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THE FORMATION AND ALKYLATION OF α-KETOAMIDE DIANIONS

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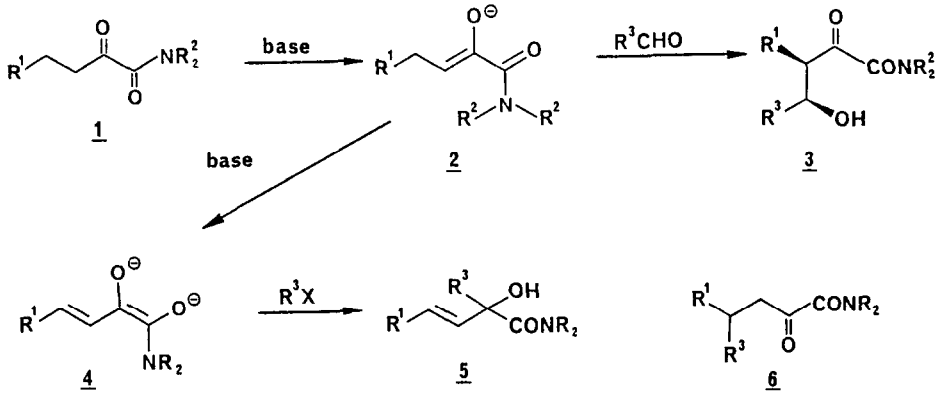
SUMMARY: Alpha ketoamides may be deprotonated twice with strong base. The dianions so formed react with alkyl halides to yield α-amido tertiary alcohols.

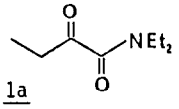
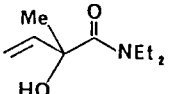
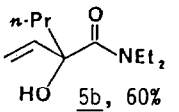
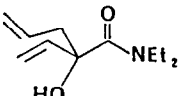
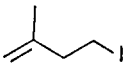
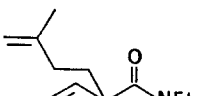
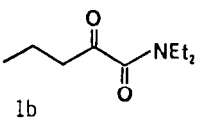
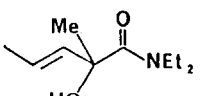
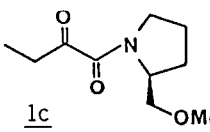
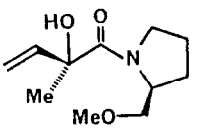
The extended enolates of crotonic acid derivatives[1a,b] have become valuable reactive intermediates in the preparation of β,γ-unsaturated carbonyl compounds via α-alkylation with electrophiles. During the course of our investigation of the kinetic aldol reactions of α-



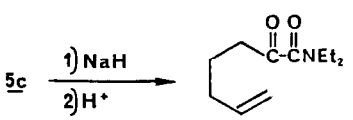
ketoamide enolates 2,[2] it occurred to us that the addition of a second equivalent of base might produce the potentially useful dianionic species 4.[3,4]

In practice, addition of ketoamides 1[5] to 2.2 equivalents of LDA·HMPA[6] in THF at -78°C followed by warming to 0°C for 20-30 min. and addition of an alkyl halide produced tertiary alcohols 5[7] in moderate yields (see Table). Reaction at the γ-carbon to produce compounds of type 6 was observed only with the mixed K-Li enolate (entry 2). The net operation of γ-alkylation with allyl bromide could also be achieved via Cope rearrangement of α-product 5c: Treatment of this compound with NaH in THF for 7 h at reflux afforded 1d in 72% yield after proton quench.

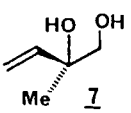
TABLE

entry	Ketoamide	deprotonation conditions	electrophile	product, yield*
1	 1a	LDA/HMPA/THF -78° → 0°C	MeI	 5a, 62% (84%)
2	1a	1) KH/THF,0° 2) LDA,-78 → 0°	MeI	5a, 43% 1b, 32%
3	1a	LDA/HMPA/THF -78° → 0°C	*n*-PrBr	 5b, 60%
4	1a	LDA/HMPA/THF -78° → 0°C		 5c, 67%
5	1a	LDA/HMPA/THF -78° → 0°		 5d, 29%
6	 1b	LDA/HMPA/THF -78° → 0°	MeI	 5e, 38% (60%)
7	 1c	LDA/HMPA/THF -78° → 0°	MeI	 5f, 39%

*yields in parenthesis were calculated allowing for recovered ketoamide.



