COMMUNICATION

Self-regulated molecular rearrangement: diastereoselective zwitterionic aza-Claisen protocol

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Treatment of *N*-but-2-enylpiperidine with acyl halides in the presence of K_2CO_3 afforded the corresponding Claisen products with high diastereoselectivity depending on the *E* or *Z* but-2-enyl geometry.

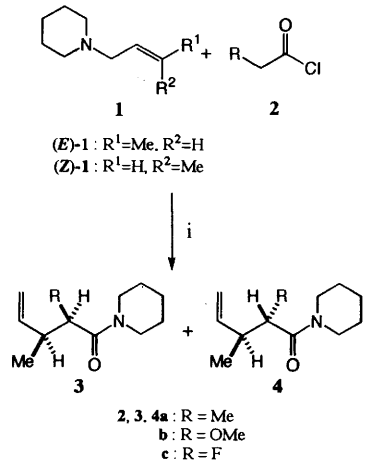
The availability of efficient synthetic methods for achieving diasteroselectivity in the construction of acyclic systems is of considerable current interest because such structures are featured in many biologically relevant substances.[1] In this regard, the Claisen rearrangement and its variants provide an excellent stereoselective route to γ,δ-unsaturated carbonyl units *via* a [3,3]-sigmatropic process.[2] The impact of Claisen protocols on modern synthetic chemistry is exemplified by the numerous attempts to apply them to new strategies for the synthesis of complex natural products.[3] Since the general reaction mechanism does not involve ionic species, the reaction conditions should have a significant effect on the formation of the required six-membered transition structures and electronic influences for allylic vinyl ether substrates.[4] For example, Denmark and co-workers demonstrated a carbanion accelerated Claisen rearrangement and research in this area undoubtedly provided mechanistic insight into the [3,3]-sigmatropic rearrangement and extended its synthetic applications.[5] Recently, Yamamoto and co-workers designed a useful method for the formation of a favourable transition-state model using Lewis acid receptors based on a molecular recognition approach.[6] There have therefore been continuing mechanistic and synthetic challenges in Claisen protocols to innovate reaction conditions for diastereo- and enantio-selection. There have been reports of [3,3]-sigmatropic rearrangements of allylic ethers and sulfides with dichloroketene[7] and allylic amines have also found limited applications.[8] In this communication we report a diastereoselective aza-Claisen protocol using zwitterionic intermediates that undergo a facile [3,3]-sigmatropic rearrangement.

Treatment of (*E*)-but-2-enylpiperidine [(*E*)-**1**, R^1 = Me, R^2 = H]† with propanoyl chloride **2a** in the presence of anhydrous K_2CO_3 in toluene at 0 °C for 1 h effected the desired [3,3]-sigmatropic rearrangement. Work-up followed by silica gel chromatography afforded an inseparable mixture of diastereoisomers **3a** and **4a** (41%) in a ratio of 94:6 as judged by 300 MHz ^{1}H NMR spectrum. Both the *E* and *Z* olefinic isomers of the starting but-2-enylpiperidine were shown to produce the same two rearranged products. However, the relative ratio of these two products depended on the olefinic geometry: (*Z*)-but-2-enylpiperidine (*Z*)-**1** with propanoyl chloride under the same conditions produced **4a** as the major component. Additional experiments with substituted acyl chlorides were carried out to produce various amides with high diastereoselectivities and the results are summarized in Table 1. The remarkable observation has been made previously that using fluoroacetyl chloride as the zwitterionic ion precursor results in a much higher diasteroselectivity (as high as 20:1) in comparison with the allyl fluoroacetate used for the Ireland variant.[9] The relative stereochemistry of the products was unambiguously verified by the direct comparison of ^{1}H NMR spectra with authentic samples which were prepared by the Ireland method[10] of corresponding but-2-enyl esters followed by amide synthesis using $(PhO)_2PON_3$.

Table 1

Entry	Piperidine **1**	RCH_2COCl **2**	Products	Ratio **3**:**4**[a]	Yield (%)[b]
1	(*E*)-**1**	Me	**3a**, **4a**	94:6	41
2	(*Z*)-**1**	Me	**3a**, **4a**	3:97	38
3	(*E*)-**1**	OMe	**3b**, **4b**	92:8	44
4	(*Z*)-**1**	OMe	**3b**, **4b**	5:95	39
5	(*E*)-**1**	F	**3c**, **4c**	95:5	61
6	(*Z*)-**1**	F	**3c**, **4c**	4:96	57

[a] Determined by the analysis of high field ^{1}H NMR of crude products. [b] Chromatographed yield.



Scheme 1 *Reagents and conditions:* i, K_2CO_3, 0 °C, 1 h, toluene

The observed preference for the relative geometry of zwitterionic species **7** rather than **8** could be rationalized in terms of two possible transformations: path A, proton abstraction from acylammonium **5** by the amine base, occurs with a preference for conformation **5a** over **5b** in order to avoid the steric interaction as illustrated in Fig. 1; path B, *anti* addition of but-2-enylpiperidine **1** to the less hindered hydrogen-substituted face of ketene **6**. The role of insoluble K_2CO_3 could be as a base to regenerate the but-2-enylpiperidine **1** from the amine salt rather than to participate directly in the formation of zwitterionic intermediate from acyl chloride. The zwitterionic intermediate **7** can form a chair-like transition-state with optimum stereoelectronics and minimum steric repulsion

† But-2-enylpyrrolidine was also used, but somewhat lower yields were obtained. Other acyclic but-2-enylamines including dibut-2-enylbenzylamine were unsuccessful.

