Unexpected epimerization at C_2 in the Horner–Wadsworth–Emmons reaction of chiral 2-substituted-4-oxopiperidines†

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The observed epimerization at C_2 in the Horner–Wadsworth–Emmons (HWE) reaction of chiral 2-substituted-4-oxopiperidines has been investigated and, on the basis of the experimental results, a mechanism for this unexpected process has been proposed.

Functionalized piperidines are among the most common building blocks in natural products and, more interestingly, in many biologically active compounds.[1] The synthesis of these types of compounds has been studied extensively and in recent years thousands of piperidine compounds have been mentioned in clinical and preclinical studies directed toward the development of new drugs. Before such compounds can be used as drugs, however, it is necessary to perform their stereoselective synthesis.

A number of review articles have covered recent progress in the stereoselective synthesis of substituted piperidines.[2] Most of the synthetic methodologies described in the literature involve a plethora of approaches specific to the synthesis of a target compound, whereas the development of general synthetic methodologies in which preformed chiral non-racemic building blocks are used for the construction of a wide variety of simple or complex structures is less common. In this context, it is worth mentioning the use of chiral non-racemic *N*-cyanomethyloxazolidines,[3] *N*-alcoxycarbonyl 2,3-dihydro-4-pyridones,[4] 6-substituted 2,3-didehydropiperidine-2-carboxylates[5] and bicyclic piperidones.[6]

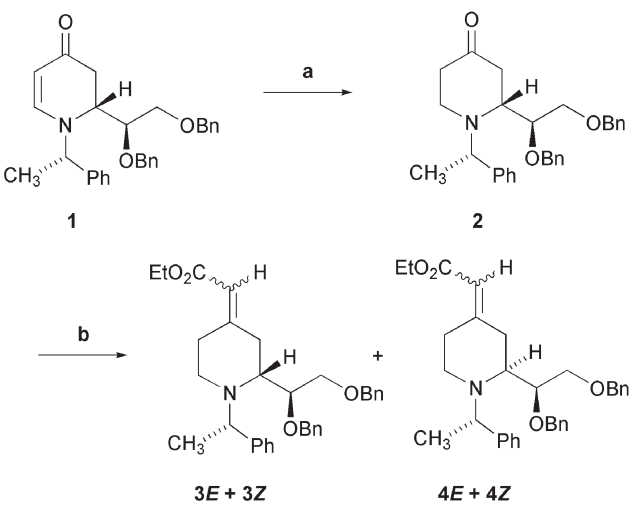
In our effort to develop a novel chiral non-racemic building block for the synthesis of substituted piperidines we have synthesized[7] enaminone **1** in a hetero Diels–Alder reaction with double stereodifferentiation. This chiral building block has proven to be a versatile intermediate in the synthesis of enantiomerically pure pipecolic acid derivatives such as (*R*)-4-oxopipecolic acid[7] and (2*R*,4*S*)-*N*-*tert*-butoxycarbonyl-4-hydroxypipecolic acid *tert*-butylamide.[8]

Previous results in this field[9] encouraged us to use Wittig-type reactions[10] as a way to introduce hydrocarbon substituents at C_4 in carbonylic compound **2**, which in turn was obtained by reduction of enaminone **1** with L-selectride® (Scheme 1).

Wittig reaction[11] of 4-oxopiperidine **2** with ethoxycarbonyltriphenylphosphonium methylide either did not occur or conversion was extremely low depending on the reaction conditions. The best result was observed using the phosphorus ylide generated by treatment of ethoxycarbonylmethyltriphenylphosphonium chloride (2.8 eq.) with potassium *tert*-butoxide (2.8 eq.). In this case the reaction was carried out for 43 h in toluene under reflux and only 15% of compound **3*E*** was isolated from the reaction mixture.

On the other hand, HWE reaction[12] of 4-oxopiperidine **2** with triethyl phosphonoacetate using DBU as the base only occurred under the reaction conditions reported by Masamune *et al.*,[13] which involve the use of lithium chloride when an amine is used as the base (Scheme 1). In addition, it was observed that in this case it was necessary to use at least 3.5 eq. of phosphonate to achieve complete conversion. Under these reaction conditions the corresponding olefins **3** were obtained in moderate to good yields as a diastereomeric *E*/*Z* mixture in which the *E* alkene was highly predominant. However, this product was surprisingly contaminated with varying amounts of the corresponding *E*/*Z* olefins **4** with the opposite configuration at C_2.[14]

The extent of epimerization at C_2 was dependent on the amount of DBU and the reaction time. On using 1.5 eq. of base and short reaction times (8 h) the formation of epimeric compounds was almost negligible and a 94/6 mixture of **3*E*/3*Z*** was obtained in 82% yield. The use of a large excess of DBU (10 eq.) and long reaction times (7 d) led to the highly preferential formation of olefins with the *S* configuration at C_2 in which compound **4*E*** was the major product (Table 1, entry 1). Olefins **4** were isolated from the reaction mixture in 78% yield.



