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LETTERS

Stereoselective Synthesis of 4,5-Disubstituted Pyrrolidin-2-ones by Cuprate Addition to Chiral Non Racemic α,β-Unsaturated-γ-Lactams.

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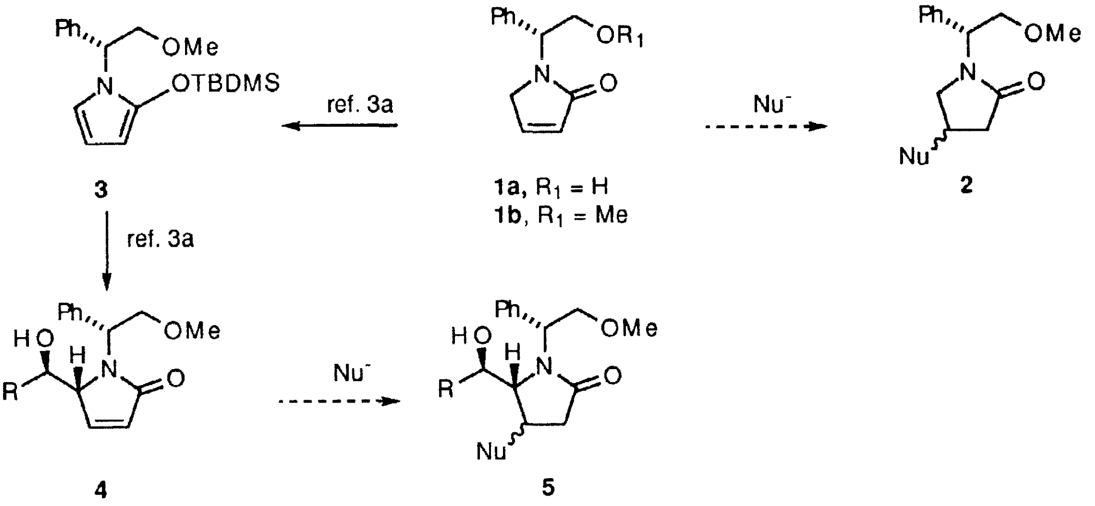
Abstract : A new access to enantiopure 4,5-disubstituted pyrrolidin-2-ones has been developed from chiral non racemic α,β-unsaturated-γ-lactams. Conjugate addition of Gilman-type cuprates results in *trans* addition with excellent diastereoselectivity. © 1998 Elsevier Science Ltd. All rights reserved.

The pyrrolidine ring is a structure very often encountered in the alkaloid field.[1] Furthermore, numerous chiral non-racemic substituted pyrrolidines and pyrrolidones are used as intermediates, chiral ligands or auxiliaries in asymmetric synthesis.[2] The development of new methods for the preparation of enantiomerically pure, highly substituted pyrrolidines and pyrrolidones is then of increasing interest. For this purpose, we recently described the preparation of **1** and its use for the asymmetric synthesis of 3- and 5-substituted pyrrolidin-2-ones.[3] We now wish to report Michael addition of organocuprates to the α,β-unsaturated γ-lactam **1b**. In conjunction with the silyloxypyrrole chemistry we have previously developed,[3ab] this provides a versatile route to enantiopure 4,5-disubstituted-pyrrolidin-2-ones **5** (Scheme 1).



Scheme 1

General investigation of the reactivity of lactam **1** led us to study the Michael addition of various nucleophiles. Conjugate additions of cuprates to such lactams have been reported in the literature, but due to the low electrophilicity of such lactams, the presence of a withdrawing group α to the carbonyl[4] or

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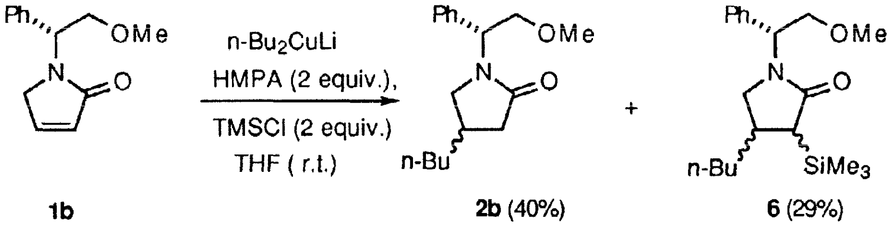
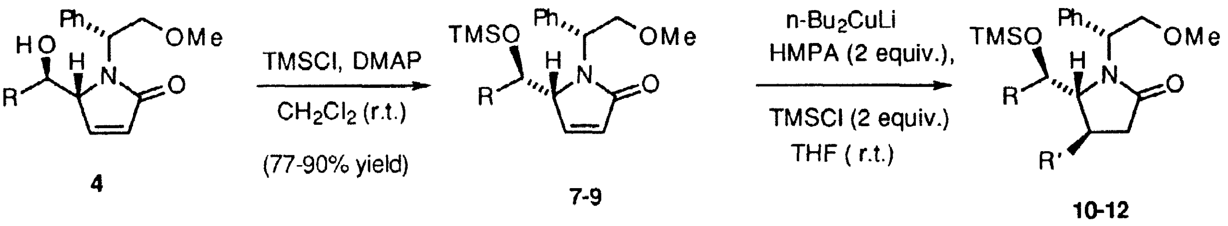
attached to the nitrogen[5] is generally necessary. In the few examples of organocuprate additions to non-activated lactams which have been reported the nitrogen is part of an oxazolidine ring.[6] Furthermore, to our knowledge, even in the case of *N*-activated lactams only one example of conjugate organocuprate addition to a non-substituted-γ-lactam has been reported.[5b]

