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LETTERS

Influence of the Chiral Auxiliary on the Stereoselectivity of the $S_{RN}1$ *C*-Alkylation of 2-Nitropropionate Anions

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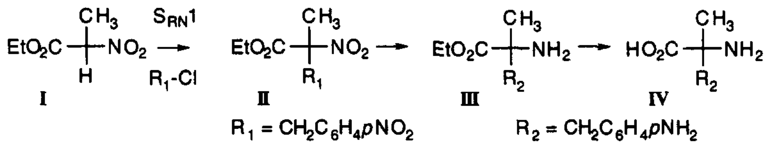
Abstract : A series of carbohydrate-derived 2-nitropropionate anions was reacted with *p*-nitrobenzyl chloride under $S_{RN}1$ reactions conditions, the diastereomeric ratios were moderate, but increased when the carbohydrate moiety was replaced by the more bulky 8-phenylmenthol. © 1999 Elsevier Science Ltd. All rights reserved.

We have recently described[1] an efficient method for the synthesis of $C^{\alpha\alpha}$-unsymmetrically disubstituted nitroesters by electron transfer *C*-alkylation of ethyl 2-nitropropionate anion. To demonstrate the utility of the method, the nitroester **II** obtained from $S_{RN}1$ reaction of **I** with *p*-nitrobenzyl chloride, was transformed into 2-(±)-amino-3-(4-aminophenyl)-2-methylpropionic acid **IV**. The synthetic potential of this reaction is now extended even further in the synthesis of optically pure aminoacids.



To this goal, we first have screened a series of easily accessible chiral auxiliaries **1a-e** derived from carbohydrates (**1a** from D-arabinose[2], **1b-c** from D-fructose[3,4], **1d-e** from D-glucose[5]). The bromoesters **2** were obtained as a mixture of diastereomers by reaction of **1** with racemic 2-bromopropanoic bromide. By the Kornblum procedure[6] the nitro esters **3** were obtained and then submitted to the $S_{RN}1$ reaction with *p*-nitrobenzyl chloride. The *C*-alkylation products **4a-f** were isolated in good to moderate yields as a mixture of diastereomers. The diastereomeric ratios (*dr*) were determined by ^1H NMR. As no asymmetric induction occurred with **3a**, we decided to increase the bulkiness at the anomeric position of the carbohydrate. With the spiro sugars **1b-c** easily accessible from cheap D-fructose the *dr* was increased to 60:40 and the diastereomers of the alkylated products were easily separable. To try to understand the role of the nature of the substituents adjacent to the carbon bearing the nitropropionate, we synthetized the two isomeric 2-*O* and 3-*O*-benzylethers of the methyl 4,6-*O*-benzylidene-α-D-glucopyranoside by the stannylene method[5] but the *dr* was always 60:40.

As 8-phenylmenthol has been successfully used as chiral auxiliary for radical[7] and ionic[8] alkylations of malonic-type derivatives, we anticipate that the anion of the nitroester **3f** will react with the *p*-nitrobenzyl radical with high diastereoselectivity. At room temperature the *dr* was 80:20, at lower temperatures either the reaction was inhibited (-40 °C) or S_N2 *O*-alkylation became preponderant (0 °C).

Therefore, based on these findings, the design of new chiral auxiliaries was envisaged to reach high levels of induction. The camphor-derived alcohol **1g** was synthetized, nevertheless it has been impossible to prepare the corresponding bromoester **2g**.

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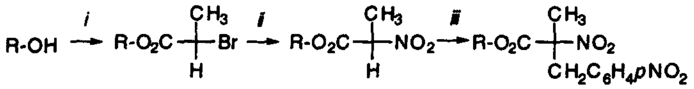
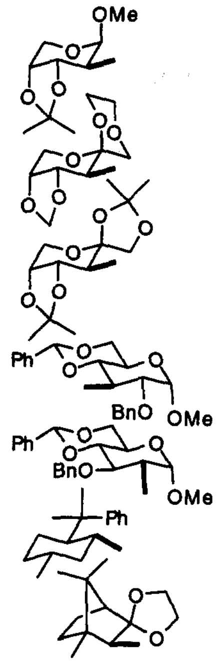


$$R\text{-}OH \xrightarrow{i} R\text{-}O_2C\text{-}C(CH_3)(H)\text{-}Br \xrightarrow{ii} R\text{-}O_2C\text{-}C(CH_3)(H)\text{-}NO_2 \xrightarrow{iii} R\text{-}O_2C\text{-}C(CH_3)(NO_2)\text{-}CH_2C_6H_4pNO_2$$

1a-g **2a-f** **3a-f** **4a-f**



entry	R—	(i) yield	(ii) yield	(iii) yield - diastereomeric ratio
a		82%	55%	87% - 50:50
b		97%	50%	50% - 60:40*
c		96%	70%	51% - 60:40*
d		58%	32%	84% - 60:40
e		85%	40%	86% - 62:38
f		97%	80%	22% - 80:20**
g		0%	-	-

i: $CH_3CHBrCOBr$, CH_2Cl_2, Py, -5°C->RT, 2 h; *ii*: $NaNO_2$, phloroglucinol, DMF, RT, 2 h;
iii: $ClCH_2\text{-}C_6H_4\text{-}p\text{-}NO_2$, NaH, DMF, 150 Watt sun lamp, RT, 1 h; *see ref 1 for exp. details.*
* *Separated by semi-prep. HPLC on SiO_2, **4b**: mp 161°C and 113°C, **4c**: mp 96°C and 88°C.*
** *The newly created asymmetric carbon is S in the major isomer, see ref 8 for a discussion.*

In conclusion, we have tested the ability of six chiral alcohols for the asymmetric induction in the $S_{RN}1$ reaction of *p*-nitrobenzyl chloride and 2-nitropropionate anions. The *dr* was not very high, but in the case of **4b** and **4c** the diastereomers were easily separated. As there is only one example of asymmetric induction in the litterature[9] ($S_{RN}1$ reaction of a chiral amide enolate and the radical from 1-iodonaphthalene), the design of efficient other chiral alcohols with bulky substituents on the adjacent carbon (camphor-derived auxiliaries) is now in progress for $S_{RN}1$ synthesis of enantiomerically pure disubstituted aminoacids.

References

1 Béraud, V.; Perfetti, P.; Pfister, C.; Kaafarani, M.; Vanelle, P.; Crozet, M. P. *Tetrahedron* **1998**, *54*, 4923-4934.
2 Paquette, L. A.; Bailey, S. *J. Org. Chem.* **1995**, *60*, 7849-7856.
3 Nouguier, R.; Mignon, V.; Gras, J.-L. *J. Org. Chem.* **1999**, *64*, 1412-14.
4 Mio, S.; Kumagawa, Y.; Sugai, S. *Tetrahedron* **1991**, *47*, 2133-2144.
5 Jenkins, D.; Dubreuil, D; Potter, B. *J. Chem. Soc. Perkin Trans.1* **1996**, 1365-1372.
6 Kornblum, N.; Blackwood, R.; Powers, J. *J. Am. Chem. Soc.* **1957**, *79*, 2507-2515.
7 Hamon, D.; Massy-Westropp, R.; Razzino, P. *Tetrahedron* **1995**, *51*, 4183-4194.
8 Ihara, M.; Takahashi, M.; Tanigushi, N.; Yasui, K.; Niitsuma, H.; Fukumoto, K. *J. Chem. Soc. Perkin Trans 1.* **1991**, 525-535.
9 Lotz, G.; Palacios, S.; Rossi, R. *Tetrahedron Lett.* **1994**, *35*, 7711-7714.