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CONJUGATE ADDITION OF ORGANOCUPRATES TO METHYL CROTONATE LINKED TO CHIRAL OXAZOLIDONES

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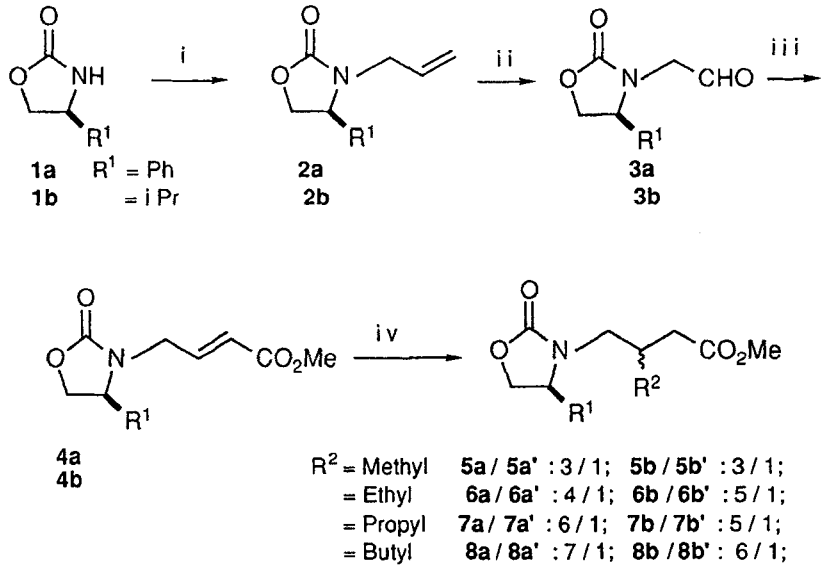
*Summary: Conjugate addition of various sp3 dialkylcuprates were performed on enoates **4a-b**, γ-aminocrotonate equivalents embodied in chiral oxazolidones. The diastereoselectivity is good to moderate and allows the access to homochiral ß-substituted GABA analogues.*

Organocuprates are valuable tools for the formation of C-C bonds when reacting with enoates; particularly the asymmetric version of the conjugated addition received considerable attention: chiral auxiliaries[1] or allylic stereocenter[2] have been used with high efficiency. We are interested in the preparation of homochiral ß-substituted analogues of GABA for biochemical evaluation.[3] Surprisingly, only few reports have appeared on the synthesis of these compounds either in racemic[4] or in enantiomerically pure form.[5] Recently such compounds have been identified as substrates for the enzymes γ-aminobutyric acid transferase[6] and glutamic acid decarboxylase.[7] Therefore we planned to add dialkycuprates to the enoates **4a-b**, which are γ-aminocrotonate equivalents where the nitrogen is included in a chiral oxazolidone.[8] In fact, examination of molecular models reveals

that in **4a-b** no diastereofacial differentiation is apparent in the enoate system. But we reasoned that in the transition state the π-copper complex would chelate the amidic oxygen to a cyclic



Reagents: i. NaH, DMF, allylbromide ii. O_3, CH_2Cl_2, DMS iii. $Ph_3P{=}CHCO_2Me$
iv. $(R^2)_2CuLi$, TMSCl -30°C

Scheme

entity controlling the diastereoselectivity of the addition. Herein we report our first results on the preparation of compounds **5a-b / 5a'-b'** to **8a-b / 8a'-b'**. Enoates **4a-b** were obtained after a three step sequence. Allylation of the commercially available oxazolidines **1a-b** using sodium hydride as base in dry DMF yielded compounds **2a-b**. Subsequent ozonolysis in dichloromethane provided the aldehydes **3a-b**, which were used in a Wittig olefination to obtain the enoates as a mixture of isomers (*E* / *Z* : 95/5). The *E* enoates **4a-b** were obtained

in 60% overall yield after chromatographic purification. It has to be noted that direct allylation of the oxazolidines **1a-b** with methyl bromocrotonate failed under several conditions (scheme).