Thus at first sight **1b** did not appear to be a good candidate for organocuprate addition reactions. Indeed, several attempts with different types of organocuprates and under different experimental conditions were investigated without success. However, it was eventually found that the reaction did occur with lower-order organocuprates (Gilman-type) at room temperature but only in the presence of TMSCl[7] and HMPA[8] as activators. Under these conditions the diastereoselectivity was very low and in addition to lactam **2b**, the lactam **6**, arising from C-alkylation[9] of the intermediate enolate with TMSCl, was obtained (Scheme 2). This parasitic tandem reaction could be avoided by performing the addition at lower temperature (<0°C), but this also resulted in much lower yields although the diastereoselectivity was slightly improved.



Scheme 2

Several studies of organocuprate additions to α,β-unsaturated γ-lactams reported in the literature have been devoted to γ-substituted γ-lactams mainly derived from pyroglutamic acid.[5,6] In these cases, the diastereoselectivity was excellent due to chiral intraannular 1,2 induction. We thus anticipated that γ-substituted α,β-unsaturated-γ-lactams **4** resulting from aldol reaction with silyloxypyrrole **3**,[3a] should give novel β,γ-disubstituted-γ-lactams in good yields and with high diastereomeric excess (Scheme 1). Thus compounds **7-9**, obtained after protection of the alcohol function of aldols **4** (TMSCl, DMAP), were submitted to the action of different Gilman-type organocuprates in the presence of 2 equiv. each of TMSCl and HMPA [10] (Scheme 3, Table). The disubstituted lactams **10-12**[11] were effectively obtained with good yields and excellent stereoselectivities. The *trans* relative configurations of the major diastereomers formed were deduced from their ^{1}H NMR spectra and are in agreement with results reported in the literature.[5]



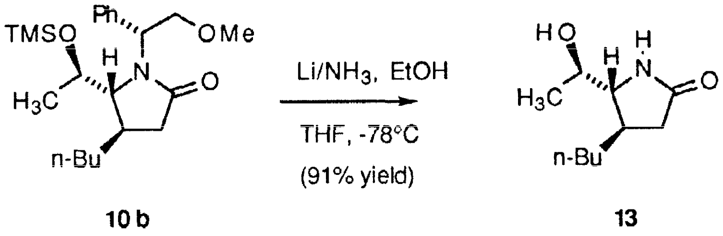
Scheme 3

unsaturated lactam	**R**	**R'**	**product**	**d.e. (%)**	**yield (%)**
7	Me	Me	**10a**	$>95^{a)}$	76.5
7	Me	*n*-Bu	**10b**	$>95^{a)}$	78
7	Me	Ph	**10c**	$96.4^{b)}$	20
8	Et	Me	**11a**	$83^{b)}$	50
8	Et	*n*-Bu	**11b**	$97^{b)}$	82
9	*t*-Bu	Me	**12a**	$>95^{a)}$	20
9	*t*-Bu	*n*-Bu	**12b**	$>95^{a)}$	80

a) no traces of the other diastereomer in the ^{1}H et ^{13}C NMR spectra , b) determined by GC-MS analyses.

Table

No traces of tandem reaction products analogous to **6** were detected. The enhanced reactivity of lactams **7-9** compared to lactam **1b** can be explained by the diminished acidity of the hydrogen at C-5 and the greater pyramidalization of the nitrogen produced by the γ-substituent. The latter results in a decreased participation of the *N*-lone pair in the amide bond and thus an increased electrophilicity of the β-position.[6]



Scheme 4

Finally the deprotected 4,5-disubstituted pyrrolidin-2-ones can be easily obtained in one step by reductive cleavage of the *N*-benzylic bond using lithium in liquid ammonia as illustrated by the synthesis of the pyrrolidin-2-one **13**[12] (Scheme 4).

In conclusion, while Michael addition of Gilman-type organocuprates to the unsubstituted γ-lactam **1b** occurs in fair yields using activators (TMSCl and HMPA), reactivity is greatly enhanced by simple alkylation at C-5 affording 4,5-dialkylated γ-lactams in high yields and stereoselectivities.

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References and notes :

1- a) Martin, S.F. "The Alkaloids", Brossi, A., Ed.; Academic Press: Orlando, 1987, vol. 30, chapter 3. b) Elbein, A.; Molyneux, R.I. "Alkaloids, Chemical and Biological Perspectives", Pelletier, S.W., Ed.; Wiley J., N.Y., 1990, vol. 5, 1-54. c) Massiot, G.; Delaude, C. "The Alkaloids", Brossi, A., Ed.; Academic Press: N.Y., 1986, vol. 27, chapter 3.

