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Stereoselective Synthesis of Enantiopure 4,5-Disubstituted Pyrrolidin-2-ones by Consecutive Cuprate Addition and *N*-Acyliminium Coupling

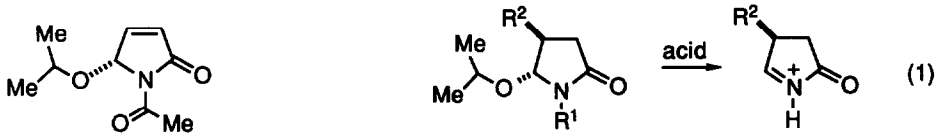
Wim-Jan Koot, Henk Hiemstra,* and W. Nico Speckamp*

Department of Organic Chemistry, University of Amsterdam,
Nieuwe Achtergracht 129, 1018 WS Amsterdam, The Netherlands

Abstract: The enantiopure γ-lactam (*R*)-1-acetyl-5-isopropoxy-3-pyrrolin-2-one (**1**), prepared from (*S*)-malic acid, undergoes cuprate addition at C4 with complete *trans*-stereoselectivity. The products react with π-nucleophiles in the presence of Lewis acid at C5 to provide enantiopure 4,5-disubstituted pyrrolidin-2-ones.

We recently reported the preparation of (*R*)-1-acetyl-5-isopropoxy-3-pyrrolin-2-one (**1**) from (*S*)-malic acid and the use of this enantiopure unsaturated γ-lactam in Diels-Alder chemistry.[1] We now wish to disclose that **1** is also an excellent substrate for highly stereoselective cuprate addition processes. We will show that in conjunction with *N*-acyliminium chemistry this methodology provides a versatile route to enantiopure 4,5-disubstituted pyrrolidin-2-ones.

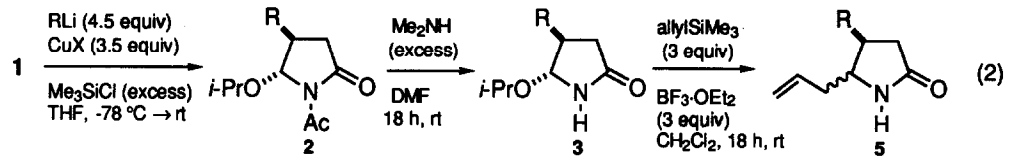
Although conjugate addition of cuprates to conjugated enones has become of general use in organic synthesis,[2] few cases of additions to α,β-unsaturated γ-lactam systems have been reported.[3] Only recently, some reports of cuprate additions to enantiopure 3-pyrroline-2-ones have appeared.[3c-g] On the basis of this literature, substrate **1** was expected to show good reactivity due to the presence of the *N*-acetyl function. Furthermore, the 5-isopropoxy function should direct the nucleophile to add at C4 in a *trans* fashion to produce **2**. After removal of the *N*-acetyl function, lactam **3** should allow the introduction of a variety of substituents at C5 via *N*-acyliminium intermediate **4** (eq 1).[4]



1 **2** R^1 = Ac; **3** R^1 = H **4** (1)

In this letter we first wish to report the results of conjugate addition to **1** of cuprates obtained from a number of commercially available organolithium solutions. The products are then allylated at C5 by treatment with allyltrimethylsilane to lead to 4,5-disubstituted pyrrolidinones. We finally show that treament of **1** with a 2-phenethylcopper reagent allows CC-bond formation at C5 to be carried out in an intramolecular fashion.

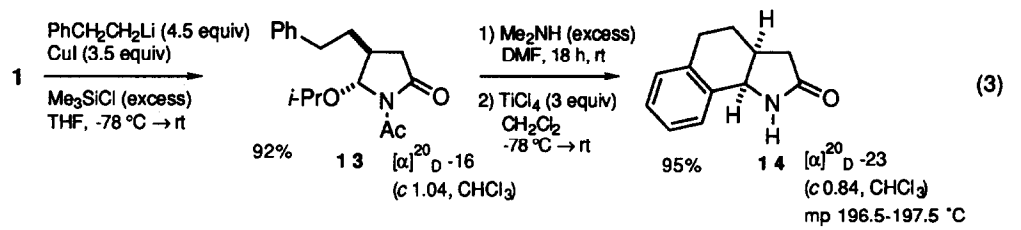
The cuprates were prepared *in situ* by adding the commercial organolithium compound (4.5 equiv) to CuI or CuBr·Me_2S (3.5 equiv) in THF (eq 2, Table I). The lithium cation appeared important in these conjugate addition reactions, because copper reagents derived from RMgX with either catalytic or stoichiometric CuX gave only complicated product mixtures. To accelerate the conjugate addition as well as to prevent side reactions, chlorotrimethylsilane (8-10 equiv) was added.[5,6] The results are listed in Table I.[7]



(2)

