Stereoselective α-Alkylation of α,β-Unsaturated Esters Utilizing Conjugate Addition of Nitrogen Nucleophiles (R_2NLi)

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Treatment of α,β-unsaturated esters (**1**) with lithium amides [$LiNPr^i_2$ and $LiN(CH_2Ph)SiMe_3$] followed by alkylation and elimination of the amino groups produced trisubstituted enoates (**2**) with high stereoselectivity.

Nitrogen anions R_2N^- are commonly used as strong bases for deprotonation of various kinds of organic compound. However, nucleophilic reactions of R_2NM, such as conjugate addition to α,β-unsaturated esters, have been given little attention.[1—3] We report here a convenient procedure for stereoselective α-alkylation of α,β-unsaturated esters *via* conjugate addition of R_2NLi followed by alkylation and elimination [equation (1)]. The results are summarized in Table 1.

Treatment of methyl crotonate (**1a**) with lithium di-isopropylamide (LDA) in THF at −78 °C for 1 h, followed by quenching with 1-iodo-octane (1.6 equiv., −78 to 20 °C) gave the β-amino ester (**3a**),† as a single stereoisomer, and methyl 2-vinyldecanoate (**4**) in 58 and 14% yields, respectively (entry 1). Formation of (**4**) indicates that removal of the γ-proton of (**1a**) to give the dienolate (the preferred process in the presence of hexamethylphosphoric triamide[1]) competes with conjugate addition of LDA.

This deprotonation process can be suppressed by employing lithium *N*-benzyltrimethylsilylamide [$LiN(CH_2Ph)SiMe_3$] (LSA) instead of LDA. A reaction of (**1a**) and LSA followed

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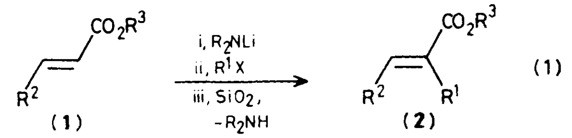
† All new compounds gave satisfactory spectral, microanalytical, and/or high-resolution mass data.

Table 1. Stereoselective α-alkylation of α,β-unsaturated esters.[a]

Entry	Substrate	Nucleophile	R^1X	β-Amino ester intermediate(s) (yield)	α-Alkylated ester (overall yield, *E*/*Z*[b])
1	(**1a**)	LDA	$n\text{-}C_8H_{17}I$	(**3a**) (58%)	(**2a**) (56%, 93/7)
2	(**1a**)	LSA	$n\text{-}C_8H_{17}I$	(**5a**) (48%), (**5b**) (33%)	(**2a**) (72%, 85/15)
3	(**1a**)	LDA	MeI	(**3b**) (75%)	[c]
4	(**1a**)	LSA	MeI	(**6a**) + (**6b**) (99%; 1 : 1)[d]	[c]
5	(**1a**)	LDA	Me_2CCHCH_2Br	(**3c**) (66%)	(**2b**) (52%, 88/12)[e]
6	(**1a**)	LSA	$PhCH_2Br$		(**2c**) (74%, 87/13)
7	(**1b**)	LDA	MeI		(**2d**) (69%, 88/12)
8	(**1c**)	LDA	MeI		(**2e**) (33%, 95/5)

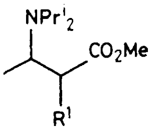
[a] All reactions were carried out on 2 mmol scale. Typical conditions are described in the text. [b] The ratios were determined by g.l.c. using a fused silica capillary column (Shimazu CBP20-M25-025). [c] Not yet attempted. [d] Determined by 90 MHz ^1H n.m.r. spectroscopy. [e] The assignments of stereostructures are tentative.



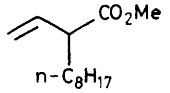
(**1**) (**2**) (1)

a; R^2 = Me, R^3 = Me
b; R^2 = $n\text{-}C_7H_{15}$, R^3 = Et
c; R^2 = Pr^i, R^3 = Et

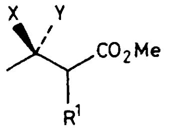
a; R^1 = $n\text{-}C_8H_{17}$, R^2 = Me, R^3 = Me
b; R^1 = prenyl, R^2 = Me, R^3 = Me
c; R^1 = $PhCH_2$, R^2 = Me, R^3 = Me
d; R^1 = Me, R^2 = $n\text{-}C_7H_{15}$, R^3 = Et
e; R^1 = Me, R^2 = Pr^i, R^3 = Et



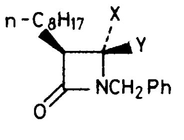
(**3**)
a; R^1 = $n\text{-}C_8H_{17}$
b; R^1 = Me
c; R^1 = prenyl



(**4**)



(**5**) **a**; R^1 = $n\text{-}C_8H_{17}$, X = H, Y = $NHCH_2Ph$
b; R^1 = $n\text{-}C_8H_{17}$, X = $NHCH_2Ph$, Y = H
(**6**) **a**; R^1 = Me, X = H, Y = $NHCH_2Ph$
b; R^1 = Me, X = $NHCH_2Ph$, Y = H



(**7**) **a**; X = Me, Y = H
b; X = H, Y = Me

by treatment with 1-iodo-octane gave only β-benzylamino esters (**5a** and **b**) in 48 and 33% yields, respectively (entry 2). These β-amino esters were convertible into the respective β-lactams (**7a**) (90%) and (**7b**) (70%) *via* hydrolysis followed by dehydration [KOH/aqueous MeOH; PPh_3, $(pyS)_2$/MeCN[4]]. The stereochemistry of (**5a** and **b**) is deducible from the stereostructures of (**7a** and **b**), confirmed by their ^1H n.m.r. spectral characteristics: (**7a**) $J_{3,4}$ 2.1 Hz; (**7b**) $J_{3,4}$ 5.4 Hz.

The amino ester enolates reacted with primary alkyl iodides and activated bromides (entries 1—6) but did not react with other alkyl halides such as 2-bromoethylbenzene and 2-iodopropane.

A typical procedure for generating α,β-unsaturation from β-aminopropionate involves quarternization followed by base-induced elimination.[5—7] The di-isopropylamino group of (**3**) may be readily removed by heating under reflux in toluene (5% solution) with silica gel (200% w/w) for 2 days.[8] The benzylamino group of (**5**) and (**6**) was eliminated only after *N*-methylation (MeI/K_2CO_3) followed by treatment with silica gel.

The α-alkylated crotonates thus obtained show high *E*/*Z* ratios (Table 1). It is noteworthy that both stereoisomeric β-benzylamino esters (**5a** and **b**) (entry 2) are convertible into the trisubstituted enoate (**2a**) (in 90 and 86% yields, respectively) in very similar *E*/*Z* ratios (86 : 14 and 91 : 9, respectively).

This three-step sequence is applicable to α-alkylation of other α,β-unsaturated esters, such as (**1b** and **c**) (entries 7 and 8). Successive treatment of (**1b**) with LDA, MeI, and silica gel gave (**2d**) in 69% yield with >88% *E* stereochemistry. This *E*/*Z* olefin ratio is very similar to that (86 : 14) of the product obtained by a Wittig–Horner reaction of octanal with the lithiated anion of triethyl 2-phosphonopropionate.

In conclusion, the synthetic equivalent of the α-carbanion of an α,β-unsaturated ester can be generated by conjugate addition of a nitrogen nucleophile (R_2NM). The present findings not only provide a new synthetic procedure for trisubstituted enoates but also open the door to a new application of metal amides in organic synthesis.

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