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Enantioselective syntheses of homophenylalanine derivatives via nitrone 1,3-dipolar cycloaddition reactions with styrenes

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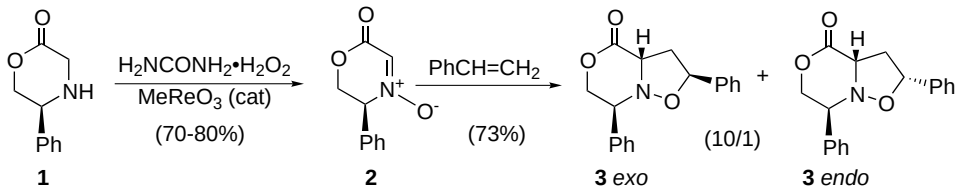
Abstract—A new two-step route to derivatives of homophenylalanine is presented. Cycloaddition of a cyclic nitrone glycine template with various styrene derivatives affords good yields of 5-substituted cycloadducts. One-step hydrogenolysis (three bonds) then affords the optically pure α-amino acids related to homophenylalanine. © 2001 Published by Elsevier Science Ltd.

A recent report from this laboratory demonstrated that nitrone **2** is a versatile partner in 1,3-dipolar cycloaddition reactions with a wide range of alkenes, a result that establishes **2** as a useful chiral glycine template for the synthesis of α-amino acids bearing unusual side-chains.[1] We now wish to report that when styrene derivatives are employed as dipolarophiles, the method also provides ready access to a wide range of derivatives of homophenylalanine. Also reported is an improved preparation of nitrone **2** based on an oxidation of the parent secondary amine.

As originally reported, oxidation of amine **1**[2] was accomplished using in situ generated dimethyl dioxirane (DMD).[1] Although the yields by this process were often excellent, they were not always reproducible and thus another oxidation method was sought. Eventually it was found that the methyltrioxorhenium/urea hydrogen peroxide (MTO/UHP) system of Goti[3] and Murray,[4] a catalytic oxidant with chemistry similar to DMD, gave yields of **2** that are consistently in the 70–80% range on a multi-gram scale (Scheme 1). The optical purity of **2** produced by this method was in excellent agreement with that previously obtained.[5]

Anticipating some specific applications of this nitrone cycloaddition methodology that would involve reaction with styrene derivatives, the cycloaddition of **2** with styrene itself was studied in some detail. Thus, reaction of styrene with nitrone **2** in chloroform for 3 hours at reflux led to a 73% yield of a 10/1 mixture of cycloadducts ***3exo*** and ***3endo***. When conducted at room temperature, the isomer ratio was essentially unchanged although the reaction took several days to go to completion. The stereochemistry of the major cycloadduct was anticipated based on the expectation of reaction occurring at the less hindered α-face of nitrone **2**. The further expectation that the phenyl group would adopt an *exo* orientation was based on our previous studies of nitrone **2** with other monosubstituted alkenes as well as results from the cycloaddition of other styrene derivatives with cyclic nitrones.[1,6] The structure of the minor cycloadduct was assumed to be as indicated, with the phenyl group in an *endo* orientation, an assumption that was verified subsequently with other cycloadducts.

Cycloadducts ***3exo*** and ***3endo***, each with three bonds susceptible to hydrogenolysis conditions (N–O, benzylic N and O), are well suited for conversion to



Scheme 1.

