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Stereoselective Synthesis of 4-Alkylidene Pyrrolidinones and Pyrrolizidinones

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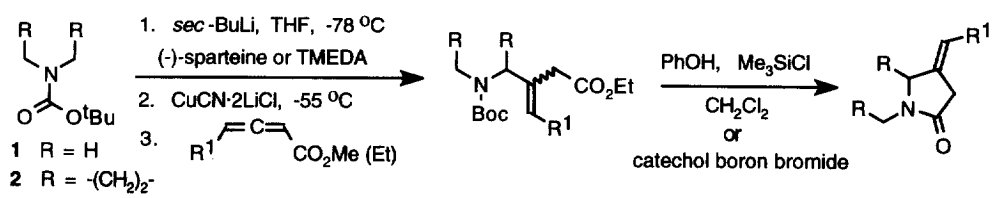
Abstract: α-Aminoalkylcuprates prepared from *tert*-butoxycarbonyl protected amines undergo a conjugate addition reaction with α,β-β,γ-allenyl esters to afford the corresponding β,γ-unsaturated esters with a high degree of stereoselectivity. Treatment of the unsaturated esters with PhOH/TMSCl or catechol boron bromide effects amine deprotection and lactamization to afford a 4-alkylidene-2-pyrrolidinone ring with preservation of the original olefin stereochemistry. The method can be used to prepare 4-alkylidene 2-pyrrolidinones and 2-pyrrolizidinones

Pyrrolidine[1] and pyrrolizidine[2] alkaloids have been the subject of numerous synthetic studies due to their wide range of biological activities. 2-Alkylidene pyrrolidines can be prepared by olefination of the corresponding lactams[3] or thiolactams[4] while simple 3-, and 4-alkylidene pyrrolidines are less readily available. 3-Alkylidene pyrrolidines have been prepared by iminium ion promoted olefin cyclizations[5], and via annulation procedures involving bifunctional reagents containing nucleophilic[6] and electrophilic sites. A samarium iodide promoted aldehyde-alkyne coupling reaction provides a route to 4-alkylidene pyrrolidines[7], which begins with α-amino acids to afford scalemic pyrrolidines. These can potentially be converted into kainic acid analogues which are important in neurobiology.[8]

The coupling of Beak's carbamate deprotonation methodology[9] with our development of α-aminoalkylcuprate chemistry[10] appeared to offer a facile entry into 4-alkylidene 2-pyrrolidinones and 2-pyrrolizidinones. The proposed synthetic route to these heterocyclic compounds involved conjugate addition of an α-aminoalkylcuprate reagent to allenyl esters followed by sequential carbamate deprotection and lactamization (eq. 1). We report that this synthetic strategy can be executed in two steps with complete control of olefin regiochemistry and good control of olefin stereochemistry.



eq. 1

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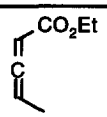
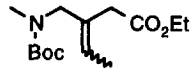
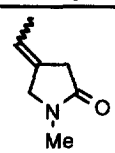
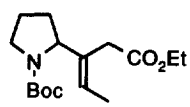
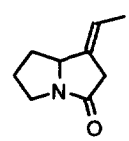
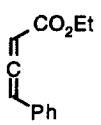
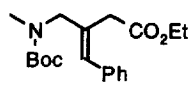
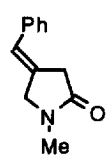
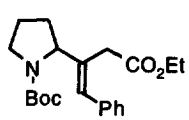
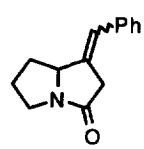
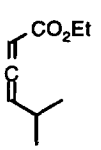
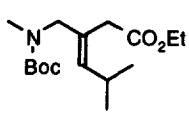
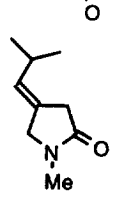
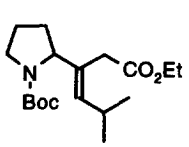
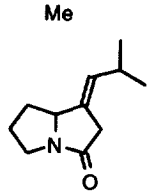
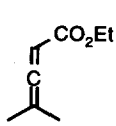
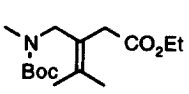
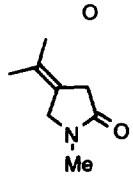
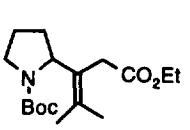
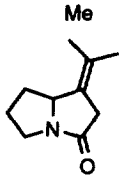
Table. Conjugate addition of α-aminoalkylcuprates to α,β-allenyl esters followed by lactamization to afford pyrrolidinones and pyrrolizidinones.

