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Highly diastereoselective nitroaldol reactions with chiral derivatives of glyoxylic acid

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Abstract—N-Glyoxyloyl-(2R)-bornane-10,2-sultam (1a) and (1R)-8-phenylmenthyl glyoxylate (1b) react stereoselectively with simple nitroalkanes giving diastereomeric nitroalcohols with high asymmetric induction. The glyoximide 1a is proved to be a highly efficient chiral inducer, superior to glyoxylate 1b. In all cases, the absolute configuration (2S) and relative configuration, *syn* for the major diastereoisomers, were confirmed. © 2003 Published by Elsevier Ltd.

The nitroaldol addition (Henry reaction) is one of the basic methods for the construction of carbon-carbon bonds.¹ The nitroalcohols formed in this process offer an easy access to a variety of numerous intermediates (2-aminoalcohols, 2-nitroketones, nitroalkenes etc.),²⁻⁴ useful in the synthesis of biologically important compounds.^{5,6} Currently, there is a substantial interest in development of a stereocontrolled version of the Henry reaction. The chiral-pool approach has been widely investigated,^{7,8} however, particular attention was paid to application of chiral catalysts, providing nitroalcohols in good yield and with high enantioselectivity.⁹⁻¹¹ On the other hand, there are in the literature only two examples of the stereoselective Henry reaction using substrates containing a chiral auxiliary, (1R)-8phenylmenthol.12

In the course of our search for the synthetic applications of chiral derivatives of α -oxoacids, we have synthesized *N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam (1a)¹³ and examined its applicability in a number of diastereoselective reactions.¹⁴ High asymmetric induction obtained during these studies prompted us to extend our investigations on addition of 1a to nitromethane (2) and two other simple nitro compounds of type 3, and to compare the efficiency of 1a with that of the glyoxylic ester of (1R)-8-phenylmenthol (1b) (Scheme 1). The latter chiral auxiliary has been proved to be very effective in many other processes, especially in the aldol condensation which is similar to the Henry reaction.¹⁵



Scheme 1.

Keywords: nitroalcohols; nitroaldol reaction; asymmetric induction; chiral auxiliary.

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Initial investigations on the reaction of **1a** with nitromethane, carried out under conditions described by Solladié-Cavallo et al.¹² for glyoxalate **1b** completely failed giving only products of splitting of the bornane-10,2-sultam. Owing to this result we excluded potassium fluoride—a common mediator of the nitroaldol reaction. To overcome this problem, we resolved to check two other procedures using neutral Al_2O_3 (method A) or tetrabutylammonium fluoride trihydrate (TBAF·3H₂O, method B). The results of these preliminary studies are summarized in Table 1.

Only moderate yields were obtained for the reactions of **1a** with **2**, promoted by both Al_2O_3 and TBAF·3H₂O (Table 1, entry 1, Method A, and entry 3, Method B, respectively); substantial amounts of the sultam auxiliary were found in the reaction mixtures. In order to improve the reaction yields we decided to use Al_2O_3 activated by heating at 120°C under reduced pressure (Method A') and anhydrous TBAF dried at 80°C in

vacuum (Method B'). Indeed, we obtained much better yields for the reactions under investigation (entries 2 and 4). Similar results were observed for the reactions of **1b** (entries 5–8). As far as the diastereoselectivity is concerned, we found that the (2R)-bornane-10,2-sultam is a more efficient chiral auxiliary compared to (1R)-8phenylmenthol; the best asymmetric induction was obtained with TBAF as the reaction promoter (entries 3 and 4).

At the next stage of our studies, we decided to use two other nitro compounds, namely 1-nitrohexane (**3a**) and 2-nitroacetaldehyde diethyl acetal (**3b**), which in the reactions with **1a** and **1b** formed four diastereoisomeric nitroalcohols (Scheme 1, Table 2).

