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Asymmetric Nucleophilic Addition of Chiral β – Enamino Esters to Acrylonitrile

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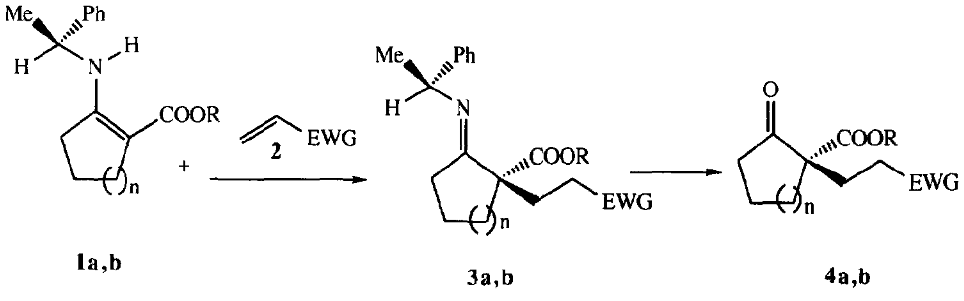
Abstract: β – enamino esters derived from β – keto esters and (S)-1- phenylethylamine, react with acrylonitrile in the presence of a Lewis acid or under high pressure activation to give, after hydrolytic work up, α,α – disubstituted β – keto esters 4 (EWG=CN) in enantiomeric excesses close to 90%.

Quaternary carbon centres are widely distributed in natural products and considerable effort has been recently directed toward their synthesis. Among the procedures designed to effect this important construction, the reaction of chiral imines with electrophilic olefins has provided a powerful means for obtaining cyclanones bearing a quaternary carbon centre at their α position[1]. As an extention of this method, it has been shown recently[2] that chiral β – enamino esters **1** react with electrophilic olefins **2** (MVK, acrylates, phenyl vinyl sulfone), in the presence of a Lewis acid or under high pressure activation, to give, via the primary Michael adducts **3**, the β – keto esters **4** which are isolated in good chemical and optical yields.The practical synthetic utility of this methodology has been substantiated by its use for the construction of (R)-(+)-2-nonyl-2(carbomethoxy) cyclopentanone, an intermediate in the synthesis of (-) malyngolide[3].



a n = 2, R = Et **b** n = 1, R = Me

In a further application of our previous study[2], we wish to report here the enantioselective synthesis of β –keto esters **4** (EWG = CN) by reaction of β – enamino esters **1** with acrylonitrile.This reaction would be of value since compounds **4** (EWG=CN) are central intermediates for the synthesis of alkaloids[4].

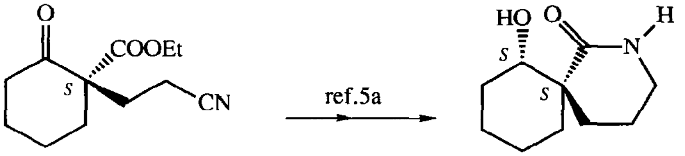
A comparative analysis of the results summarized in the Table clearly reflects the considerable influence of both the solvent and the Lewis acid on the enantioselectivities.*Best results were obtained in diethyl ether with zinc chloride* (entries 3 and 7).A similar observation was made previously for the reaction of 1 with MVK[2] Use of the more basic solvent THF resulted in rather long reaction times and a marked decrease in enantioselectivity (entries 2 and 3) A polar solvent seems necessary to obtain a significant chiral induction (compare entries 4 and

Table: Reaction of β – enamino esters **1a** and **1b** with acrylonitrile.

Entry	Substrate	cat.[a]	temp °C	solvent time(h)	%Y[b]	$[\alpha]^{25}_{D}$	%ee[e]
1	1a	MgBr$_2$	45	THF 96	67	-80	67
2	1a	ZnCl$_2$	20	THF 24	89	-90	75
3	1a	ZnCl$_2$	-18	Ether 6	85	-106[c]	89
4	1a	Et$_2$AlCl	4	Toluene 72	88	-67	56
5	1a	Et$_2$AlCl	20	THF 48	89	-91	75
6	1b	MgBr$_2$	65	THF 65	80	+17.6	66
7	1b	ZnCl$_2$	0	Ether 2.5	41	+23[d]	87
8	1b	Et$_2$AlCl	4	Toluene 72	85	+16.1	61
9	1a	12Kbar	20	THF 90	56	-97	81

[a]Reactions were conducted with molar ratio of substrate:catalyst:acrylonitrile = 1:1:1.5; Reactions under high pressure were conducted with molar ratio of substrate:acrylonitrile = 1:1. [b]Yield is based on starting β – enamino esters and refers to material purified by flash chromatography and distillation. [c]Measured in EtOH (c = 1.8).[d]Measured in EtOH (c = 2.6).[e]Determined by GPC on a chiral column[7] and by ^{1}H NMR analysis of the corresponding dioxolane in the presence of Eu(hfc)$_3$.

5). Particularly striking, and also unexpected, is that aluminum and zinc catalysts (with one and two empty coordination sites respectively) gave, under the same reaction conditions, the same enantioselectivity (cf entries 2 and 5).The last entry shows that compound **4a** could be obtained by application of high pressure conditions in slightly lower ee than the optimal one observed under Lewis acid catalyzed conditions (compare entries 9 and 3). The assignment of (S) configuration at the thus generated quaternary stereogenic center in **4a** was made on the basis of chemical correlation [4a] with spirolactame **5**[5] and is in accordance with the transition state model proposed for this Michael process[1,6].



1a **5**

In conclusion, we have shown that β – keto esters **4** (EWG = CN), potentially useful synthons in alkaloid synthesis, can be obtained in ee close to 90% by the reaction of β – enamino esters **1** with acrylonitrile.

References and notes

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6. (S) configuration at the quaternary carbon center in **4b** was assigned by analogy with **4a**.
7. We thank Pr. Tabacchi, Université de Neuchâtel (Switzerland) for the measurements.