The cuprates were prepared from the lithium or magnesium alkyls and the conjugate addition was performed in presence of TMSCl.[9] The chemical transformation was completed within 1 h at -30°C. After purification through column chromatography, mixtures of diastereomers were obtained in good yields (75-80%). The diastereomeric excess was determined by ^{1}H NMR (200 MHz), using the methoxy signal. Roughly the diastereomeric ratio (3/1 to 7/1), although moderate (see scheme) for the adducts **5a-b / 5a'-b'** to **8a-b / 8a'-b'**, is related to the size of the transferable alkyl group, irrespective to the substituent on the oxazolidone and comforts our assumption for a compact transition state. Several modifications were performed in order to improve the ratio, such as solvent change or cuprate preparation but without success. Finally adducts **5a-b / 5a'-b'** to **8a-b / 8a'-b'**, separable by chromatography, may be submitted to the self-immolative sequence of the oxazolidones (hydrolysis and /or hydrogenolysis)[10] and are therefore candidates for the obtention of various homochiral ß-substituted GABA analogues. Work in this direction is underway in our laboratory as well as the determination of the stereochemistry of the major diastereomer.

Experimental

2a : *S* 3-(1'-propene)-4-phenyl-2-oxazolidone

To a solution of NaH (25 mmol, 1.1 eq.) in dimethylformamide (50 ml) was added at 0°C a solution of **1a** (23 mmol, 1 eq.) in

dimethylformamide (10 ml). After stirring at 0°C for 1 h, a solution of allyl bromide (35 mmol, 1.5 eq.) in dimethylformamide (10 ml) added dropwise. After 1 h at room temperature, the reaction mixture was carefully hydrolyzed and extracted with diethyl ether. The organic layer was washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by chromatography on silica gel eluting with hexane / ethyl acetate (2 / 1) to give **2a** as a clear yellow oil (20 mmol, 87%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.14 - 3.26 (dd, 1H, *J* = 8, 15.3 Hz) 4.11 - 4.25 (m, 2H), 4.59 - 4.82 (AB part from ABX, 2H, J_{AX} = 8.7, J_{BX} = 6.7, J_{AB} = 8.7 Hz), 4.98-5.21 (dd, 2H, *J* = 10.2, 16.9 Hz), 5.61 - 5.79 (m, 1H), 7.24 - 7.47 (m, 5H).

2b: ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.84-0.94 (2d overlap, 6H, *J* = 6.9 Hz), 1.98-2.09 (m, 1H), 3.45-3.56 (dd, 1H, *J* = 7.8, 15.5 Hz), 3.66-3.77 (m, 1H), 4.02-4.26 (m, 3H), 5.19-5.27 (dd, 2H, *J* = 11.0, 16.9 Hz), 5.67-5.85(m,1H).

3a : *S* **3-ethanal-4-phenyl-2-oxazolidone.**

The allyl adduct **2a** (18 mmol) was dissolved in a mixture of dichloromethane/MeOH (2/1 ; 10 ml per mmol). After cooling at -78°C ozone was passed through the solution until a slight blue colour persisted. Dimethylsulfure (1 ml/mmol) was added and the mixture was stirred at 0°C for 1 h. The reaction mixture was washed with brine and the aqueous layer re-extracted with dichloromethane. The organic layer was dried over sodium sulfate and concentrated *in vacuo*. The crude product **3a** (92%) was used immediately in the next step. The same procedure was used to obtain obtention of **3b**.

4a : *S* **3-[(*E*)-methyl-2'-butenoate)-4-phenyl 2-oxazolidone.**

Crude aldehyde **3a** (15 mmol) and methyl (triphenylphosphoranylidene) acetate (16.5 mmol, 1.1 eq.) in dry THF (30 ml) were stirred overnight. The solvent was evaporated *in vacuo*, the residue was taken up in ether and filtred to remove triphenylphosphine oxyde. After evaporation *in vacuo*, the residue was purified by chromatography on silica gel eluting with hexane-ethyl acetate (2/1) to yield **4a** as a clear oil (72%).^{1}H NMR (200 MHz, $CDCl_3$): δ 3.36 - 3.59 (dd, 1H, J = 7.0, 16.7 Hz), 3.74 (s, 3H, CO_2CH_3), 4.17-4.32 (m, 2H), 4.63-4.81 (m, 2H), 5.78-5.87 (dt, 1H, J = 1.5, 18.8 Hz,), 6.69-6.81 (m, 1H), 7.25-7.48 (m, 5H).

4b: ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.83-0.90 (2d overlap, 6H, J = 6.7 Hz), 1.95-2.05 (m, 1H), 3.65-3.74 (m, 5H), 4.06-4.17 (A part from ABX, 1H, J_{AX} = 5.5, J_{AB} = 9.0 Hz), 4.20-4.38 (m, 2H), 5.92-6.02 (dt, 1H, J = 1.6, 15.7 Hz), 6.77-6.91 (m, 1H).