2- a) Huryn, D.M. *Comprehensive Organic Synthesis*, Trost, B.M.; Fleming, I., Ed.; Pergamon : Oxford, 1991, vol. 1, 64-74. b) Yoda, H.; Kitayama, H.; Katagiri, T.;Takabe, K. *Tetrahedron*, **1992**, *48*, 3313-3322. c) Hamada, Y.; Hara, O.; Kawai, A.; Kohno, Y.; Shioiri, T. *Tetrahedron*, **1991**, *47*, 8635-8652.d) Corey, E.J.; Yuen, P.-W.; Hannon, F.J.; Wierda, D.A. *J. Org. Chem.*, **1990**, *55*, 784-786.

3- a) Baussanne, I.; Royer, J. *Tetrahedron Lett.*, **1996**, *37*, 1213-1216.b) Baussanne, I.; Schwardt, O.; Royer, J.; Pichon, M.; Figadère, B.; Cavé, A. *Tetrahedron Lett.*, **1997**, *38*, 2259-2262. c) Baussanne, I.; Chiaroni, A.; Husson, H.-P.; Riche, C.; Royer, J. *Tetrahedron Lett.*, **1994**, *35*, 3931-3934. d) Baussanne, I.; Travers, C.; Royer, J. *unpublished results*

4- a) Dyer, J.; Keeling, S.; Moloney, M.G. *Tetrahedron Lett.*, **1996**, *37*, 4573-4576. b) Meyers, A.I.; Snyder, L. *J. Org. Chem.*, **1993**, 58, 36-42.

5- a) Nagashima, H.; Ozaki, N.; Washiyama, M.; Itoh, K. *Tetrahedron Lett.*, **1985**, *26*, 657-660. b) Hagen, T.J. *Synlett*, **1990**, 63-66. c) Koot, W.-J.; Hiemstra, H.; Speckamp, W.N. *Tetrahedron Lett.*, **1992**, *31*, 7969-7972. d) Woo, K.C.; Jones, K. *Tetrahedron Lett.*, **1991**, *32*, 6949-6952. e) Herdeis, C.; Hubmann, H.-P. *Tetrahedron : Asymmetry*, **1992**, *3*, 1213-1221. f) Diaz, A.; Siro, J.G.; Garcia-Navio, J.L.; Vaquero, J.J.; Alvarez-Builla, J. *Synthesis*, **1997**, 559-562.

6- a) Hanessian, S.; Ratovelomanana, V. *Synlett*, **1990**, 501-503. b) Hanessian, S.; Ratovelomanana, V. *Synlett*, **1991**, 222-224.

7-a) Alexakis, A.; Berlan, J.; Besace, Y. *Tetrahedron Lett.*, **1986**, *27*, 1047-1050. b) Corey, E.J.; Boaz, N.W. *Tetrahedron Lett.*, **1985**, *26*, 6019-6022.

8- Nakamura, E.; Matsuzawa, S.; Horiguchi, Y.; Kuwajima I. *Tetrahedron Lett.*, **1986**, *27*, 4029-4032.

9- Woodburg, R.P.; Rathke, M.W. *J. Org. Chem.* **1978**, *43*, 881-884.

10- *Typical procedure for cuprate addition* :To a solution of CuI (3 equiv.) in anhydrous THF (2 mL/mmol) at 0°C and under an argon atmosphere, was added the organolithium solution (6 equiv.). After stirring for 10 min., the solution was cooled to -78°C and TMSCl (2 equiv.) followed by HMPA (2 equiv.) were added. After 5 min., a solution of the lactam (1 equiv.) in anhydrous THF (4 mL/mmol) was slowly added to the mixture. Cooling was removed and the solution was stirred at room temperature. After completion of the reaction (1 to 3 h), the mixture was quenched with an aqueous solution of saturated NH_4Cl and 11% ammonia solution (2/1). The water layer was extracted with CH_2Cl_2 (3 times). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was then purified by flash chromatography on silica gel 60.

11- All new compounds gave satisfactory spectroscopic and analytical (or HRMS) data.

12- **13**: $[\alpha]_D$ -54 (c=2.7, CH_2Cl_2) ; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) : 7.58 (bs,1H), 4.45 (bs, 1H), 3.60 (m, 1H), 3.10 (dd, J = 4.0, 5.6 Hz, 1H), 2.55 (dd, J = 8.9, 17.0 Hz, 1H), 2.10 (m, 1H), 2.01 (dd, J = 5.2, 17.0 Hz, 1H), 1.52 (m, 1H), 1.20-1.40 (m, 5H), 1.21 (d, J = 6.2 Hz, 3H), 0.90 (t, J = 6.6 Hz, 3H) ; ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ (ppm) : 178.7, 69.6, 66.5, 36.7, 36.1, 34.9, 29.1, 22.4, 19.6, 13.7.