Pergamon

Tetrahedron Letters, Vol. 35, No. 43, pp. 8037-8040, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01729-8

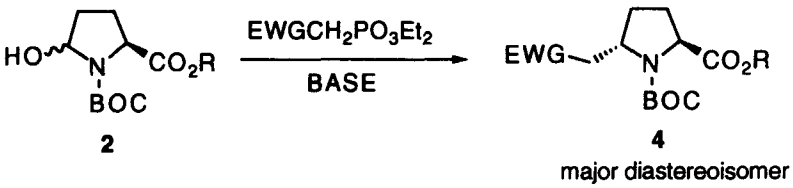
Diastereoselective Functionalization of 5-Hydroxy Prolinates by Tandem Horner-Emmons-Michael Reaction

Ivan Collado[a], Jesús Ezquerra[a], Juan José Vaquero[b] and Concepción Pedregal[a]*

[a] Centro de Investigación Lilly, S. A. Paraje de la Cruz s/n, 28130 Valdeolmos, Madrid, Spain.
[b] Departamento de Química Orgánica, Universidad de Alcalá, 28871 Alcalá de Henares, Madrid, Spain.

Abstract: The tandem Horner-Emmons-Michael reaction of the hemiaminal derived from *N*-BOC protected pyroglutamic esters with stabilised phosphonates gives 5-substituted prolinates in high diastereomeric and enantiomeric excess through a 1,4-asymmetric induction process.

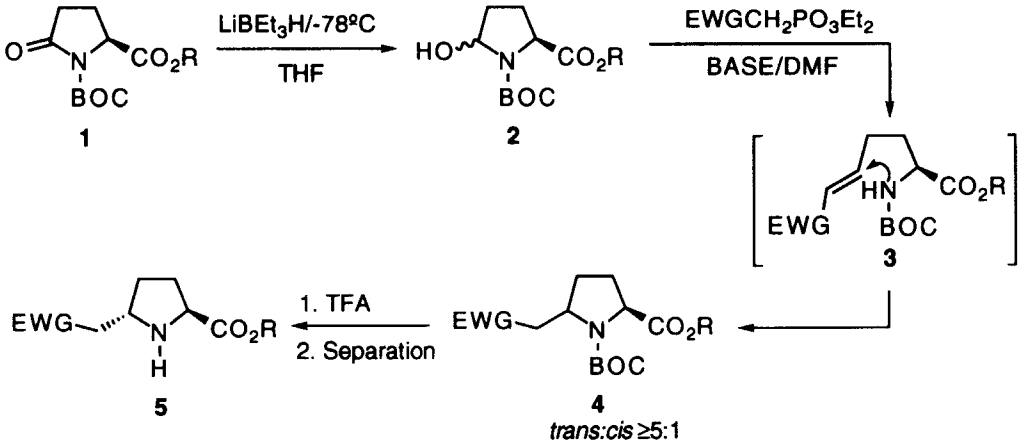
The diastereoselective synthesis of 5-substituted prolines has usually been accomplished by nucleophilic attack on *N*-acyliminium ions,[1] reduction of the corresponding cyclic imines[2] or by mesylate displacement from a suitable substituted α-amino acid.[3] While the reduction of prolinate derived imines provides the *cis* relationship between the two substituents, the other methods are preferred for the *trans* selectivity. In this paper, we would like to report a new stereoselective route to 5-substituted prolinates **4** based on the Horner-Emmons-Michael tandem reaction of the hemiaminal **2** with different phosphonates (Scheme 1) as an alternative means for introducing carbon-functional groups in a stereoselective fashion.



Scheme 1

The olefination of α-hydroxypyrrolidines *via* Wittig[4] or Horner-Emmons[5] reactions is known in the literature. Further intramolecular Michael 5-*exo*-*trig*[6] cyclisation gives rise to α-substituted pyrrolidines. When using chiral substrates,[5] high 1,2-asymmetric induction has been achieved in this two step procedure but the tandem version of these reactions turned out not to be diastereoselective. We have found good 1,4-asymmetric induction in a Horner-Emmons-Michael tandem reaction of **2** with stabilised phosphonates.

N-Boc-pyroglutamate **1** (Scheme 2) was prepared from L-glutamic acid following standard procedures[7] and reduction of the amide carbonyl group, to produce **2**, was accomplished with $LiBEt_3H$[8] in THF at -78°C in 99% yield.



Scheme 2

Several stabilised phosphonates with different electron withdrawing groups (EWG), were reacted with **2**, whilst varying the reaction conditions (one pot or stepwise reaction, the influence of the R group bulkiness and the choice of base on the stereochemical reaction outcome). Results are summarised in Table 1.

Reaction of the hemiaminal **2** in DMF with several stabilised phosphonates at room temperature proceeded in good yields[9] giving rise to prolinates **4** with good degree of stereocontrol (*trans:cis* ratio ≥5:1).