The conjugate addition of the cuprates proceeded in fair to good yield. Only in the case of methyllithium yields remained unsatisfactory despite efforts to optimize the process. The type of copper(I) salt used appeared important in view of the remarkable differences in the results of the conjugate addition of *n*-BuLi and *t*-BuLi in the presence of CuBr·Me_2S. While *t*-BuLi reacted in fair yield, *n*-BuLi gave no more than a trace of the desired product. However, when CuI was used, both *t*-BuLi and *n*-BuLi reacted in good yield. The stereoselectivity of the reaction was very high. The ^1H NMR spectra of the crude products only showed the presence of a single *trans*-addition product in all cases. The assignment was based on the ^1H NMR vicinal coupling constant of H5. In a *trans*-lactam this coupling is 0-1 Hz, whereas a *cis*-lactam gives a coupling of 5-6 Hz.[8]

The products obtained from the cuprate additions were then used in *N*-acyliminium ion chemistry.[4] To this end, compounds **2** were first deacylated[9] with dimethylamine in DMF and then immediately treated with allyltrimethylsilane and $BF_3·Et_2O$ (eq 2).[7] The deacylated intermediates **3** were not purified because of their sensitivity to hydrolysis at C5. Simple evaporation of the solvent (DMF) also resulted in the removal of the formed *N,N*-dimethylacetamide, giving almost pure **3** (>95%; R = Me, Ph, *t*-Bu). Allylation of **6** and **7** gave inseparable *cis/trans* mixtures of lactams **10** and **11**, respectively, in good yields. On the other hand, allylation of **8** gave lactam **12** as a single isomer in 67%. When $TiCl_4$ was used as Lewis acid, a somewhat higher yield was obtained (77%). The expected *trans*-stereochemistry of **12** was confirmed by the ^1H NMR data, *viz* a coupling of ca. 2-3 Hz between H4 and H5.[8] By analogy, the major isomers of **10** and **11** were also assigned the *trans*-stereochemistry. The stereoselectivity of allylation thus shows the expected order *t*-Bu>Ph>Me with regard the steric size of the C4 substituent.



(3)

In order to probe the possibility of an intramolecular *N*-acyliminium ion reaction, the conjugate addition reaction was carried out with a copper reagent derived from 2-phenethyllithium[10] to give **13** as a single isomer in excellent yield (eq 3). After deacylation of **13** as before, the cationic cyclization was readily accomplished by using $TiCl_4$ as Lewis acid ($BF_3·Et_2O$ was not effective). As expected, only the *cis*-fused product (the ^1H NMR coupling between the angular hydrogens was 6.4 Hz)[8] was obtained as a nicely crystalline solid.

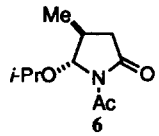
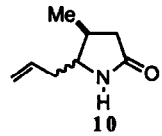
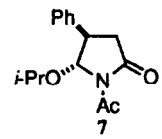
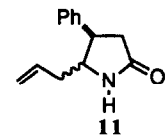
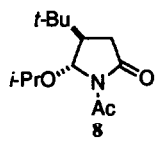
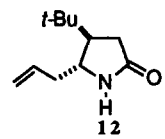
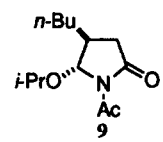
In conclusion, we have shown that **1** undergoes cuprate addition reactions in a highly stereoselective way in fair to good yields. The enantiopure products obtained can subsequently be functionalized with carbon

nucleophiles at C5 via *N*-acyliminium intermediates to provide 4,5-disubstituted pyrrolidinones. One possible application of products like **10-12** could be the hydrolytic ring opening to stereochemically defined GABA analogues.[11]

ACKNOWLEDGEMENT

This investigation was supported by the Netherlands' Foundation for Chemical Research (SON) with financial aid from the Netherlands' Organization for the Advancement of Pure Research (NWO).

Table I. Results of Cuprate Addition and Allylation.[a]

RLi / CuX	cuprate addition product		allylation product[b]	
	 **6**	$[\alpha]^{20}_D$ -44 (*c* 0.92, $CHCl_3$)	 **10**	65%[c] (*cis*/*trans* = 22:78)
MeLi / $CuBr{\cdot}Me_2S$	31%			
MeLi / CuI	31%			
	 **7**	$[\alpha]^{20}_D$ -16 (*c* 1.78, $CHCl_3$)	 **11**	84%[c] (*cis*/*trans* = 19:81)
PhLi / $CuBr{\cdot}Me_2S$	56% (18% s.m.)			
	 **8**	$[\alpha]^{20}_D$ -47 (*c* 1.01, $CHCl_3$)	 **12**	$[\alpha]^{20}_D$ +29 (*c* 0.49, $CHCl_3$) mp 58.5-60.5 °C
***t*-BuLi** / $CuBr{\cdot}Me_2S$	54% (18% s.m.)			
***t*-BuLi** / CuI	84%		67%[c] (77%)[d]	
	 **9**	$[\alpha]^{20}_D$ -30 (*c* 2.75, $CHCl_3$)		
***n*-BuLi** / $CuBr{\cdot}Me_2S$	<5%			
***n*-BuLi** / CuI	71%			

[a]See reference 7 for representative procedures. [b]Yields obtained after deacylation and allylation. [c]$BF_3{\cdot}Et_2O$ as Lewis acid. [d]$TiCl_4$ as Lewis acid.

