Tetrahedron Letters No. 41, pp 3961 - 3964.

0040-4039/78/1008-3961$02.00/0

# ASYMMETRIC SYNTHESIS OF α-SUBSTITUTED KETONES AND ACIDS VIA CHIRAL N,N-SUBSTITUTED AMIDES

Marc LARCHEVEQUE, Eliana IGNATOVA and Thérèse CUVIGNY

Laboratoire de Synthèse Organique associé au C.N.R.S. tour 44-45
Université P. et M. Curie, 4, place Jussieu 75230 - PARIS
Cédex 05, France.

Effective asymmetric synthesis with C-C coupling and simultaneous generation of a new chirality center are rare.

Recently the use of carbanions in α position to functions such as oxazolines has allowed to synthesize chiral acids with good optical yields (1). But there is actually no versatile method for the regio and enantioselective α-alkylation of ketones. Indeed, the use of imines and related compounds gives rather good results; the reactions, however, are restricted to the alkylation of symmetric ketones (2).

In order to obtain more sophisticated derivatives, we employed a new type of compounds : the N,N-disubstituted amides.

Indeed, these compounds are easy to obtain by reacting an anhydride or an acid chloride with a secondary amine ; moreover they are readily α-alkylated in hyperbasic media (3) so that it is possible to synthesize various derivatives from commercial acetamide.

We have now developped a method permitting the asymmetric synthesis of α-substituted ketones and acids from chiral amides in good chemical yields and in quite high enantiomeric purity.

We have utilized ephedrine (l or d) to prepare the chiral amide 1 ; this compound is interesting because it is commercially available and cheap ; moreover it possesses a hydroxyl function capable of favouring the asymmetric induction by chelation.

The amide 1 is obtained by heating a mixture of anhydride and ephedrine (7 mn to 65°C) ; the yield is almost quantitative (4).

The metalation is achieved by using two equivalents of lithium diisopropyl amide in ether. This one is rather difficult and it is necessary to wait about two hours at room temperature

for the reaction to be complete ; however the steric hindrance limits the side reactions. The alkylation is then achieved by addition of a mixture of alkyl halide and HMPT (5). It must be outlined that the nature of the counter-ion plays an important part in the asymmetric induction and that the use of magnesium cation increases appreciably the yield of the asymmetric synthesis (Table 1).

Table 1

Effect of the counter-ion on the asymmetric synthesis
(Alkylation temperature : + 10°C)

| $R_1$ | $R_2$ X | M | 3 A/3 B | Overall * Yield % | Optical Purity % |
|---|---|---|---|---|---|
| Me | Et I | Li | 76 / 24 | 4 70 | 35 |
| Me | Et I | Mg | 95 / 5 | 4 53 | 44 |
| Me | i hex. I | Li | - | 5 60 | 60 |
| Me | i hex. I | Mg | - | 5 55 | 78 |

* from amide 1

We can assume that the steric hindrance due to the greater size of magnesium increases the disymmetry of the intermediate dianion 2.

Hydrolysis in neutral medium affords a mixture of the two diastereoisomers 3 A and 3 B. We could in some cases estimate the ratio 3 A/3 B by using $^{13}C$ NMR (spectra were obtained in deuteriated DMSO to 170°C in order to avoid rotation isomers).

It is of interest to note that the use of magnesium cation generally generates only one of the two diastereoisomers nearly pure (Table 2) (6).

The amide 3 may be cleaved in two ways :

- the reaction with two equivalents of methyl lithium (T : -5°C) produces a substituted methyl ketone 4.
- the reaction with hot hydrochloric acid gives the chiral acids 5 ; in both cases, ephedrin is recovered in good yield after cleavage. Chemical yields are good ; however, in some cases, the reaction with methyl lithium leads to an appreciable amount of racemisation.

Thus, by using common compounds, this method allows to synthesize chiral ketones and acids with good optical yields in very mild conditions (ordinary temperature).

