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A New Synthesis of *p*-Hydroxy Phenylglycine and Some Analogues from *p*-Benzoquinone

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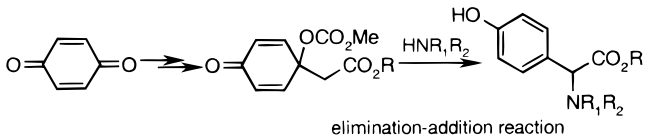
ABSTRACT



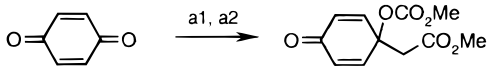
A new route to *p*-hydroxy phenylglycine and *N*-substituted analogues has been developed starting from *p*-benzoquinone. 1,2-Addition of methyl lithioacetate to *p*-benzoquinone and subsequent quenching of the oxygen anion with methyl chloroformate, followed by an elimination–addition reaction with an appropriate amine, resulted in the desired amino acid derivatives. A diastereoselectivity of 60% was achieved using 8-phenylmenthyl acetate as the chiral auxiliary.

D-(−)-2-(*p*-Hydroxyphenyl)glycine (HPG) is an important intermediate in the synthesis of the life-saving semisynthetic antibiotics amoxicillin and cefadroxil. The preparation of the racemic compound has been achieved using different approaches involving the Strecker synthesis,[1] the hydantoin route[2] and the ammonolysis of *p*-hydroxymandelic acid, obtained by the condensation of phenol and glyoxilic acid.[3] Both the hydantoin approach and the *p*-hydroxymandelic acid route involve an electrophilic addition reaction on phenol. A serious problem in this electrophilic addition reaction is the formation of a mixture of *ortho*- and *para*-substituted product due to the activation of both the *ortho* and the *para* positions by the electron-donating effect of the OH group. The Strecker approach has as drawback that it requires the expensive *p*-hydroxy benzaldehyde as a starting material.

In this paper we report a new synthetic route to HPG, starting from inexpensive *p*-benzoquinone. In this route the *ortho/para* problem is circumvented, because the *para* arrangement is already present in the starting material. Our strategy involves functionalization of one carbonyl group in *p*-benzoquinone, which then leads to exclusive formation of *para*-substituted product.

The first step of this synthesis is a 1,2-addition of methyl lithioacetate to benzoquinone[4] and subsequent quenching of the oxygen anion with methyl chloroformate to give **2** in 94% yield (Scheme 1).

Scheme 1. 1,2-Addition of Methyl Lithioacetate to *p*-Benzoquinone and Quenching with Methyl Chloroformate



1 **2**

a1. MeOAc, LDA, THF, -78°C. a2. $ClCO_2Me$, -78 °C → 0°C, 94%.

The key step is the base-induced β-elimination of the carbonate group leading to intermediate **3**, followed by a nucleophilic addition to the α-carbon atom (Scheme 2).

Quinone methide compound **3** is a highly reactive species, as it escapes isolation under the conditions of the reaction.

(1) Steiger, R. E. *Organic Synthesis Collective Volume 3*; John Wiley and Sons: New York, 1955; p 84.
(2) Greenstein, J. P.; Winitz, M. *Chemistry of the Amino Acids*; John Wiley and Sons: New York, 1961; p 700.
(3) Powar, N. P.; Chandalia, S. B. *J. Chem. Tech. Biotechnol.* **1989**, *46*, 219.
(4) Fischer, A.; Henderson, G. N. *Tetrahedron Lett.* **1983**, *24*, 131.

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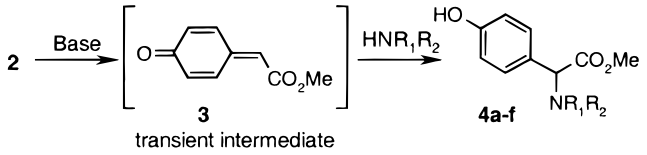
Scheme 2. Elimination−Addition Reaction



Even after the addition of a nonnucleophilic base and in the absence of potential nucleophiles, **3** could not be isolated. A one-pot approach in THF as the solvent, in which the reactive intermediate **3** is trapped with an amine in an elimination−addition reaction, proved to be very successful. Six different amines have been introduced using this procedure, as summarized in Table 1.

