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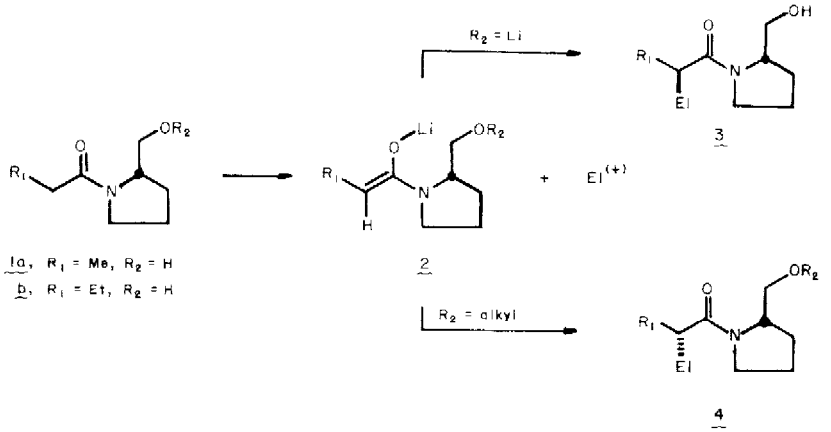
ENANTIOSELECTIVE ALKYLATION OF CHIRAL ENOLATES

D. A. Evans* and J. M. Takacs

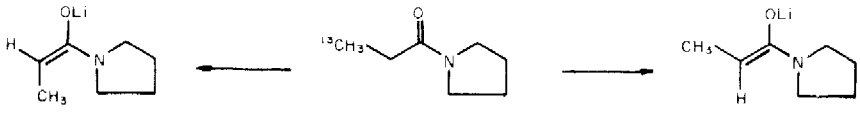
Contribution No. 6262 from the Laboratories of Chemistry
California Institute of Technology
Pasadena, California 91125

Summary: Alkylations of chiral amide enolates derived from (ℓ)-prolinol have been shown to yield versatile hydroxy-amides in high diastereomeric purity. Their use in the preparation of optically active carboxylic acids is described.

Our interest in the synthesis of biologically active molecules with numerous acyclic stereocenters, requires access to a variety of simple chiral subunits in high optical purity. A number of detailed reports for the preparation of optically enriched carbonyl derivatives have appeared delineating the importance of both enolate geometry and enantiotopic face discrimination in chiral enolate design.[1] In this communication we wish to report our observations of asymmetric induction in the reactions of chiral amide enolates derived from (ℓ)-prolinol with various electrophiles.[2]



In model experiments designed to explore the stereoselective enolization of prolinol-derived amides, ^{13}C-labeled amide 5 was treated with lithium diisopropylamide, LDA (25°C, THF or THF-HMPT). The resultant enolate, either 6E or 6Z, exhibited a single discernable methyl

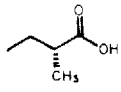
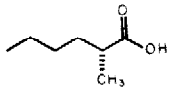
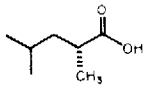
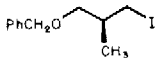
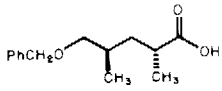
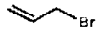
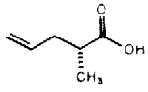
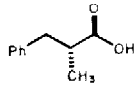
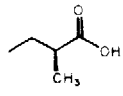


6E 5 6Z

resonance in the ^{13}C NMR spectrum (11.7 ppm in THF or 12.3 ppm in 10% HMPT-THF). The tentative assignment of the Z-enolate geometry in this system and to enolate 2 rests upon limited precedent[3] and allylic strain arguments which may play a significant role in amide enolization. The results in Table I implicate that the enolization of 1 is ≥97% stereoselective.

The hygroscopic hydroxy-amides 1 were conveniently prepared by acylation of (ℓ)-prolinol with the appropriate anhydride (65°C, neat, >90%) and purified by distillation prior to use.

Table I. Enantioselective Alkylations and Conversions to Carboxylic Acids.