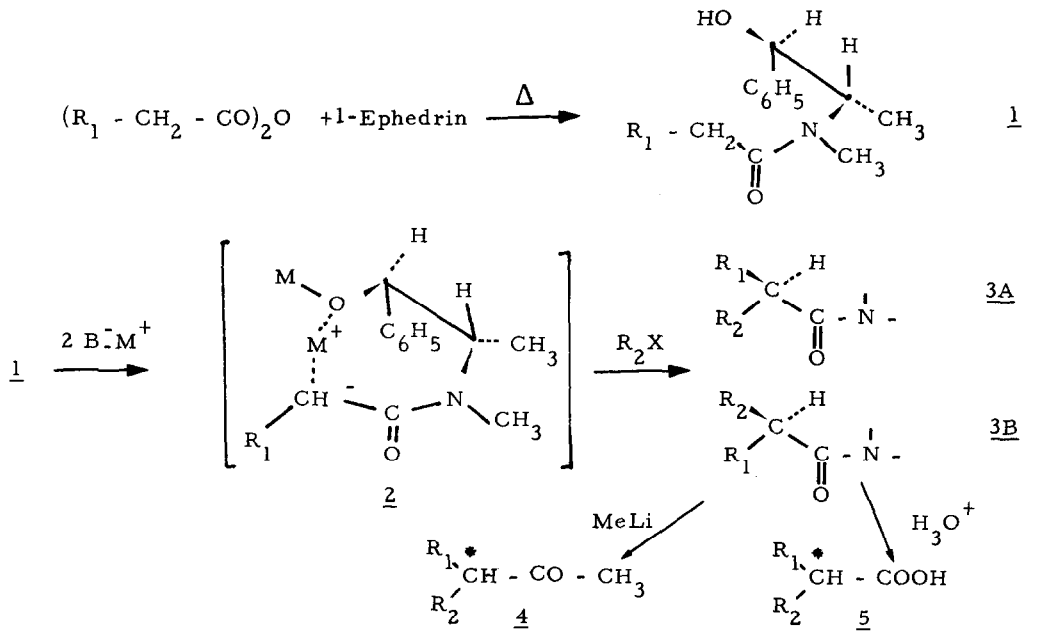


Table 2

Alkylation of 2 (M = Mg) with $R_2$ I ( T : 20° C )

| $R_1$ | $R_2$ | Ephedrine | 3% | 3A/3B ($^{13}$C) | 4 or 5 | Chem.[a] Yield % | $\alpha_D^{20}$ (c, solvent) | α (litt.) | Opt. Yield % |
|---|---|---|---|---|---|---|---|---|---|
| Me | Et | l | 75 | > 95/ 5 | 4 | 53 | -10°, 9 (C=0, 81; $CHCl_3$) | -24°, 9 (7) | 44 |
| Me | i hex. | l | 90 | | 5 | 55 | -12°, 8 (C=5, 1; $CHCl_3$) | -16°, 6 (8) | 77 |
| Me | n Bu | l | 95 | > 95/ 5 | 5 | 68 | -14°, 5 ( neat ) | +18°, 7 (9) | 78 |
| Me | n Bu | l | 95 | | 4 | 63 | -15°, 9 (C=3, 2; $CHCl_3$) | — | ~ 65[b] |
| Me | n Bu | d | 95 | | 4 | 65 | +14°, 2 (C=3, 2; $CHCl_3$) | — | ~ 58[b] |
| Et | n Bu | l | 93 | > 90/10 | 4 | 72 | - 1°, 90 (C=5, 2; EtOH) | - 0°, 7 (10) | 55[b] |
| Et | Benzyl | l | 84 | ~ 100/ 0 | 4 | 65 | -30°, 3 (C=8, 56; $C_6H_6$) | -40°, 9 (11) | 74 |

Table 2 : a/ from amide 1

b/ Determined NMR spectroscopically with Tris-(3-(trifluoromethylhydroxy-methylene)-d-camphorato), europium(III)

We are currently investigating the reactional pathway of th is reaction, and are trying to apply it to the synthesis of other compounds such as aldehydes for instance.

Acknowledgement: We are grateful to Dr Villieras for recording of $^{13}C$ NMR spectra and stimulating discussion in relation to this study.

1 - A.I. MEYERS and E.D. MIHELICH
Ang. chem., Int. Ed., 15, 270, 1976

2 - A.I. MEYERS, D.R. WILLIAMS and M. DRUELINGER, J. amer. chem. Soc., 98, 3032, 1976
S. HASHIMOTO, S. YAMADA and K. KOGA, J. amer. chem. Soc., 98, 7452, 1976
D. ENDERS and H. EICHENAUER, Tetrahedron Letters, 191, 1977
A.I. MEYERS, G. POINDEXTER and Z. BRICH, J. Org. chem., 43, 892, 1978
H. EICHENAUER, E. FRIEDRICH, W. LUTZ and D. ENDERS,
Ang. chem., Int. Ed., 17, 206, 1978

3 - P. DESLONGCHAMPS, U.O. CHERIYAN and D.R. PATTERSON
Canad. J. chem., 53, 1682, 1975
P. HULLOT, Th. CUVIGNY, M. LARCHEVEQUE and H. NORMANT
Canad. J. chem., 54, 1098, 1976 and 55, 266, 1977

4 - This procedure avoidsthe epimerisation of the carbon α to the phenyl :
W. MITCHELL, J. chem. Soc., 1153, 1940

5 - The alkylation of lithiated derivatives is complete in about 12 hours at -20°C when using a bromide ; but it is necessary with magnesium to work at ordinary temperature with an iodide.

6 - It must be outlined that these results are obtained with a free hydroxyl group ; when this function is protected as a methoxy, the asymmetric induction is not so good (the ratio 3A/3B is 60/40 with lithium : $R_1=CH_3$, $R_2X=C_2H_5I$, alkylation temperature : -30°C).

7 - C. DJERASSI and L.E. GELLER,
J. amer. chem. Soc., 81, 2789, 1959

8 - KA-KONG CHAN and G. SAUCY,
J. Org. chem., 42, 3828, 1977

9 - P.A. LEVENE and R.E. MARKER,
J. Biol. chem., 98, 1, 1932

10 - J. KENYON and D.P. YOUNG,
J. chem. Soc., 266, 1941

11 - T. KASHIWAGI, K. FUJIMORI, S. KOZUKA and S. OAE,
Tetrahedron, 26, 3647, 1970

**(Received in UK 20 July 1978; accepted for publication 11 August 1978)**