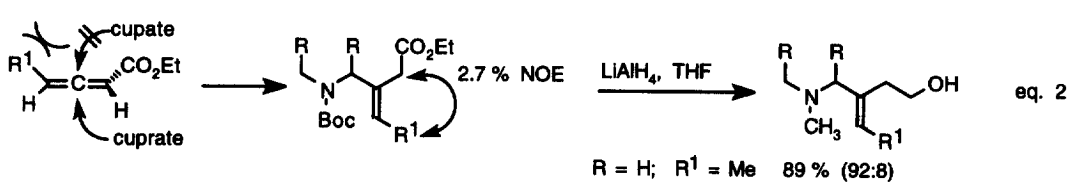
entry	carbamate	allene	rxn cond[a]	1,4-adduct	% yield[b] (dr)[c]	heterocycle[d]	% yield[b] (dr)[c]
1	1		A		82 (91:9)		83[e]
2	1		B		74 (86:14)		65 (84:16)
3	2		A		85		60
4	1		A		48		63
5	2		A		45		92 (66:33)
6	1		A		65		60
7	2		A		77		67
8	1		A		42		62
9	2		A		80		60
10	2		A				83[e]

[a] A = Carbamate deprotonation (*s*-BuLi, sparteine or TMEDA, THF, -78 °C) followed by sequential addition of 1.0 equiv of CuCN· 2LiCl (-55 °C, 45 min) and allenyl ester [TMSCl (2.5 equivs), -55 °C to r.t.]. B = Same conditions as in A, except 0.5 equiv CuCN· 2LiCl per RLi was employed. [b] Isolated yields based upon products purified by chromatography. [c] Diastereomeric ratio determined by ^{1}H NMR analysis; > 95:5 unless noted. [d] Boc deprotection and lactam formation was effected with PhOH/TMSCl in methylene chloride (25 °C, 2 h). [e] Catechol boron bromide was employed.

The α,β-β,γ-allenyl esters were prepared from α-phosphoranylidene esters and acid chlorides according to an established procedure in yields of 47-58%.[11] This Wittig Horner reaction could be extended to the preparation of methyl 4-phenyl-2,3-pentadienoate (47%), but not to the preparation of methyl 2,4-diphenyl-2,3-butadienoate (5%), ethyl 2-carboethoxy-2,3-pentadienoate, or ethyl 4-carboethoxy-2,3-butadienoate.

In a typical procedure, 1.0 mmol of the *tert*-butoxycarbonyl protected amine was deprotonated[9] with *sec*-butyllithium (1.2 mmol, THF, 1 h) / TMEDA at -78 °C followed by addition of either 0.5 or 1.0 equivalents of CuCN·2LiCl to afford the cuprate reagents. Addition of the allenyl ester at -55 °C, followed by slow warming to room temperature afforded the β,γ-unsaturated esters without any trace of the α, β-enoates. Treatment of the carbamates with phenol / TMSCl in methylene chloride resulted in sequential Boc deprotection and lactamization under the reaction conditions. The conjugate addition reaction gave slightly lower yields with the reagent prepared from two equivalents of RLi / CuCN·2LiCl (entry 1 vs 2), which is fortunate since the cyanocuprate reagent, RCuCNLi, is more efficient because the former reagent transfers only one α-aminoalkyl ligand.

