Pergamon

Tetrahedron Letters 40 (1999) 9019–9020

TETRAHEDRON
LETTERS

Diastereospecific alkylation of heterocyclic β-amino esters

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Received 21 July 1999; accepted 29 September 1999

Abstract

Heterocyclic β-amino esters can be diastereoselectively alkylated with alkyl halides to lead to direct precursors of bicyclic alkaloids. © 1999 Elsevier Science Ltd. All rights reserved.

We have recently described the synthesis of the (–) indolizidine 209B,[1a] starting from the synthon **2** prepared by the alkylation of the pyrrolidyl acetate **1** by various alkyl halides and using LDA as a base. Good yields and excellent *de* (>95%) were observed. But Knight et al.[2] reported a curious result concerning the pyrrolidyl acetate **3** and the piperidyl acetate **5** allylation using LiHMDS as a base: the formation of compound **4** was then observed as an unseparable mixture of two diastereomers (1.3:1) even though the alkyl derivative **6** was isolated with only 70% *de*.

The piperidine ring system is a sub-unit present in many naturally occurring compounds[3] so we decided to study the alkylation of the piperidyl acetate **7**. Herein we wish to report new diastereoselective conditions for the alkylation of such heterocyclic β-amino esters.

The enantiopure β-amino ester **7** did not react in the conditions used with pyrrolidine derivatives **1**, but **7** was diastereoselectively alkylated with different alkyl or alkenyl halides when using LiHMDS as a base. Under these conditions alkylated compounds **8** (Scheme 1) were isolated in very good yields and with *de*s always higher than 95%. It can be noted that only primary halides react with these conditions.

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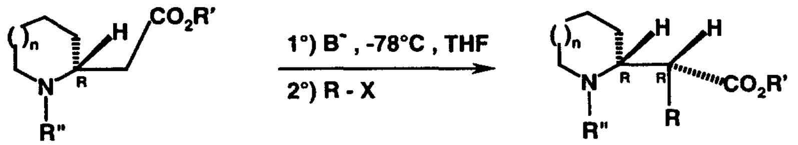
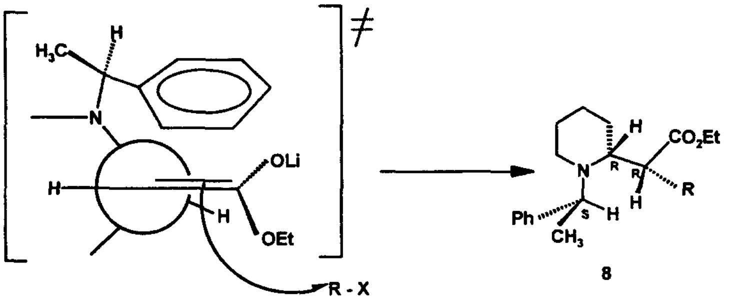
PII: S0040-4039(99)01917-6



1 R' = Et ; R" = CH(CH_3)Ph (S) ; n = 0 → **2** R = alkyl , alkenyl [1b]
3 R' = Me ; R" = Boc ; n = 0 → **4** R = allyl [2a]
5 R' = Me ; R" = Boc ; n = 1 → **6** R = allyl [2b]
7 R' = Et ; R" = CH(CH_3)Ph (S) ; n = 1 → **8** R = alkyl , alkenyl

Compound	R	Yield (%)	d.e. (%)	$[\alpha]^{20}_{D}$ (CH_2Cl_2.Conc.)
8a	CH_3	80	98	+ 11.1 (1.1)
8b	C_2H_5	70	98	+ 15.5 (0.8)
8c	n-C_3H_7	55	98	+ 9.3 (1.0)
8d	n-C_4H_9	60	98	+ 10.4 (1.1)
8e	n-C_6H_{13}	45	90	+ 5.1 (1.0)
8f	CH_2-C_6H_5	76	100	+ 5.6 (0.9)
8g	CH_2-CH=CH_2	92	98	+ 22.8 (1.1)
8h	CH_2-CH=CH-CH_3[a]	70	98	---

a : As a mixture of *E* and *Z* isomers



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Scheme 1.

The high diastereoselectivity can be explained by the conformation of the transient lithium *E* enolate where the $A^{1,3}$ strain is minimized.

The π-stacking between the phenyl group and the C=C double bond could explain the better selectivity observed with the piperidylacetate **7** compared to the compound **5** bearing an *N*-Boc substituent.

In conclusion, kinetic piperidinic β-amino esters **3** with 2*R*,2′*R* absolute configurations (*syn* relationship) can be obtained with a very high diastereoselectivity by a direct *C*-alkylation of β-amino esters **2** using LiHMDS as a base.

References

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