Entry	Amide	Electrophile[a]	Ratio 3:4[b]	(% Yield)	Hydrolysis Product[c]	(% Yield)	$[\alpha]_D$[d]	(lit.)	Overall Yield	(config.)
A	1a	CH_3CH_2I	92:8	(98)		(84)	-15.95°	(19.6°)[e]	82	(R)
B	1a	n-C_4H_9I	94:6	(99)		(78)	-16.71°	(18.7°)[f]	77	(R)
C	1a	i-C_4H_9I	97:3	(89)		(96)	-21.86° C=5.39	(19.4°)[g] (C=5.23, Et_2O)	85	(R)
D	1a		97:3	(59)		(91)			54	
E	1a		96:4	(98)		(87)	-7.62°	(8.24°)[h]	81	(R)
F	1a	$PhCH_2Br$	88:12	(75)		(92)	-18.89°	(-25.4°)[i]	69	(R)
G	1b	CH_3I	94:6	(98)		(96)	+17.03°	(19.6°)[e]	95	(S)

a) All reactions run in THF with metallation by LDA at 25°C. Entries A,B: add electrophile at 25°C. Entries C, D, E, G: add 2 eq of HMPT followed by cooling and addition of electrophile at -100°C. Entry F: add electrophile at -100°C. b) All diastereomer ratios determined by gas chromatography. c) Hydrolysis performed in refluxing 1 N HCl for 2-3 h. d) All rotations reported neat unless noted. e) A. Kjaer and S. E. Hansen, Acta Chem. Scand., 11, 898 (1957). f) P. A. Levene and R. E. Marker, J. Biol. Chem., 98, 1 (1932). g) P. A. Levene and I. W. Bass, J. Biol. Chem., 70, 211 (1926). h) G. I. Fray and N. Polgar, J. Chem. Soc., 2036 (1956). i) G. Helmchen, et al., Angew. Chem. Int. Ed., 18, 63 (1979).

Addition of one equiv of 1 to a 0.3 M solution of two equiv of LDA in THF at or below room temperature (20 min) afforded the desired enolate 2 (R_2 = Li) which was subsequently alkylated with the indicated alkyl halides under conditions optimized for each pair of substrates (Table I).[4,5] In all experiments, diastereoisomer analysis (3:4) was carried out by gas chromatography.[6] This analytical method proved to be invaluable in determining, with a high degree of precision, the efficiency of chirality transfer during enolate alkylation. These diastereomer ratios and the optical rotations of the derived carboxylic acids show good agreement as to the enantiomeric purity of the newly formed center, precluding significant racemization under the relatively mild hydrolysis conditions (1.0 N HCl, 100°C, 2 h).[7] Of particular note are the selectivities observed in entries C, D, E (3:4, >25:1) which serve as models for projected natural product syntheses. The preparation of optically active 2-methyl-hexanoic acid (entry B, $[\alpha]_D$ = -16.7°) has also been reported *via* butyl iodide alkylations of a chiral oxazoline (+14.1°)[1a] and an ephedrine derived amide (-14.5°)[1d] permitting direct comparison of this work with current literature methods. The observed stereoselectivity is relatively insensitive to deprotonation conditions; however, it is critically dependent on counterion, solvent, electrophile and alkylation temperature, and each example in Table I has been individually optimized. Solutions of the *lithium* dianion, 2, in THF or THF/HMPT mixtures appear to be generally applicable, although in certain cases mixed salts (2, R_2 = Na, K, BR_2) show promise for improved selectivity.[8] Alkyl iodides are preferred to bromides or tosylates in non-allylic electrophiles

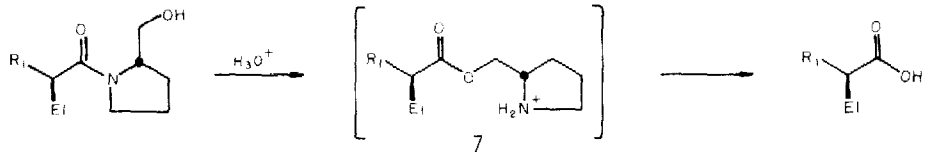
It was anticipated that the hydroxyl moiety, R_2, would perform a crucial role, *via* enolate chelation, in establishing an enantiotopic bias in the alkylation of enolate 2. The results in Table II substantiate this point. It is striking that O-alkyl and silyl-protected enolates exhibit the *opposite* sense of chirality transfer to that observed for 2 where R_2 = Li.