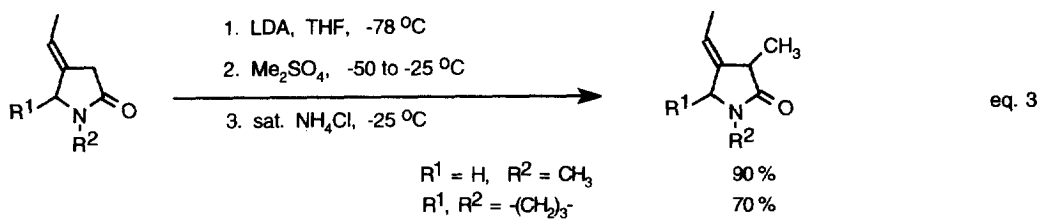
The conjugate addition reaction proceeds in modest to good yields with allenyl esters containing a single substituent in the 4-position (Table). Allenyl esters with an alkyl substituent on the unreactive olefin undergo the conjugate addition reaction in higher yields (entries 1-3, and 6-7) than those substituted with a phenyl group in the 4-position (entries 4-5) and this may reflect differences in electron density at the sp-hybridized allenic carbon atom. Allenyl esters containing an aryl substituent at the 2-position did not undergo conjugate addition reactions with the α-aminoalkylcuprates, consistent with the general tendency of reduced reactivity of 2-alkyl substituted enones and enoates toward organocuprate reagents.[12] γ,γ-Disubstituted allenyl esters gave modest to good yields of the conjugate adducts (entries 8-9) indicating a modest steric effect that may account for the observed stereoselectivity of the reaction (see eq. 2). The stereoselectivity of the reaction can be readily accounted for by consideration of steric hindrance between the approaching cuprate reagent and the substituent on the 4-position of the allenyl ester. Approach of the cuprate from the opposite side of the substituent places the substituent and the α-aminoalkyl group *trans* to each other in the unconjugated double bond of the 1,4-adduct (eq. 2). The stereochemistry of this double bond, with one exception, is largely maintained during the deprotection and subsequent lactamization process. The conjugate adduct (eq. 2, R = H; R^1 = Me) was reduced with $LiAlH_4$ (in order to eliminate the rotomers resulting from a barrier to rotation about the carbamate C-N bond), and led to a 92:8 mixture of diastereomers identical to the diastereomeric ratio of the starting 1,4-adduct. Difference NOE experiments on the 1,4-adduct (eq. 2, R = H; R^1 = Me) confirmed the (*E*) olefin stereochemistry (i.e., R^1 *cis* to the ester functionality). The single example affording poor olefin stereoselectivity (entry 5) points to olefin isomerization during the Boc-deprotection and lactamization step since the 1,4-adduct appears to be a single stereoisomer.



Treatment of the 1,4-adduct with phenol and chlorotrimethylsilane effected cleavage of the Boc protecting group and promoted lactam formation in modest yields (Table, 60-67%). The uncyclized product could not be isolated from the reaction mixture nor was the α,β-unsaturated lactam observed. Cleavage of the Boc protecting group with catechol boron bromide[13] also effected lactamization and in higher yields (83%, entries 1, 10).

The lactams can be deprotonated with lithium diisopropylamide and alkylated with electrophiles (eq. 3) providing a synthetic strategy permitting substitution at all four carbons of the pyrrolidine ring system. The alkylation reaction proceeds without isomerization of the double bond.

In summary, the conjuate addition of α-aminoalkylcuprates to allenyl esters provides a rapid synthesis of 4-alkylidene 2-pyrrolidinones and 2-pyrrolizidinones with excellent regio- and stereocontrol of the C=C double bond. The resultant lactams can be alkylated providing a flexible synthetic strategy for introducing alkyl substituents at all four positions of the lactam ring.



Acknowledgement: This work was generously supported by the National Science Foundation (CHE-9408912).

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