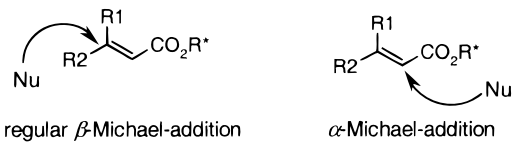
Table 1. Results of the One-Pot Elimination−Addition Reaction Using Six Different Amines

entry	R_1	R_2	equiv	base	yield (%)
a	H	H	excess	NH_3	80−90
b	CH_2Ph	H	10	DBU	95
c	$(CH_2)_3CH_3$	H	10	DBU	100
d	C_6H_{11}	H	10	DBU	99
e	$C(CH_3)_3$	H	10	DBU	92
f	piperidine		10	DBU	87

For the synthesis of HPG (entry a), **2** was dissolved in THF and added to liquid ammonia at −30 °C. The presence of THF appeared to be essential, because in its absence no addition product was formed. Apparently, THF is beneficial for the nucleophilicity of the amine. In the synthesis of **4a** no additional base was required to eliminate the carbonate group. The reactions with benzylamine, *n*-butylamine, cyclohexylamine, *tert*-butylamine, and piperidine (entries b−f) were performed at 0 °C with 10 equiv of the amines and required a small amount of DBU (5−10 mol %) as a catalyst to initiate the elimination of the carbonate group. These elimination−addition reactions went to completion in a few hours in very high yield. Using a lesser amount of amine, e.g., 5 equiv, resulted in a minor decrease in the yield of the corresponding addition products, whereas less than 3 equiv resulted in a substantial decrease.

In addition to the abovementioned synthesis of **4**, we also studied the diastereoselectivity in this elimination−addition reaction using a chiral acetate ester. It should be noted that this is a special case of the Michael addition reaction (Scheme 3). In a regular Michael addition, the nucleophile

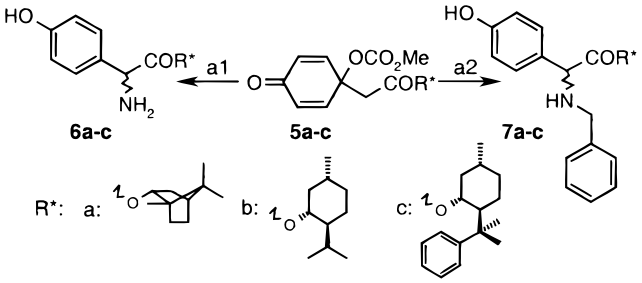
Scheme 3. α-Michael Addition vs β-Michael Addition



"attacks" at the β-position with respect to the chiral auxiliary. In our case, however, the nucleophile comes in at the α-position, implying that the chiral auxiliary is even closer to the reaction center (Scheme 3).

This anomalous behavior can be attributed to the electron-withdrawing effect of the dienone functionality, resulting in an electron deficiency at the α-carbon atom. A nucleophilic attack at this carbon atom results in aromatization of the dienone group, which explains the high reactivity of intermediate **3**. To study the diastereoselectivity, esters derived from three different chiral alcohols have been investigated as chiral auxiliaries (Scheme 4). The syntheses of **5a**−**c** were

Scheme 4. Elimination−Addition Reaction Using Chiral Auxiliaries



	yield (%)	de (%)*
6a	55	0
6b	40	15-20
6c	57	60
7a	90	0
7b	90	15-20
7c	90	60

* Determined by ^{1}H NMR.

a1. Ammonia, THF, -30 °C. a2. Benzylamine, THF, DBU, 0 °C.

performed in a manner analogous to the sequence shown in Scheme 1, using the corresponding acetate derived from the chiral auxiliaries **a**−**c** in the 1,2-nucleophilic addition reaction to *p*-benzoquinone (yields 80−90%). Two different nucleophiles have been studied in the elimination−addition reaction, i.e., ammonia and benzylamine. The reactions were performed under the same conditions as described above. The reactions with ammonia, however, required considerable longer reaction times, up to 10 h. The results are summarized in Scheme 4. The bornyl group (a) did not show any diastereoselectivity, which is in line with the rather poor inducting capabilitiy of this group. The menthyl group (b), however, gave a diastereoselectivity of 15−20%. In this study, the best results were obtained using the 8-phenylmenthyl group (c) as a chiral auxiliary. The shielding effect of the additional phenyl group apparently is quite effective, resulting in a diastereoselectivity of 60%. Fine-tuning of the chiral auxiliary might result in a further improvement of the diastereoselectivity, which is currently under investigation.

Benzylamine appeared to be a very effective nucleophile. The yields of the addition products were in all cases very high. However, the addition of ammonia was less effective as a result of its poor nucleophilicity.

In summary, a new synthesis of *p*-hydroxy phenylglycine from the inexpensive *p*-benzoquinone has been developed, in which the well-known *ortho/para* problem is circumvented. A de up to 60% was achieved using different kinds of chiral auxiliaries.

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Supporting Information Available: ^{1}H NMR spectra of compounds **2**, **4a**−**f**, **5a**−**c**, **6a**−**c**, and **7a**−**c**. This information is available free of charge via the Internet at http://pubs.acs.org.

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