Scheme 1 *Reagents and conditions*: (a) L-selectride®, THF, −78 °C, 85%; (b) $(EtO)_2P(O)CH_2CO_2Et$, LiCl, DBU, CH_3CN, r.t.

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Table 1 Epimerization of compounds **3*E*** and **3*Z***

Entry	Epimerization procedure[a]	**4/3**	**4*E*/4*Z***	Yield[b] (%)
1	A	92/8	88/12	78
2	B	91/9	81/19	51
3	C	93/7	90/10	50
4	D	92/8	85/15	59
5	E	92/8	76/24	74

[a] A, HWE reaction of **2** with triethyl phosphonoacetate for 7 d using 10 eq. of DBU as base. B, treatment for 7 d of the mixture **3*E*** + **3*Z*** of 2*R* configuration with 10 eq. of DBU in the presence of LiCl. C, treatment for 7 d of the mixture **3*E*** + **3*Z*** of 2*R* configuration with 10 eq. of DBU in the absence of LiCl. D, HWE reaction of **2** with triethyl phosphonoacetate for 7 d using 10 eq. of DBN as base. E, treatment for 7 d of the mixture **3*E*** + **3*Z*** of 2*R* configuration with 10 eq. of DBN in the presence of LiCl. [b] **4*E*** + **4*Z*** isolated yield.

Epimerization at C_2 was quite unexpected and additional experiments were performed in an effort to determine a plausible pathway for this reaction.

Firstly, the behavior of piperidone **2** and the olefin mixture **3*E*** + **3*Z*** was screened under the reaction conditions that led to a high level of epimerization. The aim of this experiment was to elucidate which compound underwent this epimerization process. Under these conditions it was found that ketone **2** remained unaltered after several days whereas the mixture **3*E*** + **3*Z*** evolved to give, after 7 days, a mixture of olefins (**4*E*** + **4*Z***)/(**3*E*** + **3*Z***) = 91/9 (Table 1, entry 2).

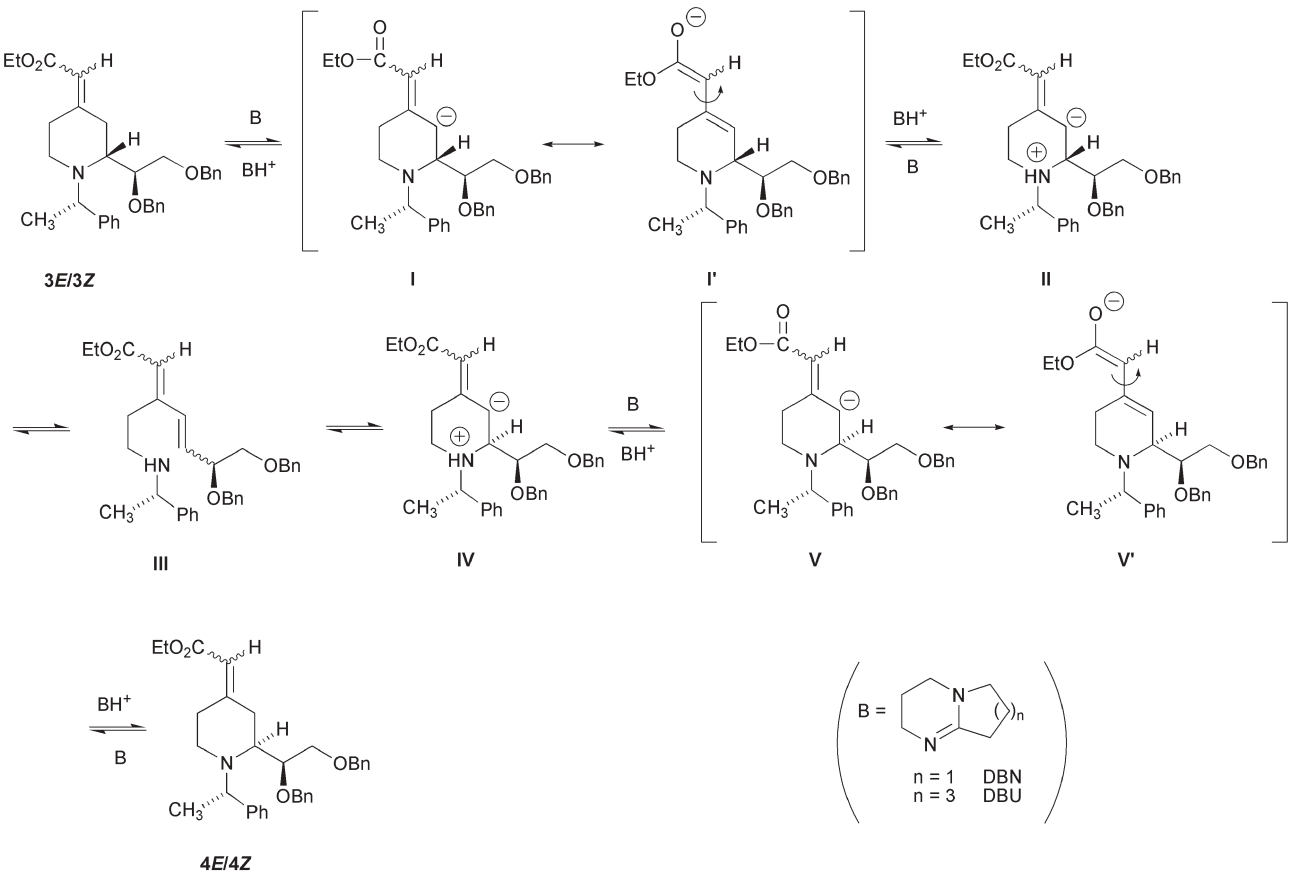
Similar behavior was observed under the same conditions without lithium chloride (Table 1, entry 3), whereas a solution of **3*E*** + **3*Z*** in acetonitrile in the absence of DBU and lithium chloride remained unaltered after several days – even under reflux conditions.

