with respect to methyl prolinate) in water (10 ml) was added with stirring. The mixture was additionally stirred at room temperature for 10–15 min, then the aqueous layer was separated and washed with toluene (2 × 10 ml) to remove the liberated benzaldehyde. The aqueous layer was filtered and concentrated *in vacuo* at 45 °C. The residue was dissolved in MeOH (7 ml), and the precipitate of KCl was filtered off. Propylene oxide (0.64 ml, 9 mmol) was added to the resulting solution and the mixture was kept for 2 days. A white crystalline precipitate of amino acid **4** was formed (in the cases of compounds **4e**,**f**, methanol was diluted with dry Et_2O to precipitate the product). The product was filtered off and dried at 60–70 °C.

‡ rac-*(*RS*)-2-[(*SR*)-Hydroxy(phenyl)methyl]pyrrolidine-2-carboxylic acid* **4a**. Yield 45%, white powder, mp 248.5–249.0 °C. ^{1}H NMR (400 MHz, D_2O) δ: 1.66–1.87 (m, 2H, 4-CH_2), 2.14 (dt, 1H, 3-C*H*H, *J* 13.5, 8.3 Hz), 2.22 (ddd, 1H, 3-CH*H*, *J* 13.5, 7.6, 4.6 Hz), 3.11 (dt, 1H, 5-C*H*H, *J* 11.6, 7.8 Hz), 3.36 (ddd, 1H, 5-CH*H*, *J* 11.6, 8.2, 5.3 Hz), 5.18 (s, 1H, CH), 7.42–7.47 (m, 5H, Ph). ^{13}C NMR (125 MHz, D_2O) δ: 23.5, 30.3, 46.8, 74.3, 79.0, 127.7, 129.4, 129.7, 138.5, 174.6. IR (*ν*/cm^{-1}): 3324, 3059, 1618, 1494, 1446, 1395, 1369, 1326, 1285, 1188, 1094, 1058, 1031, 927, 833, 701, 635, 602, 580, 538. Found (%): C, 65.03; H, 6.85; N, 6.39. Calc. for $C_{12}H_{15}NO_3$ (%): C, 65.14; H, 6.83; N, 6.33.

rac-*(*RS*)-2-[(*SR*)-Hydroxy(4-methylphenyl)methyl]pyrrolidine-2-carboxylic acid* **4b**. Yield 48%, white powder, mp 249.8–250.0 °C. ^{1}H NMR (400 MHz, D_2O) δ: 1.64–1.87 (m, 2H, 4-CH_2), 2.13 (dt, 1H, 3-C*H*H, *J* 13.5, 8.7 Hz), 2.22 (ddd, 1H, 3-CH*H*, *J* 13.5, 7.6, 4.4 Hz), 2.36 (s, 3H, Me), 3.09 (dt, 1H, 5-C*H*H, *J* 11.7, 7.8 Hz), 3.33–3.41 (m, 1H, 5-CH*H*), 5.17 (s, 1H, CH), 7.31 (d, 2H, Ar, *J* 8.0 Hz), 7.36 (d, 2H, Ar, *J* 8.0 Hz). Found (%): C, 66.53; H, 7.48; N, 5.92. Calc. for $C_{13}H_{17}NO_3$ (%): C, 66.36; H, 7.28; N, 5.95.

rac-*(*RS*)-2-[(*SR*)-Hydroxy(4-chlorophenyl)methyl]pyrrolidine-2-carboxylic acid* **4c**. Yield 44%, white crystals, mp 258.9–259.2 °C. ^{1}H NMR (400 MHz, D_2O) δ: 1.68–1.88 (m, 2H, 4-CH_2), 2.15 (dt, 1H, 3-C*H*H, *J* 13.3, 8.4 Hz), 2.22 (ddd, 1H, 3-CH*H*, *J* 13.3, 7.4, 4.4 Hz), 3.15 (dt, 1H, 5-C*H*H, *J* 11.6, 7.8 Hz), 3.37 (ddd, 1H, 5-CH*H*, *J* 11.6, 7.9, 5.3 Hz), 5.17 (s, 1H, CH), 7.41 (app d, 2H, Ar, *J* 8.6 Hz), 7.46 (app d, 2H, Ar, *J* 8.6 Hz). Found (%): C, 56.10; H, 5.76; N, 5.46. Calc. for $C_{12}H_{14}ClNO_3$ (%): C, 56.37; H, 5.52; N, 5.48.

For characteristics of products **4d–f**, see Online Supplementary Materials.

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