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Asymmetric Synthesis of 3-Alkyl Pipecolic Acids

A. Zaparucha, M. Danjoux, A. Chiaroni, J. Royer* and H.-P. Husson

Institut de Chimie des Substances Naturelles, CNRS,
91198 Gif-Sur-Yvette Cedex, France

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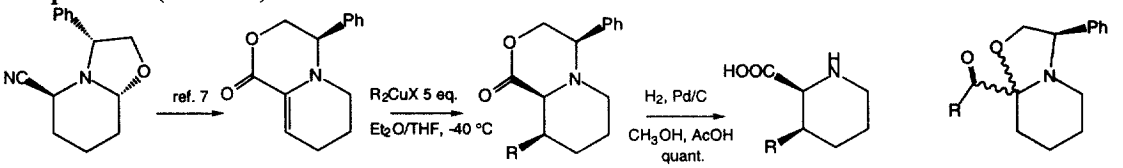
Abstract: The Michael addition of R_2CuLi or $R_2CuMgBr$ to 4-phenyl-3,4,7,8-tetrahydro-6H-pyrido (2,1-c)(1,4)oxazin-1-one **2**, readily obtained from 2-cyano-6-phenyloxazolopiperidine **1**, led to the formation of alkylated lactones **4a-d** in high yield and with complete diastereoselectivity. Transformation of lactones **4a-d** to 3-alkyl pipecolic acids was achieved by simple hydrogenolysis.

Pipecolic acid (**5**, R=H) a natural non-proteinogenic amino acid, has generated considerable interest as a proline analog.[1] Lately, much attention has been focused on unnatural pipecolic acid derivatives substituted on the piperidine ring as building blocks for the synthesis of peptides,[2] immunosuppressants,[3] enzyme inhibitors [4-5] or NMDA antagonists.[6]

In continuation of our studies on the asymmetric synthesis of piperidine derivatives from the 2-cyano-6-phenyloxazolopiperidine synthon **1**, we were interested in the synthesis of variously substituted pipecolic acids based on the use of a common intermediate **2**. The latter, initially obtained as a by-product in the synthesis of 2-alkyl pipecolic acids was easily prepared on a multigram scale from 2-cyano-6-phenyloxazolopiperidine **1** in three steps.[7]

We investigated the Michael addition of various dialkyl cuprate reagents [8] to compound **2** (Scheme).



1 **2** **4 a-d** **5 a-d** **3 a-d**

$(CH_3)_2CuLi$ (**4a**: 78%); $(C_2H_5)_2CuMgBr$ (**4b**: 85%); $(n\text{-}C_3H_7)_2CuLi$ (**4c**: 88%); $(n\text{-}C_4H_9)_2CuMgBr$ (**4d**: 82%)

Scheme

When reactions were performed in THF alone, only compounds **3a-d** resulting from 1,2-addition of the organocuprate followed by recyclization, were obtained as a mixture of diastereomers. On the contrary, we were pleased to observe the formation of compounds **4a-d**, obtained in each case as a single diastereomer in good yield, when the reactions were

* fax 33 1 69 07 72 47 ; e-mail : jacques.royer@icsn.cnrs-gif.fr

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performed at –40 °C in diethyl ether with the minimum amount of tetrahydrofuran for complete dissolution of starting material **2**. [9] The configurations of the newly formed chiral centers of **4a-d** were determined by NMR studies and confirmed by X-ray analysis of compound **4a**.[10] These configurations correspond to an axial addition of the organometallic reagent onto a quasi-*trans* conformer of **2**. The stereoselectivity of the reaction was not controlled directly by the steric interaction of the phenyl group but by the conformation of the bicyclic ring system.

Hydrogenolysis of the chiral moiety of **4a-d** was achieved in the presence of a small amount of acetic acid in methanol [7] and led to the unnatural pipecolic acids **5a-d** [11] in nearly quantitative yield.

In conclusion we have developed an short, efficient and totally stereoselective method of preparing 3-alkyl pipecolic acids.

References and notes :

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[9] A general procedure for the Michael addition of cuprate reagents to compound **2** was as followed : to a suspension of CuI (952 mg, 5 equiv.) in 10 mL of dry diethyl ether at -40°C under nitrogen was added dropwise an ether solution of the Grignard or lithium reagent (10 equiv.) and the mixture was stirred for 30 minutes at -40 °C. Compound **2** (229 mg) dissolved in THF/Et_2O 1/2 (3 mL) was then added dropwise. The reaction mixture was stirred at –40 °C until complete consumption of starting material **2** (monitored by TLC) and the reaction was then quenched by addition of saturated ammonium chloride and saturated ammonia. After extraction with diethyl ether, the organic layers were washed with brine and dried over $MgSO_4$. Distillation of the solvents under reduced pressure afforded the crude product which was purified by flash chromatography on silica gel (eluant cyclohexane/diethyl ether).

[10] Atomic coordinates have been deposited with the Cambridge Crystallographic Center.

[11] **5a**: $[\alpha]_D$ -9 (c 0.4 , EtOH); ^{13}C NMR (63.5 MHz, $CDCl_3$) δ: 13.1, 22.9, 29.9, 35.7, 44.7, 63.4, 170.0 This compound has been previously described in racemic form: Shuman RT, Ornstein PL, Paschal JW, Gesellchen PD *J. Org. Chem.* **1990**; *55*: 738-741.