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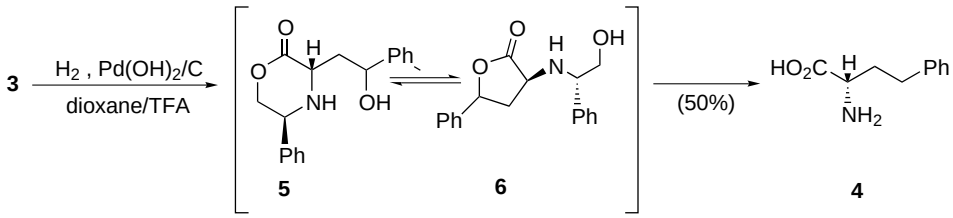
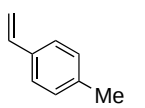
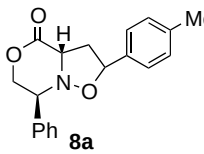
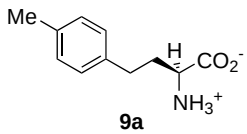
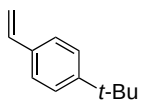
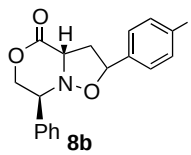
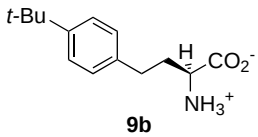
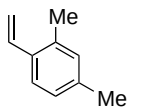
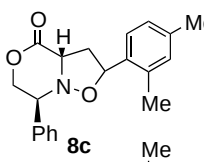
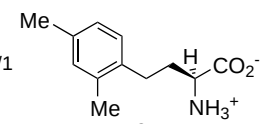
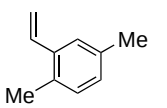
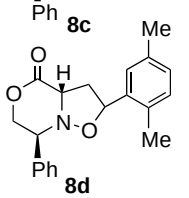
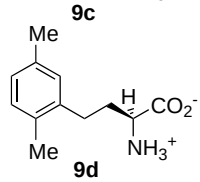
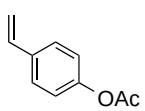
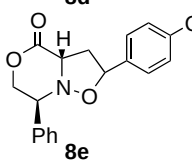
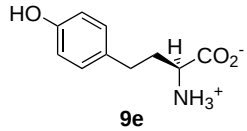
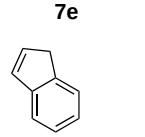
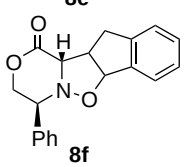
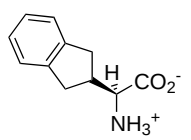
homophenylalanine (**4**). Thus, hydrogenolysis (60 psi) of **3** in the presence of Pearlman's catalyst in a dioxane–trifluoroacetic acid (10/1) solvent system afforded pure homophenylalanine in 50% yield after trituration with ether (Scheme 2). Alternatively, pure homophenylalanine could be obtained by ion-exchange chromatography of the crude product. The specific rotation of the crude product ($[\alpha]_D = +41°$) was in good agreement with the literature value for the (*S*) enantiomer ($[\alpha]_D = +45°$),[7] confirming that the cycloaddition reaction had indeed occurred from the less hindered α face of nitrone **2**. Based on our earlier work, including the isolation of intermediates along the reaction pathway, the one-pot conversion of cycloadducts **3** to homophenylalanine (**4**) under the indicated hydrogenolysis conditions is thought to proceed as indicated, with initial N–O cleav-



Scheme 2.

Table 1. Isoxazolidine **8a–f** and homophenylalanine derivatives **9a–f** produced from substituted styrenes and **2**

styrene	cycloadduct[a]	yield[b]; *exo/endo*[c]	substituted homophenylalanine	yield; $[\alpha]_D$; mp (°C)
 **7a**	 **8a**	71%; 10/1	 **9a**	50%; +51° (c=0.17, 1N HCl); 285-95° (HCl salt)
 **7b**	 **8b**	85%; 7/1	 **9b**	74%; +31° (c=0.20, MeOH); 232-34°
 **7c**	 **8c**	49%; >20/1	 **9c**	49%; +37° (c=0.19, MeOH); 220-226° (HCl salt)
 **7d**	 **8d**	55%; 5/1	 **9d**	27%; +33° (c=0.18, MeOH); 227-232° (HCl salt)
 **7e**	 **8e**	84%; 5/1	 **9e**	45%; +34° (c=0.11, 1N HCl); 215-220° (dec)
 **7f**	 **8f**	70%; 10/1	 **9f**	54%; +28° (c=0.20, 1N HCl); 225° (dec)

[a]Reactions were performed with 1.5 - 5 eq. styrene in $CHCl_3$ at reflux for 3 - 5 hours.

[b]Combined yields (unoptimized) of *exo* and *endo* isomers isolated chromatographically.

[c]Determined by integration of ^1H NMR spectra of unpurified reaction mixture.

age followed by rapid translactonization to give γ-lactone **6**. This lactone can be isolated under different hydrogenolysis conditions.[8] Conversion of **6** to homophenylalanine (**4**) then involves cleavage of the remaining benzylic oxygen and nitrogen bonds.