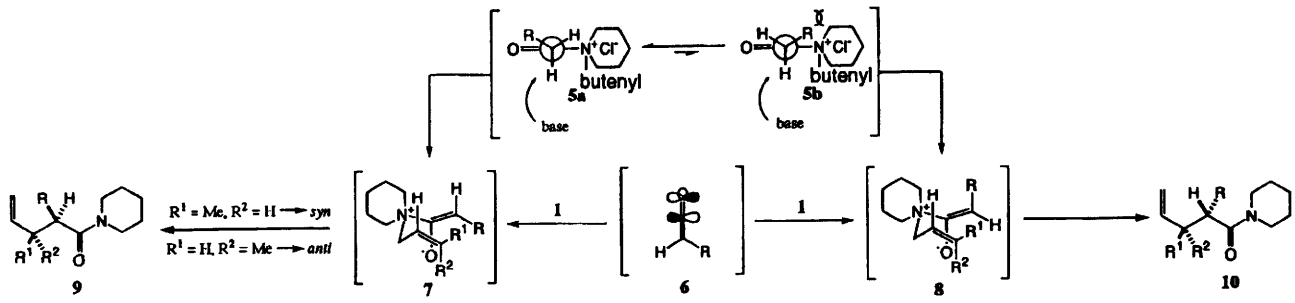
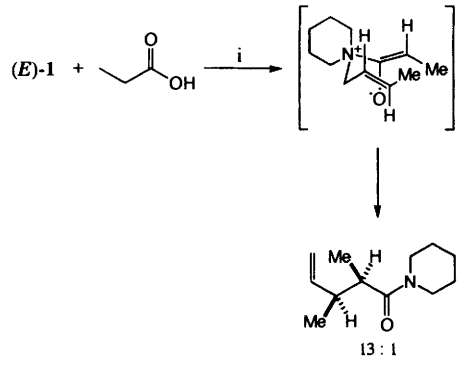


Fig. 1 Possible stereochemical course of reaction



Scheme 2 *Reagents and conditions:* i, PPh_3Br_2, 0 °C, 2 h, toluene

between appendages on the piperidine ring, and could give a smooth rearrangement to generate major product **9** as depicted in Fig. 1. The fluorine-substituted **3c** and **4c** also showed high diastereoselectivity: however, lack of steric control in forming the zwitterionic enolate suggests that stereoelectronic effects, *e.g.* repulsion between nonbonding electrons, are the most significant factor.[11] Therefore the formation of **7** through path B might be more plausible since stereochemical control in path A is only due to steric interactions.

The identical rearrangement with propionic acid and (*E*)-but-2-enylpiperidine was also investigated. Treatment of propionic acid with 3 equiv. of (*E*)-but-2-enylpiperidine in the presence of triphenylphosphine dibromide in toluene at 0 °C for 2 h afforded **3a** as a major product. The reaction was efficiently diastereoselective (13 : 1), but in only 28% yield.

In summary, we have demonstrated a synthetic methodology for the diastereoselective aza-Claisen protocol using zwitterionic species with efficient diastereoselectivities and moderate chemical yields.[12] Studies are in progress to develop more practical procedures and to incorporate chiral auxiliaries into the asymmetric synthesis.

Experimental

Typical procedure

To a suspended solution of (*E*)-*N*-but-2-enylpiperidine (*E*)-**1** (166 mg, 1.2 mmol) and anhydrous K_2CO_3 (250 mg, 1.88 mmol) in toluene (1.5 cm^3) was added dropwise propanoyl chloride **2a** (132 mg, 1.44 mmol) in toluene (1 cm^3) at 0 °C. The reaction was allowed to proceed for 1 h and then quenched by the addition of water at 0 °C. The aqueous layer was extracted with diethyl ether (3 ×). The combined organic extracts were washed with aq. HCl (10%), saturated aq. $NaHCO_3$ and brine, separated, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (hexane–EtOAc, 1 : 1) to afford an inseparable mixture of the rearranged amides **3a** and **4a** (96 mg, 0.49 mmol, 41%) in a ratio judged by high field ^1H NMR to be 94 : 6, respectively: δ_H(300 MHz; $CDCl_3$) 0.99 (d, *J* 7.47 Hz, $CHCH_3$), 1.07 (d, *J* 6.67, $CHCH_3$), 1.42–1.64 (m, piperidine ring $-CH_2CH_2CH_2-$), 2.42 (m, $CHCH_3$), 2.61 [m, COCH, (CH_3)-CH], 3.34–3.69 (m, $-CH_2NCH_2-$), 4.88–5.03 (m, $CH{=}CH_2$) and 5.77 (m, $CH{=}CH_2$); ν_{max}(neat)/cm^{-1} 3095, 2935, 1638, 1439 and 1071; *m*/*z* (EI) 195 (M^+, 11.5%), 180 (32.2), 140 (60.9), 84 (81.6), 69 (29.9), 55 (54.0) and 41 (100).

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