On the basis of these experimental results we can state that in the presence of DBU compounds obtained in the HWE reaction suffered an epimerization reaction that does not affect the starting piperidone.

Having established the essential role of the base for epimerization, the extent of this reaction with a range of different bases was investigated. Epimerization was not detected after several days either in the presence of LDA or KO^{t}Bu, stronger bases than DBU, or in the presence of DIPEA, TMG, Et_3N or DABCO, which have similar pK_a values to DBU (11–13). On the other hand, DBN acted as mediator for epimerization and a mixture (**4*E*** + **4*Z***)/(**3*E*** + **3*Z***) = 92/8 was obtained after 7 days at room temperature in the HWE reaction or from **3*E*** + **3*Z*** (Table 1, entries 4, 5).

Treatment of an 83/17 mixture of **4*E*/4*Z*** with LiCl (3.5 eq.) and DBU (10 eq.) for 7 days at room temperature resulted in the minoritary formation of olefins with the *R* configuration at C_2 and, once again, an (**4*E*** + **4*Z***)/(**3*E*** + **3*Z***) = 92/8 mixture of compounds with a 93/7 ratio for **4*E*/4*Z*** was obtained after 7 days.

The ratio (**4*E*** + **4*Z***)/(**3*E*** + **3*Z***) observed after 7 days (*ca.* 90/10) seemed to be independent of the epimerization conditions and on the configuration at C_2, which suggests that this ratio corresponds to a thermodynamic equilibrium between alkenes **4** and **3**. Moreover, the *E*/*Z* ratio changed significantly during epimerization, indicating that this equilibrium must be reached through an



Scheme 2 Proposed epimerization mechanism.

enolate intermediate in which rotation around the C_4–$C_{4'}$ exocyclic bond is possible (structures **I′** and **V′**, Scheme 2).

With this background information in hand, a possible mechanism for the formation of compounds with the opposite configuration at C_2 is outlined in Scheme 2. The initially formed dienolate **I/I′** is re-protonated at the piperidine nitrogen to afford zwitterion **II**, in which epimerization at C_2 is possible through a retro 1,6/1,6 addition sequence in which there is a 1,5 functionality distance between the carbonyl group and the amino group. Deprotonation of zwitterion **IV** and subsequent protonation of dienolate **V/V′** would lead to the formation of compounds **4*E*** and **4*Z***. This process is mediated by a base strong enough to accept a proton from C_3 with a conjugate acid that is acidic enough to transfer a proton to the piperidine nitrogen. Of the bases tested this requirement is only fulfilled by the amidine type bases DBU and DBN. Initial deprotonation at C_5 is also possible and the enolate generated would evolve to yield the starting compounds. A retro-conjugate addition/conjugate addition sequence has been reported previously in 2,5-disubstituted pyrrolidine alkylations.[15]

Isolation or trapping of intermediates was not possible but the reaction was followed by ^{1}H NMR spectroscopy and the appearance of signals at *ca.* 6.0 and 6.5 ppm was observed. These signals can be attributed to protons bonded to the highly conjugated disubstituted double bond of compound **III**.

On the basis of these results we reasoned that to avoid epimerization at C_2 the HWE reaction must be conducted using LDA as the base. Indeed, reaction of compound **2** with triethyl phosphonoacetate (3.0 eq.) in the presence of LDA (3.5 eq.) led to the exclusive formation of compounds **3*E*** and **3*Z*** in a 97/3 ratio in nearly quantitative yield (97%) after 14 h. This approach constitutes a valuable synthetic methodology for the synthesis of compounds with the *R* configuration at C_2.

In conclusion, a mechanism that accounts for the unexpected epimerization at C_2 in the Horner–Wadsworth–Emmons reaction of 2-substituted-4-oxopiperidines has been proposed and is supported by experimental results. This study has established the optimal conditions for the diastereodivergent synthesis of *E*/*Z* mixtures of 2-[(*S*)-1,2-dibenzyloxyethyl]-4-ethoxycarbonylmethylene-*N*-[(*S*)-1-phenylethyl]piperidine of *R* and *S* configuration at C_2 starting from 4-oxopiperidine **2**.

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