1d



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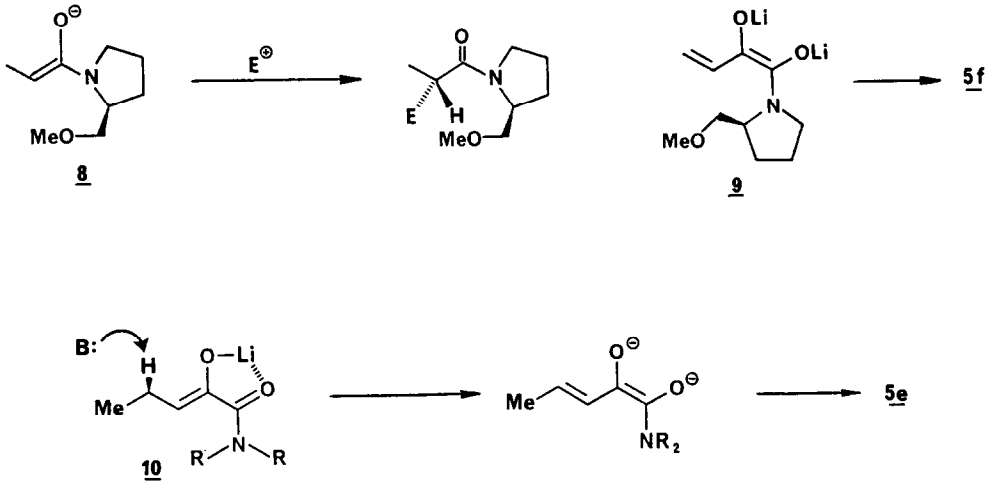
Dianions 4 appear to be thermally unstable and slowly decompose at temperatures required for their formation from 1. With LDA as a base, starting ketoamide could always be recovered from the reaction mixture; longer deprotonation times or higher temperatures led to increased consumption of starting material at the expense of overall yield. The use of lithium tetramethylpiperidide (LiTMP) as a base resulted in complete deprotonation at -10°C without the use of HMPA (no recovered ketoamide), but overall yields were not significantly improved. The high basicity of dianions 4 is evidenced by the predominant dehydrohalogenation of homoallyl halides (entry 5, Table); likewise, attempted alkylation with benzyl bromide gave recovered ketoamide plus stilbene.

A reasonable level of asymmetric induction was obtained with the alkylation of chiral amide 1c.[5,7] Reduction of 5f (as a mixture of diastereomers) with one equivalent of Red-Al followed by $NaBH_4$ afforded the known diol 7[8] $[\alpha]_D^{22}$ = +4.844° (C = 3.0 in CH_2Cl_2) in 63% yield. A chiral shift NMR experiment using $Eu(tfc)_3$ confirmed the value of 75% e.e. for this material. If the alkylation of 1c occurs in the same facial sense as that of enolate 8,[9] then the geometry of the dianionic species must be that shown by 4 and 9.

Also noteworthy is the clean production of the trans olefin from deprotonation of 1b (entry 6), as determined by a 15 Hz olefinic J value for 5e. This result can be rationalized by γ-deprotonation occurring from the least sterically crowded rotamer of the Z[10] monoenolate 10. Interestingly, this is the opposite geometry obtained from deprotonation of α,β-unsaturated esters.[11]

Application of this methodology to problems in natural products synthesis is underway in our laboratory.



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1. (a) For a recent review of the enolate chemistry of α,β-unsaturated acids and esters, see: N. P. Petragnani and M. Yonashiro, Synthesis 521, pp. 555-562 (1982). (b) α,β-unsaturated amides: J. A. Oakleaf, M. T. Thomas, A. Wu, and V. Snieckus, Tetr. Lett., 645 (1978).

2. The results of these investigations will be published in due course.

3. This type of α-dicarbonyl dianion is apparently unknown. However, for studies on 1,3-cyclohexadien-2,3-diolates, see: A. S. Kende and R. G. Eilerman, Tetr. Lett., 697 (1973). M. Takata, M. Hojo, and A. Takeda, Chem. Lett., 445 (1984).

4. α-alkyl and aryl enediolates have been produced from the appropriate α-hydroxyesters: L. J. Ciochetto, D. E. Bergbreiter, and M. Newcomb, J. Org. Chem. 42, 2948 (1977).

5. Ketoamides used in this study were prepared from the appropriate secondary amine, diethyl oxalate, and ethyl or propylmagnesium bromide: T. Covigny, M. Larcheveque, and H. Normant, Synthesis, 857 (1978).

6. J. L. Herrmann, G. R. Kieczykowski, and R. H. Schlessinger, Tetr. Lett., 2433 (1973).

7. All new compounds were characterized by 200 MHz ^{1}H NMR, IR and mass spectrometry.

8. Lit. $[\alpha]_D^{22}$ = +6.47° (C = 5.6 in CH_2Cl_2): E. L. Eliel and K. Soai, Tetr. Lett., 2859 (1981). Preparation of this compound constitutes a formal synthesis of (-)-mevalolactone.

9. D. A. Evans and J. M. Takacs, Tetr. Lett., 4233 (1980).

10. This geometrical assignment is consistent with our observation that monoenolates of α-ketoamides give syn aldol products 3.[2]

11. A. S. Kende and B. H. Toder, J. Org. Chem. 47, 163 (1982).

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