5a/5a': *S,R and S* **3-[(methyl)2'-methyl-butanoate]-4-phenyl-2-oxazolidone.**

To a solution of Me_2CuLi [1.3 mmol, 3 eq., prepared from CuI (3 eq.) and MeLi (6 eq.), and TMSCl (0.17 ml, 3 eq.)] was added at -40°C a solution of enoate **4a**, (1 eq., 0.4 mmol) in dry ether (3 ml). The mixture was stirred at -40°C for 30 min and allowed to reach room temperature. The reaction was quenched with saturated NH_4Cl and extracted with Et_2O. The organic layer was dried, filtered and concentrated *in vacuo*. The residue was puified by chromatography on silica gel (hexane / ether : 3 / 2) to give **5a / 5a'** as an oil (100 mg).

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.81 - 0.84 (d, 3H, J = 6.5 Hz), 2.11 (m, 3H), 2.46 - 2.62 (part A from ABX system, 1H, J_{AX} = 5.8, J_{AB} = 14.1

Hz), 3.17 - 3.28 (part B from ABX system, 1H, J_{BX} = 7.8, J_{AB} = 14.1 Hz), 3.45 (s, 3H), 4.00 - 4.11 (part X from ABX system, 1H, $J_{AX} + J_{BX}$ = 13.7 Hz) 4.48 - 4.74 (m, 2H,), 7.13 - 7.35 (m, 5H,). Minor isomer : 0.73 - 0.76 (d, J = 6.5 Hz,), 3.53 (s).

5b / 5b': ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.81-0.93 (m, 9H), 1.80-1.85 (m, 1H), 2.04-2.33 (m, 3H), 2.90-3.37 (AB part from ABX, 2H, J_{AX} = 4.5, J_{BX} = 9.2, J_{AB} = 13.8 Hz), 3.54-3.77 (m, 4H), 4.02-4.17 (m, 2H); minor isomer 3.66 (s).

References and notes.

1. Yamamoto, Y. *Angew. Chem.,Int.Ed. Engl.* **1986**, *25*, 947.
2. (a)Yamamoto, Y.; Nishii, S.; Ibuka, T. *J. Am. Chem. Soc.* **1988**, *110*, 617 and references therein. (b) Jako, I; Uiber, P.; Mann, A.; Wermuth, C.G.; Boulanger, Th.; Norberg, B.; Evrard, G.; Durant, F. *J. Org. Chem.* **1991**, *56*, 5729.
3. (a) Le Coz, S.; Mann, A.; Wermuth, C.G. *Synth .Comm.***1989**, *19*, 3007. (b) Mann, A.; Boulanger, T.; Brandau, B.; Durand, F.; Evrard, G.; Heaulme, T.A.; Desaulles, E.; Wermuth, C.G. *J. Med. Chem.*, **1991**, *34*, 1307. (c) Allan, R.D.; Bates, M.C.; Drew, C.A.; Duke, R.K.; Hambley, T.W.; Johnston, G.A.R.; Mewett, K.N.; Spence, I. *Tetrahedron* **1990**, *46*, 2511.
4. Andruszkiewicz, R.; Silverman, R.B. *Synthesis* **1989,** 953.
5. Chênevert, R.; Desjardins, M. *Tetrahedron Lett.* **1991**, *32*, 4249.
6. Silverman, R.B.; Invergo, B.J.; Levy, M.A.; Andrew, C.R. *J.Biol. Chem.* **1987**, *262*, 3192.
7. Silverman, R.B.; Andruszkiewicz, R.; Nanavati, S.M.; Taylor, C.P.; Vartanian, M.G. *J. Med. Chem.,* **1991**, *34*, 2295.

8. Evans, D.A.; Sjogren, E.B.; Bartoli, J.; Dow, R.L. *Tetrahedron Lett.* **1986**, *27*, 4957 and referennes therein.

9. (a) Corey, E.J.; Boaz, N.W. *Tetrahedron Lett.* **1985**, *26*, 6019.

(b) Alexakis, A.; Berlan, J.; Besace, Y. *Tetrahedron Lett.* **1986**, *27*, 1047.

10. Gawley, R.E.; Rein, K.; Chemburkar, S. *J. Org. Chem.* **1989**, *54*, 3002.

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