When the reaction was performed at 0°C for one hour, in an attempt to isolate the intermediate olefin, it was possible to identify a mixture of unreacted **2** together with olefin **3**[10] and cyclised isomers **4** by ^{1}H-NMR analysis of the reaction crude mixture. This result is in contrast with those previously found[5] where it was possible to isolate the intermediate olefin, showing that in our case the intramolecular Michael cyclization is very favoured and the overall transformation is a real tandem process.

The ester group present on **2** was shown to have an effect on the stereochemical reaction outcome. Thus, the diastereomeric ratio of prolinates **4** increases with the bulkiness of the ester group (Me< Et< *tert*-Bu, Table 1, entries a, c, g) using the same base and EWG moiety. The same steric effect is observed with the bulkiness of the ester group present in the phosphonate (Table 1, compare entries a, g with b and i respectively).

The nature of the base used to generate the anion of the phosphonate also influenced the reaction, since the use of KH compared with NaH, gave higher diastereoselectivity as previously observed[5] (Table 1, entries c-e, g).

Finally, the nature of the electron withdrawing group of the reacting phosphonate also affected the stereochemical reaction outcome (table 1, entries c-f). The reaction diastereoselectivity is dependent on the electrophilicity of the intermediate olefin **3**. Thus, for the same base and ester group on the substrate, the best

diastereoselectivity (de ≥ 76%) was achieved when CH_3CO was the EWG group on the phosphonate and the worst with PO_3Et_2 (de ≥ 43%).

All the effects are additive since when the *tert*-butyl ester derivative **2** was reacted with the *tert*-butyl-diethyl phosphonoacetate and KH as base the best diastereomer ratio was obtained 17:1 (de ≥ 88%)(entry i).

Table 1

Entry	R	EWG	Base	4 % yield[a,b]	5 %yield[c]	5 $[\alpha]_{D25}$
a	CH_3	$CO_2C_2H_5$	NaH	75 (4.5:1)	78	-17.9 (c = 1.45, $CHCl_3$)
b	CH_3	$CO_2C(CH_3)_3$	NaH	77 (6:1)	77	-17.2 (c = 1.35, $CHCl_3$)
c	C_2H_5	$CO_2C_2H_5$	NaH KH	81 (5:1) 72 (8:1)	74 79	-18.0 (c = 1, $CHCl_3$)
d	C_2H_5	CN	NaH KH	73 (5:1) 82 (8:1)	64 68	-28.4 (c = 1, CH_2Cl_2)
e	C_2H_5	$COCH_3$	NaH KH	69 (7.5:1) 82 (8.5:1)	86[d,e]	
f	C_2H_5	$PO(OC_2H_5)_2$	NaH	81 (2.5:1)	85[d]	
g	$C(CH_3)_3$	$CO_2C_2H_5$	NaH KH	79 (7:1) 91 (9:1)	60 62	-16.4 (c = 0.67, $CHCl_3$)
h	$C(CH_3)_3$	$COCH_3$	KH	85 (10:1)	88[d,e]	
i	$C(CH_3)_3$	$CO_2C(CH_3)_3$	KH	83 (17:1)	46	-19.3 (c=1.90, $CHCl_3$)

[a] In brackets *trans:cis* ratio. This ratio was obtained by ^{1}H-NMR analysis after the Boc was removed from the crude reaction product. [b] A mixture of conformers of the *N-tert*-Butoxycarbonyl group in the NMR spectra can be observed[11] making direct measurement of the diastereomeric mixture difficult. [c] Isolated yield after separation of the *cis* diastereoisomer. [d] Diastereoisomers could not be separated by chromatography. [e] Products epimerised on standing and on column chromatography.

Both optical purity and absolute stereochemistry were checked for compound **5a**, by comparison with the literature value for the same compound prepared by an independent route. This compound is an intermediate in the synthesis of *trans*-carbapenam-3-carboxylic acid, ($[\alpha]_D$ = -18.75 (c =1.52, $CHCl_3$)).[12]

In summary, the presented tandem Horner-Emmons-Michael reaction represents a highly stereoselective approach for the synthesis of 5-substituted prolinates. Further studies of this novel process are in progress.

ACKNOWLEDGEMENTS: This research was supported by the Spanish **FARMA II** programme (Ministerio de Industria). I. C. is grateful to Ministerio de Educación for a Doctoral fellowship. We are also grateful to Dr. S. R. Baker (Lilly Research Centre, U. K.) for useful suggestions.

