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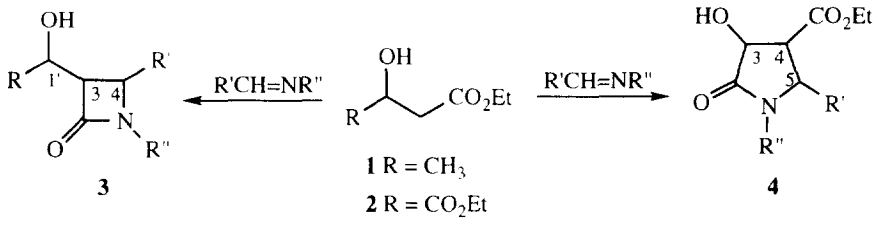
Stereoselectivity in the Condensation Reactions between Malate Enolate and Imines to 2-Pyrrolidinone Derivatives

Deok-Chan Ha*, Kyeong-Soon Yun, Hye-Sang Park, Won-Keun Choung, and Young-Eun Kwon

Department of Chemistry, Korea University, 5-1-2 Anam-dong, Seoul, Korea 136-701

Abstract: Enolate dianion of diethyl (*S*)-malate was stereoselectively condensed with nonenolizable *N*-arylimines to give 2-pyrrolidinone derivatives. The presence of HMPA changes the diastereoselectivity of this cyclization reaction.

The use of chiral molecules from natural sources as a building block of target molecules is greatly exploited in organic synthesis.[1] Enolate of ethyl 3-hydroxybutyrate **1**, readily available in optically pure form, was condensed with imines to produce 2-azetidinones **3** with appropriate substituents for carbapenem synthesis.[2,3] This approach produces excellent diastereocontrol between C(3) and C(1') of **3** due to the chelated (*Z*)-form of enolate dianion of **1**.[4] In a similiar fashion, enolate dianion of diethyl malate **2** was also alkylated with high stereoselectivity.[5] Surprisingly, however, study on the reactions between malate enolate and imines, which would produce 2-pyrrolidinone **4** instead of 2-azetidinone **3** due to the ring strain, has not been reported. If this enolate-imine condensation from **2** follows a similiar pattern to that of **1**, the stereoselective formation of **4** would be a valuable approach for the synthesis of 3-hydroxy-4-hydroxymethylpyrrolizidine alkaloid, necine, derivatives.[6]



3

1 R = CH_3
2 R = CO_2Et

4

Thus, enolate dianion of diethyl (*S*)-malate **2**, generated with two equivalent of lithium hexamethylsilazide in THF at -78 °C, was reacted with several nonenolizable *N*-arylimines[7] (Table 1). Though the yields of these condensation reactions were less than desired, diastereoselectivity at two newly generated stereocenters, C(4) and C(5) of **5**, has been improved compared to the selectivity at C(3) and C(4) of **3** prepared by the reaction between enolate of (*S*)-**1** and the corresponding imine. When four equivalents of HMPA were added to the enolate before the addition of imine, **7** was predominantly formed. This result was strikingly different compared to the reaction for **3** from **1** which proceeded with the same diastereoselectivity at C(3) relative to C(1') regardless of the presence of HMPA.

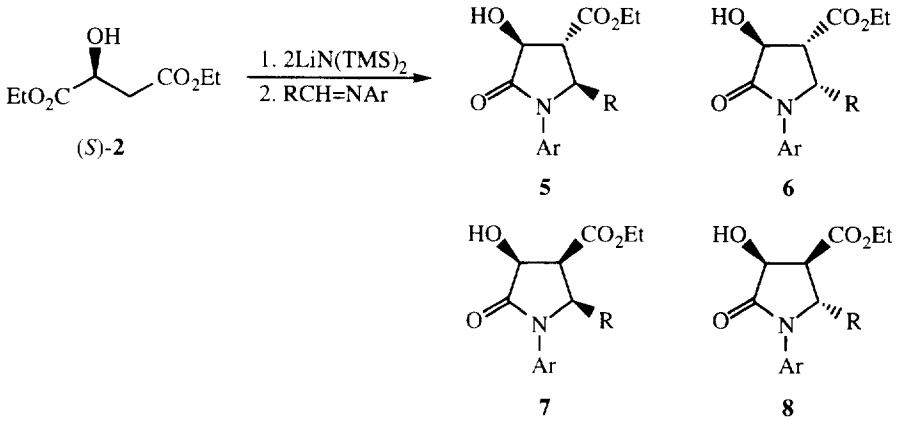


Table 1. Condensation Reactions of Malate Enolate and Nonenolizable *N*-Arylimines