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6. According to ^{1}H NMR, 1,4-addition occurred also without addition of TMSCl, but was immediately followed by deacylation. However the yield of the crude product was low and some other unidentified products were formed also.

7. All compounds showed IR, ^{1}H NMR, ^{13}C NMR and microanalytical data in accordance with their structure. **A typical cuprate addition reaction:** To a solution of CuI (560 mg, 2.94 mmol) in THF (10 mL) was added 2.46 mL of *t*-BuLi (4.18 mmol, 1.7 M in pentane) at 0 °C. After stirring for 1.5 h, the solution was cooled to -78 °C and Me_3SiCl (1.4 mL, 11 mmol) was added. This mixture was stirred for 5 min. A solution of **1** (200 mg, 1.09 mmol) in THF (10 mL) was then added. The cooling was removed after 5 min and the solution stirred for another 2 h. The reaction mixture was quenched with aq saturated NH_4Cl and the water layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried over $MgSO_4$. Flash chromatography (EtOAc/hexanes 1:3) yielded **8** (221 mg, 0.92 mmol, 84%) as a colourless oil. R_f 0.40 (EtOAc/hexanes 1:3); $[\alpha]^{20}_D$ -47 (*c* 1.01, $CHCl_3$); IR ($CHCl_3$) 2960, 2935, 2865, 1740, 1695, 1365, 1355, 1280, 1275, 1055 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.87 (s, 9 H, *t*-Bu), 1.12 & 1.18 (2 × d, 3 H, *J* = 6.1 Hz, $CH(CH_3)_2$), 1.91 (d, 1 H, *J* = 9.1 Hz, H4), 2.36 (d, 1 H, *J* = 18.4 Hz, H3), 2.47 (s, 3 H, Ac), 2.90 (dd, 1 H, *J* = 9.1, 18.4 Hz, H3), 3.92 (sept, 1 H, *J* = 6.1 Hz, $CH(CH_3)_2$), 5.60 (s, 1 H, H5); ^{13}C NMR (50 MHz, $CDCl_3$): δ 175.9, 171.1, 86.1, 70.7, 48.7, 33.7, 31.9, 26.7, 25.2, 22.7, 22.6. **A typical allylation reaction:** A solution of **8** (221 mg, 0.92 mmol) and Me_2NH (0.6 mL, 9.0 mmol) in DMF (5 mL) was stirred in a closed flask at rt for 18 h. The solvent was removed *in vacuo*, and the crude product was dissolved in CH_2Cl_2 (10 mL). To this solution were added at rt allyltrimethylsilane (0.44 mL, 2.77 mmol) and $BF_3{\cdot}Et_2O$ (0.34 mL, 2.76 mmol) and the solution was stirred at rt for 18 h. The reaction mixture was quenched with aq saturated $NaHCO_3$. The water layer was extracted with Et_2O (3 × 20 mL) and the combined organic layers were dried over K_2CO_3. Purification by flash chromatography (EtOAc) yielded **12** (116 mg, 0.64 mmol, 67%) as colourless crystals. R_f 0.20 (EtOAc); $[\alpha]^{20}_D$ +29 (*c* 0.49, $CHCl_3$); mp 58.5-60.5 °C (hexane); IR ($CHCl_3$) 3425, 2990, 1685, 1365 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (s, 9 H, *t*-Bu), 1.88 (m, 1 H, H4), 2.11 (m, 1 H, CH_2=CHC*H*H), 2.17 (dd, 1 H, *J* = 5.4, 17.9 Hz, H3), 2.35 (m, 1 H, CH_2=CHC*H*H), 2.42 (dd, 1 H, *J* = 10.3, 17.9 Hz, H3), 3.49 (quintet, 1 H, *J* = 4 Hz, H5), 5.09 (m, 1 H, *H*CH=CH-CH_2), 5.16 (s, 1 H, HC*H*=CH-CH_2), 5.75 (m, 1 H, CH_2=C*H*-CH_2), 6.25 (br s, 1 H, NH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 133.8, 118.8, 54.9, 49.2, 42.6, 32.8, 32.1, 26.8; Anal. Calcd. for $C_{11}H_{19}NO$: C, 72.88; H, 10.56; N, 7.73. Found: C, 72.76; H, 10.58; N, 7.79.

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9. It should be noted here, that *N*-acyliminium ion chemistry is not possible with **two** acyl functions attached to the nitrogen.[4] However, nucleophilic substitution at C5 was recently achieved by using the tetracarbonyliron complex of **1** (manuscript in preparation).

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