References and Notes

1 Using alkylcopper reagents: (a) Yoda, H.; Kitayama, H.; Yamada, W.; Katagiri, T.; Takabe, K. *Tetrahedron: Asymmetry* **1993**, *4*, 1451-1454. (b) Skrinjar, M.; Nilsson, C.; Wistrand, L-G. *Tetrahedron: Asymmetry* **1992**, *3*, 1263-1270. (c) Wistrand, L-G.; Skrinjar, M. *Tetrahedron* **1991**, *47*, 573-582. Using TMSCN: (d) Katoh, T.; Nagata, Y.; Kobayashi, Y, Arai, K.; Minami, J.; Terashima, S. *Tetrahedron Lett.* **1993**, *34*, 5743-5746. Enol ethers: (e) Shono, T.; Matsumura, Y.; Tsubata, K.;

Uchida, K. *J. Org. Chem.* **1986**, *51*, 2590-2592. Allyl silanes: (f) Altmann, K. H. *Tetrahedron Lett.* **1993**, *34*, 7721-7724. (g) Morimoto, Y.; Nishida, K.; Hayashi, Y.; Shirahama, H. *Tetrahedron Lett.* **1993**, *34*, 5773-5776. (h) Polniaszek, R. P.; Betmont. S. E.; Alvarez, R. *J. Org. Chem.* **1990**, *55*, 215-223. (i) Gramain, J-C.; Remuson, R. *Heterocycles* **1989**, *29*, 1263-1273. (j) Shono, T.; Matsumura, Y.; Onomura, O.; Sato, M. *J. Org. Chem.* **1988**, *53*, 4118-4121.

2 (a) Lubell, W. D.; Ibrahim, H. H. *J. Org. Chem.* **1993**, *58*, 6438-6441. (b) van der Werf, A.; Kellogg, R. M. *Tetrahedron Lett.* **1991**, *32*, 3727-3730. (c) Fushiya, S.; Chiba, H.; Otsubo, A.; Nozoe, S. *Chem. Lett.* **1987**, 2229-2232. (d) Shiosaki, K.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 1229-1239.

3 Ohta, T.; Hosoi, A.; Kimura, T.; Nozoe, S. *Chem. Lett.* **1987**, 2091-2094.

4 Nagasaka, T.; Yamamoto, H.; Hayashi, H.; Watanabe, M.; Hamaguchi, F. *Heterocycles* **1989**, *29*, 155-164.

5 (3*S*,4*S*) 1-Ethoxycarbonyl-2-hydroxy-3,4-di(methoxymethyl) pyrrolidine has been use as chiral starting material in a Horner-Emmos-Michael reaction. Shishido, K.; Sukegawa, Y.; Fukumoto, K.; Kametani, T. *J. Chem. Soc. Perkin Trans. I* **1987**, 993-1004.

6 Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734-736.

7 (a) Ethyl and methylpyroglutamate were prepared as described by Silverman, R. B.; Levy, M. A. *J. Org. Chem.* **1980**, *45*, 815-818. (b)*Tert*-butylpyroglutamate was obtained from proline as described by Yoshifuji, S.; Tanaka, K-I.; Kawai, T.; Nitta, Y. *Chem. Pharm. Bull.* **1986**, *34*, 3873-3878. (c) The *N*-urethane protection was made following Grieco's procedure, Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 2424-2426.

8 Pedregal, C.; Ezquerra, J.; Escribano, A.; Carreño, M. C.; García Ruano, J. L. *Tetrahedron Lett.* **1994**, *35*, 2053-2056 and references cited therein for other reduction procedures.

9 **General Procedure for the Tandem Horner-Emmons-Michael Reaction of 5-Hydroxy-*N*-Boc-Prolinates:** to a stirred suspension of sodium or potassium hydride (1.2 mmol) in anhydrous DMF (5 mL) the stabilised phosphorane (1.2 mmol) was added. The mixture was stirred at room temperature for 1 hour and then a solution of hemiaminal **2** (1 mmol) in DMF (5 mL) was added. The reaction was stirred overnight at room temperature, quenched with saturated aqueous NH_4Cl solution and extracted with ether (3 x 15 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent was evaporated to dryness and purified by flash chromatography yielding a mixture of diastereoisomers **4**. To this mixture of diastereoisomers **4** (1 mmol) in CH_2Cl_2 (10 ml) TFA (10 mmol) was added and the reaction stirred overnight. The reaction solution was washed with saturated $NaHCO_3$ solution (3 x 10 mL), dried over Na_2SO_4 and evaporated to dryness to afford a residue which was purified by flash chromatography to isolate **5**.

10 The Z-isomer was not detected.

11 Hondrelis, J.; Lonergan, G.; Voliotis, S.; Matsoukas, J. *Tetrahedron* **1990**, *46*, 565-576.

12 Bycroft, B. W.; Chhabra, S. R. *J. Chem. Soc., Chem. Commun.* **1989**, 423-425. Additionally, compounds **5a**, **5c** and **5d** were treated with (R)-(-)-methoxy-α-(trifluoromethyl) phenylacetyl chloride in the presence of pyridine, giving an enantiomeric excess (ee) >95% based on careful ^{1}H-NMR analysis of the corresponding Mosher amide.

(*Received in UK* 6 *July* 1994; *revised* 25 *August* 1994; *accepted* 2 *September* 1994)