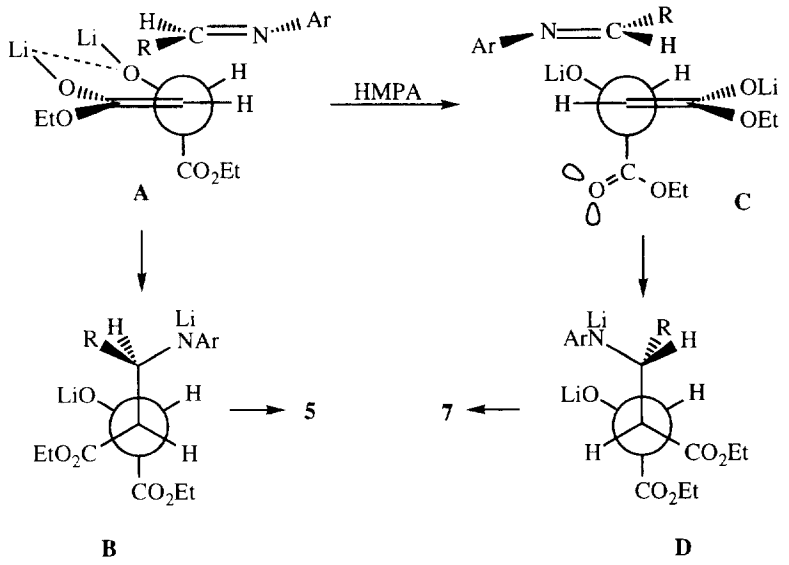
Entry[a]	R	Ar	Yields (%)[b,c]	Solvent[d]	**5** : **6** : **7** : **8**[e]
1	Ph	*p*-MeOPh	60	THF	3 : 1
2	Ph	*p*-MeOPh	32	THF-HMPA	> 30 : 1
3	*p*-MeOPh	*p*-MeOPh	trace	THF	
4	*p*-MeOPh	*p*-MeOPh	32	THF-HMPA	10 : 1
5	2-Furyl	*p*-MeOPh	34	THF	5 : 1
6	Ph-C≡C-	*p*-MeOPh	43	THF	4 : 1
7	Ph-C≡C-	*p*-MeOPh	32	THF-HMPA	**7** only
8	Ph-CH=CH-	*p*-MeOPh	trace	THF	

a) The reactions were generally performed on a 5-mmol scale. b) The reaction mixture was warmed to 0°C 1hr after addition of imine at -78 °C and allowed to stand for 2-3 hrs before quenching with saturated NH_4Cl. c) Yields were obtained after chromatography (silica gel, hexane / ethyl acetate). d) Four equivalents of HMPA were added before the addition of imine. e) The ratio was determined by ^{1}H-NMR (300 MHz).

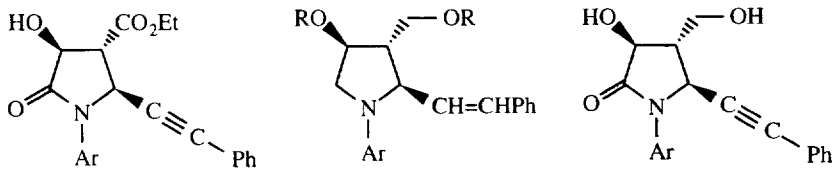
Relative stereochemistry at C(4) and C(5) against the C(3) position of **5** and **7** (R = Ph, Entry 1 and 2, Table 1), purified by recrystallization of the diastereomeric mixtures, was determined by NOE enhancement experiments.[8] NOEs were observed only between the hydrogens at C(3) and C(5) in **5**, but **7** displayed NOEs between all three hydrogens at C(3), C(4) and C(5) positions.[9]