Similarly to the reactions of 1a or 1b with 2 (Table 1), the yields of reactions of 3a and 3b were higher when activated catalysts were applied (Table 2, Methods A' and B'). As regards stereoselectivity, we often observed

Table 1. Reactions of chiral aldehydes 1a and 1b with nitromethane (2)

Entry	Aldehyde	Method ^a	Time (h)	Yield ^{b,c} (%)	Diastereoisomeric ratio ^d 4:5
1	1a	А	48	30	83:17
2	1a	\mathbf{A}'	4	80	77:23
3	1a	В	2	38	97:3
4	1a	\mathbf{B}'	8	50	98:2
5	1b	А	17	78	85:15
6	1b	\mathbf{A}'	24	90	73:27
7	1b	В	5.5	43	53:47
8	1b	\mathbf{B}'	2.5	86	75:25

^a Method A: 3 equiv. of neutral Al₂O₃, 1.5 equiv. of nitromethane, THF, rt; Method A': 3 equiv. of activated Al₂O₃ used; Method B: 0.5 equiv. of TBAF·3H₂O, 1.5 equiv. of nitromethane, THF, -78° C; Method B': 0.5 equiv. of anhydrous TBAF used.

^b Yields are given for isolated products.

^c All new products were fully characterized.

^d Calculated by HPLC analysis and ¹H NMR.

Table 2. Reactions of chiral aldehydes 1a and 1b with nitro compounds 3a and 3b

Entry	Aldehyde	Nitro compound	Method ^a used	Time (h)	Yield ^{b,c} (%)	Diastereoisomeric ratio ^d 6:7:8:9
1	1a	3a	А	26	5	74:26:0:0
2	1a	3a	A'	8	93	68:14:12:6
3	1a	3a	В	2	29	90:10:0:0
4	1a	3a	\mathbf{B}'	2.5	58	51:35:7:7
5	1b	3a	А	17	60	62:22:10:6
6	1b	3a	\mathbf{A}'	24	85	58:24:12:6
7	1b	3a	В	22	43	34:30:24:12
8	1b	3a	Β'	1	90	33:28:23:16
9	1a	3b	А	26	0	_
10	1a	3b	\mathbf{A}'	1	78	64:16:15:5
11	1a	3b	В	5	45	100:0:0:0
12	1a	3b	\mathbf{B}'	2.5	80	100:0:0:0
13	1b	3b	А	17	39	88:7:5:0
14	1b	3b	\mathbf{A}'	6	96	68:21:8:3
15	1b	3b	В	2	47	62:17:15:6
16	1b	3b	\mathbf{B}'	1	64	66:24:10:0

^a Method A: 3 equiv. of neutral Al₂O₃, 1.5 equiv. of nitro compound, THF, rt; Method A': 3 equiv. of activated Al₂O₃ used; Method B: 0.5 equiv.

of TBAF·3H₂O, 1.5 equiv. of nitro compound, THF, -78°C; Method B': 0.5 equiv. of anhydrous TBAF used.

^b Yields are given for isolated products.

^c All new products were fully characterized by ¹H, ¹³C NMR, IR, ESI MS, and elemental analysis.

^d Calculated by HPLC analysis and ¹H NMR.

formation of the four possible diastereoisomers; in most cases, we were able to separate them, isolate them in a chromatographically pure form and characterize them. The best results were obtained for the reaction of glyoximide **1a** with **3b**, when a single diastereoisomer was formed (Table 2, entry 11, Method B, and entry 12, Method B', respectively). In general, the use of **1a**, as compared with **1b**, led to better stereochemical results, however, in both cases, the use of activated Al_2O_3 and anhydrous TBAF decreased slightly the sterereoselectivity (e.g. entries 3, 4, 13, and 14).

The configurational assignments for the diastereomeric nitroalcohols were made using various analytical and spectral methods, including X-ray analysis and NOE measurements; chemical correlations were also performed. All these results will be presented in detail in a full paper. On the basis of the above-mentioned analyses, we found that, in all cases, the major diastereoisomers **4** and **6** possess the (2S) absolute configuration at the hydroxylic stereogenic center. The relative configuration of nitro and hydroxy groups is *syn* for all major diastereoisomers **6**, in contrary to the *anti* configuration found in products obtained via the chiral-pool approach. Thus, our methodology seems to be complementary to the chiral pool as concerns relative configuration of newly created stereogenic centers.

In summary, we have shown that the derivative of glyoxylic acid bearing (2R)-bornane-10,2-sultam as a chiral auxiliary is a very convenient substrate for the preparation of optically pure nitroalcohols that could be used as starting materials in the synthesis of various natural products.

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