Table II. Dependence of Chirality Transfer on R_2 Substituent in Enolate 2a.

R_2	Electrophile	Ratio 3:4[b]
Li	CH_3CH_2I	92:8
CH_3	CH_3CH_2I	22:78
$CH_3OCH_2CH_2OCH_2$	CH_3CH_2I	22:78
t-Bu$(CH_3)_2$Si	CH_3CH_2I	23:77
$CH_3OCH_2CH_2OCH_2$	$CH_2{=}CHCH_2Br$	29:71
t-Bu$(CH_3)_2$Si	$CH_2{=}CHCH_2Br$	38:62

a) All reactions run in THF with metallation by LDA at 25°C followed by addition of alkyl halide at -78°C (except R_2 = Li; alkylation carried out at 25°C). Conditions have not been optimized. b) Diastereomer ratio determined by gas chromatography.

One design criterion relevant to the selection of prolinol as a suitable chiral auxiliary centered upon the incorporation of a hydroxyl group proximal to the amide carbonyl which would facilitate amide hydrolysis via acid-catalyzed N → O acyl transfer.[9] Although the details are not yet fully documented, analysis of the non-acidic products after partial hydrolysis shows replacement of the amide carbonyl absorbance (1605 cm^{-1}) with a new band at 1720 cm^{-1} consistent with the amino ester derived from 7. Upon standing at room temperature these derived amino esters slowly revert back to the prolinol amides by O → N acyl transfer. Competitive hydrolysis



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of hydroxyamide 3b (R_2 = H, El = CH_2=$CHCH_2$) and methoxyamide 3a (R_2 = CH_3, El = CH_2=$CHCH_2$) demonstrates at least a ten-fold rate enhancement due to the hydroxyl substituent.

The condensation of lithium enolate 2 with an aldehyde yields a complex mixture of diastereomers, however, the study of these amides in highly enantioselective aldol condensations via the derived zirconium enolates will be reported shortly.[10]

Acknowledgements. Support from the National Science Foundation is gratefully acknowledged.

References and Notes

1. (a) A.I. Meyers, G. Knaus, K. Kamata, and M.E. Ford, J. Am. Chem. Soc., 98, 567 (1976); (b) A.I. Meyers, E.S. Snyder, and J.J.H. Ackerman, ibid., 100, 8186 (1978); (c) M.A. Hoobler, D.E. Bergbreiter, and M. Newcomb, ibid., 100, 8182 (1978); (d) M. Larcheveque, E. Ignatova, and T. Cuvigny, J. Organomet. Chem., 177, 5 (1979); (e) E. Ade, G. Helmchen, and G. Heiligenmann, Tetrahedron Lett., 1137 (1980).

2. We wish to thank Dr. P.E. Sonnet for communication of independent observations in this area prior to publication. P.E. Sonnet, J. Org. Chem., in press.

3. C.H. Heathcock, C.T. Buse, W.A. Kleschick, M.C. Pirrung, J.E. Sohn, and J. Lampe, J. Org. Chem., 45, 1066 (1980).

4. Satisfactory spectral data and elemental analyses obtained for all new compounds.

5. Although deprotonation is complete at -78°C, ambient temperatures are generally employed for convenience.

6. Analyses performed on free hydroxy or TMS derivative using 22 meter methyl-silicone or Carbowax 20M™ fused glass silica capillary columns.

7. For example in entry F (Table I) the diastereomer ratio (3:4) is 87.6:12.4 by VPC analysis while the enantiomer ratio as determined by optical rotation of the corresponding acid is 87.2:12.8. See also: G. Helmchen, G. Nill, D. Flockerzi, and M.S.K. Youssef, Angew. Chem. Int. Ed. Engl., 18, 63 (1979).

8. For example, a 94:6 diastereoselection is observed upon sequential treatment of amide 1a with KH, 1 eq. of LDA and followed by alkylation with ethyl iodide in THF-HMPA solution at -78°.

9. A.P. Phillips and R. Baltzly, J. Am. Chem. Soc., 69, 200 (1947).

10. D.A. Evans and L.R. McGee, Tetrahedron Lett., in press.

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