Pergamon

Tetrahedron Letters 39 (1998) 2107–2110

TETRAHEDRON LETTERS

Stereoselective Hetero-Claisen Rearrangement of Camphor derived Oxazoline-*N*-oxides.

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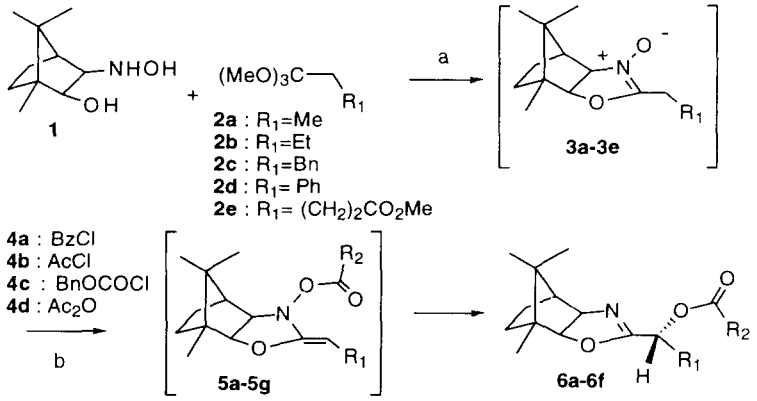
Received 26 November 1997; accepted 1 January 1998

Abstract: Camphor derived oxazoline-*N*-oxides in the presence of various acylating agents afforded α-acyloxyoxazolines resulting from a diastereoselective [3,3] rearrangement. The configuration of the newly formed asymmetric center was established by chemical correlation. The observed diastereoselectivity accounts a concerted rather than a stepwise process.

Stereoselective formation of C-O bond by oxygenation of enolates is well precedented in literature[1]. We anticipated that the same transformation could be achieved *via* a stereoselective hetero Claisen rearrangement using oxazoline-*N*-oxides as starting material. In fact, the rearrangement of cyclic or acyclic nitrones in the presence of acetic anhydride or benzoyl chloride is well known[2]. Oxazoline-*N*-oxides reacted similarly with imidoyl chloride and afforded α-amino oxazolines[3]. However the exact nature of the mechanism involved in such transformations is still questionable[2f], both stepwise and concerted processes being both likely. We present in this paper the first asymmetric version of these rearrangements starting with camphor derived oxazoline-*N*-oxides which afforded stereoselectively α-acyloxysubstituted oxazolines. Furthermore this outcome gives insight into the mechanism of these reactions.

Condensation of hydroxylamino*iso*borneol **1** with orthoesters **2a-2e**, following a described procedure[4], afforded oxazoline-*N*-oxides **3a-3e**. The easy hydrolysis of these dipoles precludes their isolation, thus acylating agents **4a-4d** were introduced directly into the reaction medium together with triethylamine or a mixture of triethylamine and 4-dimethylaminopyridine. After standing at room temperature for 16 hours, oxazolines **6a-6f** resulting from a [3,3] transposition were isolated (Scheme 1)[5].



Scheme 1 : a) $R_1CH_2C(OMe)_3$ (3 eq), $CaCO_3$ (5 eq), PhMe, 40 °C, 3 h.
b) **4a-4e** (2.7 eq), Et_3N (2.9 eq), -20 °C to 20 °C, 16h.

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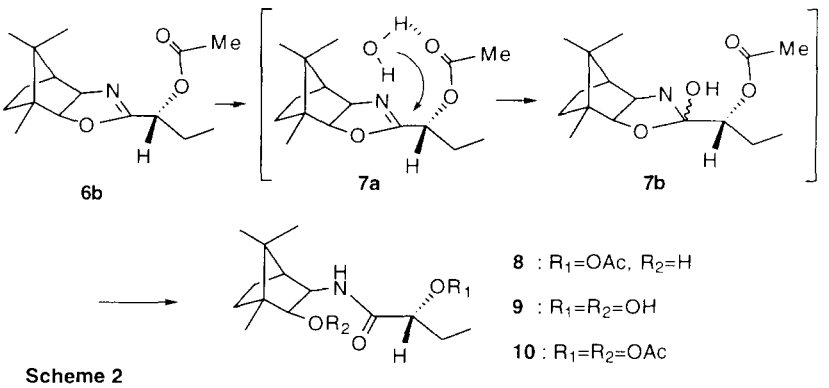
0040-4039/98/$19.00
PII: S0040-4039(98)00062-8

Results are summarized in the table. Yields are combined for the three steps: oxazoline-*N*-oxides formation, acylation and transposition. The moderate yields observed in these reactions are probably due to the instability of both starting material oxazoline-*N*-oxides **3**, and also of the acyloxyoxazolinium intermediates precursors of **5**. As shown, the effect of substitution pattern on side chain and the effect of various acylating agents on the chemical yield and diastereoselectivity were examined. Benzoyl chloride **4a** and acetyl chloride **4b** gave results in the same range in terms of yields and selectivities (entries 1-3) while acetic anhydride **4d** gave somewhat higher yield. Diasteroselectivities[6] were generally good except with benzyloxy chloroformate **4c** (entry 4). On the other hand, transposition was not observed with phenyl substituted oxazoline-*N*-oxide **3d** (entry 7). This lack of reactivity might be due to the greater stabilisation of intermediate **5f** in which conjugation with the phenyl substituent precluded further transposition.