The cycloaddition/hydrogenolysis protocols also work well for other styrene derivatives. Table 1 summarizes the results of cycloadditions of nitrone **2** with a total of six additional styrene compounds **7a**–**f**. The unoptimized yields of purified products for these reactions ranged from 49 to 85% with *exo*/*endo* isomer ratios ranging from a low of 5/1 (**8d** and **8e**) to essentially all *exo* (**8c**). The *exo*/*endo* stereochemical assignments of cycloadducts **8** were verified by their ^{1}H and ^{13}C NMR spectra, including NOE experiments.

As summarized in Table 1, exposure of the cycloadducts **8** to the hydrogenolysis protocol described previously afforded the corresponding α-amino acids in a single operation. This represents a particularly facile preparation of these novel materials. All optically active homophenylalanine derivatives except homotyrosine (**9e**)[9] are new compounds.[10,11]

A further demonstration that the two cycloadduct isomers **8** are *endo*/*exo* isomers rather than the result of poor nitrone facial selectivity was seen in the hydrogenolysis of cycloadduct **8b**, derived from 4-*tert*-butylstyrene. Hydrogenolysis of the pure major stereoisomer of **8b** (*exo*) afforded crude α-amino acid **9b** that exhibited a specific rotation of +25°. The specific rotation of the crude α-amino acid derived from hydrogenolysis of a 1/1 mixture of the isomeric **8b** cycloadducts (*exo* and *endo*) was +29°. Had the two stereoisomers been the result of different nitrone facial selectivity in the cycloaddition reaction the specific rotation of this product would have approached zero. The specific rotation of purified **9b** is +31°.

These results demonstrate the value of nitrone **2** for the formation of uncommon derivatives of homophenylalanine. Cycloaddition with various styrene derivatives followed by one-step hydrogenolysis affords novel optically pure α-amino acids in a total of two synthetic operations. Further application of the method to other types of targets will be reported subsequently.

Acknowledgements

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5. After our initial development work was completed, nitrone **2** was prepared by an alternative synthesis and several cycloaddition reactions were reported. (a) Tamura, O.; Gotanda, K.; Terashima, R.; Kikuchi, M.; Miyawaki, T.; Sakamoto, M. *Chem. Commun*. **1996**, 1861; (b) Tamura, O.; Kuroki, T.; Sakai, Y.; Takizawa, J.; Yoshino, J.; Morita, Y.; Mita, N.; Gotanda, K.; Sakamoto, M. *Tetrahedron Lett*. **1999**, *40*, 895; (c) Tamura, O.; Gotanda, K.; Yoshino, J.; Mirita, Y.; Terashima, R.; Mayumi, K.; Miyaweaki, T.; Mita, N.; Yamashita, M.; Ishibashi, H.; Sakamoto, M. *J. Org. Chem*. **2000**, *65*, 8544–8551.
6. Tufariello, J.; Ali, A. *Tetrahedron Lett*. **1978**, 4647.
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8. Treatment of styrene adduct **3*exo*** with Zn/HOAc afforded lactone **6** as the acetate, hydrolysis of which (K_2CO_3/MeOH) afforded pure **6** (*cis*). Exposure of **6** to hydrogen (60 psi; Pearlman's catalyst) in dioxane–TFA (10/1) and isolation as before then afforded homophenylalanine (**4**).
9. (a) Zambias, R. A.; Hammond, M. L.; Heck, J. V.; Bartizal, K.; Trainor, C.; Abruzzo, G.; Schmatz, D. M.; Nolstadt, K. M. *J. Med. Chem*. **1992**, *35*, 2843; (b) Melillo, D. G.; Lawsen, R. D.; Mathre, D. J.; Shukis, W. F.; Wood, A. W.; Collelvori, J. R. *J. Org. Chem*. **1987**, *52*, 5143.
10. The structures of all compounds reported in this work were confirmed by ^{1}H and ^{13}C NMR, mass spectrometry and IR where appropriate. Suitably purified samples of nitrone **2**, all new homoaromatic α-amino acids, and selected cycloadducts also exhibited consistent high resolution mass spectral data for their molecular ions.
11. Racemic **9a** has been previously described and racemic **9c** mentioned in the following reference: Oldfield, M. F.; Bennett, R. N.; Kiddle, G.; Wallsgrove, R. M.; Botting, N. P. *Plant Physiol. Biochem*. **1999**, *37*, 99.