Our explanation of the observed stereochemical results of these condensation reactions is as follows. The imine approached the sterically less demanding π-side of intramolecularly chelated (*Z*)-enolate **A** to give erythro amidoester **B** which cyclized to 2-pyrrolidinone **5**. Chelation is highly improbable in the presence of HMPA and conformer **C** was favored over **A** on the basis of steric repulsion between enolate and the alkoxide parts in **C**.[10] Cyclization of the threo amidoester **D** would give all-*cis* isomer **7** (Entry 2 and 4, Table 1). In conformer **C**, the perpendicularly disposed carbethoxy group directed the antiperiplanar approach of imine. Studies

strongly suggested that the lone pair on homoallylic heteroatom increased reactivity between HOMO of ester enolate and LUMO of electrophile through secondary orbital interaction.[11,12] Thus, the lone pair on carbonyl oxygen antiparallel to the perpendicular σ-bond might be responsible for the diastereoselectivity at the C(4) position of **7**. We imagine that the selectivity at C(5) of **5** and **7** arises from repulsive interactions between the substituents of imine and the alkoxide part of the enolate.



The diastereomeric mixture **9**, obtained by condensation between malate enolate dianion and phenylpropargylidene *p*-anisidine (Entry 6, Table 1), was converted to potentially useful intermediates **11** and **12** for pyrrolizidine alkaloid synthesis. Thus, treatment of **9** with five equivalents of lithium aluminium hydride in THF heated at reflux for 24 hours produced diol **10** (74 %) which was converted to a diastereomeric mixture **11** (80%) with TBSCl and triethylamine in DMF. When the mixture **9** was reduced with $LiBH_4$ in diglyme, diastereomerically pure **12** was isolated in 70% yield together with 18% of a minor diastereomer of **12** after SiO_2 chromatography. Further studies for synthesis of pyrrolidine and pyrrolizidine alkaloids from **12** and **7** (entry 7, table 1) are in progress.



9

10 : R = H
11 : R = TBS

12

(Ar = *p*-methoxyphenyl)

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7. Imines were prepared from the corresponding aldehydes and *p*-anisidine crystallized in ethanol.
8. **5** (R = Ph): mp 156-157 °C; FT-IR (KBr) 3540, 1712, 1514, 1247, 1024 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7 Hz, 3H, CH_3), 3.14 (t, *J* = 8 Hz, 1H, C*H*CO_2Et), 3.70 (s, 3H, OCH_3), 4.22 (q, *J* = 7 Hz, 2H, CO_2CH_2), 4.75 (d, *J* = 8 Hz, 1H, C*H*Ph), 5.27 (d, *J* = 8 Hz, C*H*OH), 6.75 (d, *J* = 9 Hz, 2H, ArH), 7.18 (d, *J* = 9 Hz, 2H, ArH), 7.23 (m, 5H, ArH). **7** (R = Ph): mp 150-152 °C; FT-IR (KBr) 3334, 1709, 1515, 1252, 1025 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.22 (t, *J* = 7 Hz, 3H, CH_3), 3.18 (t, *J* = 8 Hz, 1H, C*H*CO_2Et), 3.63 (s, 3H, OCH_3), 4.20 (m, 2H, CO_2CH_2), 4.81 (d, *J* = 8 Hz, 1H, C*H*Ph), 5.28 (d, *J* = 8 Hz, 1H, C*H*OH), 6.74 (d, *J* = 9 Hz, 2H, ArH), 7.20 (d, *J* = 9 Hz, 2H, ArH), 7.23 (br s, 5H, ArH).
9. The chemical shifts of major signals from **5**, **6**, **7** and **8** in ^{1}H-NMR are all different and stereochemistry of **6** and **8** are tentatively assigned based on the stereochemical behavior of the reaction between **1** and imine.
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