Entry	Oxazoline-*N*-oxide (R_1)	Acylating agent (R_2)	Yield	Selectivity (de %)	α-Acyloxy oxazoline
1	**3a** (Me)	**4a** (Ph)	64	92	**6a**
2	**3b** (Et)	"	46	>95	**6b**
3	"	**4b** (Me)	41	92	**6c**
4	"	**4c** (BnO)	38	32	**6d**
5	"	**4d** (Me)	61	94	**6c**
6	**3c** (Bn)	"	67	95	**6e**
7	**3d** (Ph)	"	0	-	-
8	**3e** $(CH_2)_2CO_2Me$	"	58	95	**6f**

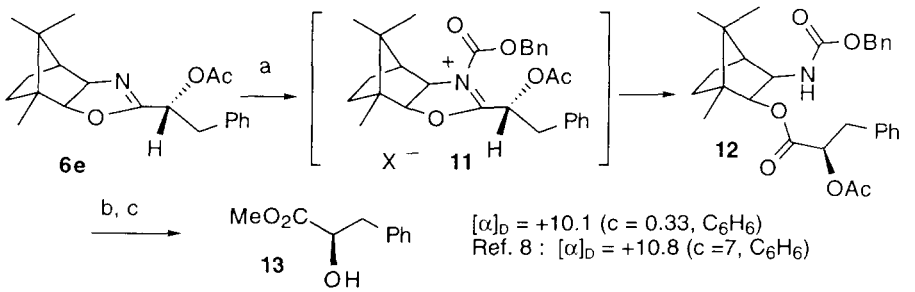
Table

Surprisingly in contrast to other camphor derived oxazolines, α-acyloxy oxazolines **6a-6f** proved to be rather unstable and are spontaneously hydrolyzed on standing. This particular reactivity might be due to the anchimeric assistance of the ester group of the side chain. Hydrogen bonding between the carbonyl of ester and a molecule of water, as depicted in intermediate **7a**, could led to the unstable tetrasubstituted intermediate **7b**. Subsequent fragmentation of **7b** gave rise to the ester amide **8** (Scheme 2). Thus oxazoline **6b** afforded quantitatively compound **8** after one week. The regioselectivity of this hydrolysis, which could theoreticaly led to oxazolidine C-O or C-N bond cleavage, was ascertained by derivatization of **8** to **9** and **10** (Scheme 2).



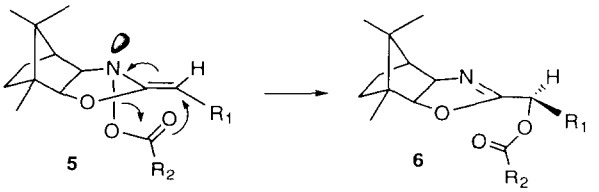
Scheme 2

Finaly, a chemical correlation has been achieved to determine the direction of the asymmetric induction of the newly created asymmetric center in oxazolines **6a-6f**. Accordingly, oxazoline **6e** after acylation under Schotten-Baumann condition[7] afforded ester urethane **12**. This compound was in turn saponified and reesterified to give the known hydroxy ester **13**[8] (Scheme 3).



Scheme 3: a) CbzCl (1.1 eq), $NaHCO_3$(2.2 eq),CH_2Cl_2/H_2O :1/1, 20 °C, 16 h, **12**, 71 %. b) NaOH (2.5 N, 10 eq), MeOH, 80 °C, 16h. c) CH_2N_2 (excess), Et_2O, 0 °C, 5 min, **13**, 63 %, 2 steps overall.

This chemical correlation suggests a model for the transition step during the transposition in which a *Z* keteneaminoketal **5** would be the subject of a [3,3] sigmatropic transposition by the α face of this intermediate (Scheme 4). The good diastereoselectivities generally observed in these reactions are also in favor of such a concerted process[9, 10].



Scheme 4

Acknowlegements : We thank N. Miquel who contributed to the initial phase of this work and A. Gavard for valuable technical assistance.

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5) ***Typical procedure*** : Into a 10 mL two necked argon flushed flask, equiped with magnetic stirrer and stopcocks, **1** hydrochloride salt (1.0 mmol, 222 mg) and finely powdered anhydrous $CaCO_3$ (1.1 mmol, 110 mg) were added. Anhydrous toluene (1 mL) and orthoester **2c** (3 mmol, 630 mg) were introduced *via* a syringe and the resulting suspension was stirred at 40°C for 3 hours. The reaction medium was evaporated *in vacuo* at room temperature to take off the formed methanol and the remaining toluene solution was cooled to -20°C under argon. Triethylamine (2.87 mmol, 400 µL) and a catalytic amount of 4-dimethylamino pyridine were added. After 15 min. at this temperature, acetic anhydride (2.65 mmol, 250 µL) was introduced. After stirring at the same temperature for 1 hour, the reaction medium was sirred at 20°C for additional 16 h. Water (5 mL) was added and the biphasic slurry was passed through a cotton plug and then extracted with CH_2Cl_2. After usual work up and purification by preparative TLC (SiO_2, pentane/ethyl acetate 2:1), **6e** (228 mg, 67%) was isolated as a viscous colourless oil.

6) Diastereoselectivities were measured by integrating characteristic MeCO group signals in ^1H NMR spectra of oxazolines **6c**, **6e** and **6f** and CHOCOR$_2$ signals for oxazolines **6a**, **6b** and **6d**.

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