ON THE SYNTHESIS OF N-SUBSTITUTED 5-OXOPERHYDRO-1,4-OXAZEPINES FROM N-SUBSTITUTED 1,2-AMINOETHANOLS. A DICHOTOMY OF REACTION PATHWAYS

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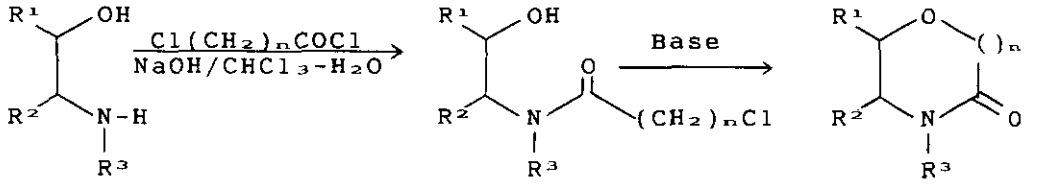
Dedicated to Dr. Masatomo Hamana.

Abstract- The reaction of N-substituted N-(1,2-diphenyl-2-hydroxiethyl)-β-chloropropionamides with NaH/DME affords cyclization to the 5-oxoperhydro-1,4-oxazepines or alcoholysis of the amide moiety depending on the nature of the substituent attached to the nitrogen atom. Some of the compounds synthesized show significant antitumour activity.

The transformation of 1,2-aminoalcohols (1) in 3-oxomorpholines (2) is a well established process and occurs by reaction of the amino alcohol with haloacyl halide followed by a base-induced cyclization to the six membered ring system[1] (Scheme 1, n=1). The extension of the reaction to



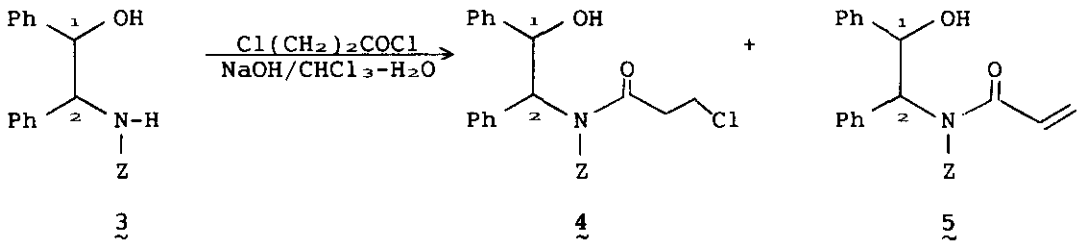
1 2

Scheme 1

the related 5-oxoperhydro-1,4-oxazepines (Scheme 1, n=2), has to the best of our knowledge, no precedent in the literature.[2]

In this paper we wish to report our results in connection with the transformation of N-substituted 1,2-diphenylaminoethanol derivatives in the corresponding 5-oxoperhydro-1,4-oxazepines.

The reaction of diastereomeric aminoalcohols (3)[3] with 3-chloropropionyl chloride gave a mixture of the desired N-substituted N-(1,2-diphenyl-2-hydroxiethyl)-β-chloropropionamide (4) as main products along with the related acrylamides (5) (Scheme 2). Column chromatography ($CHCl_3$:AcOEt 9:1) affords pure 4 and 5.[4]

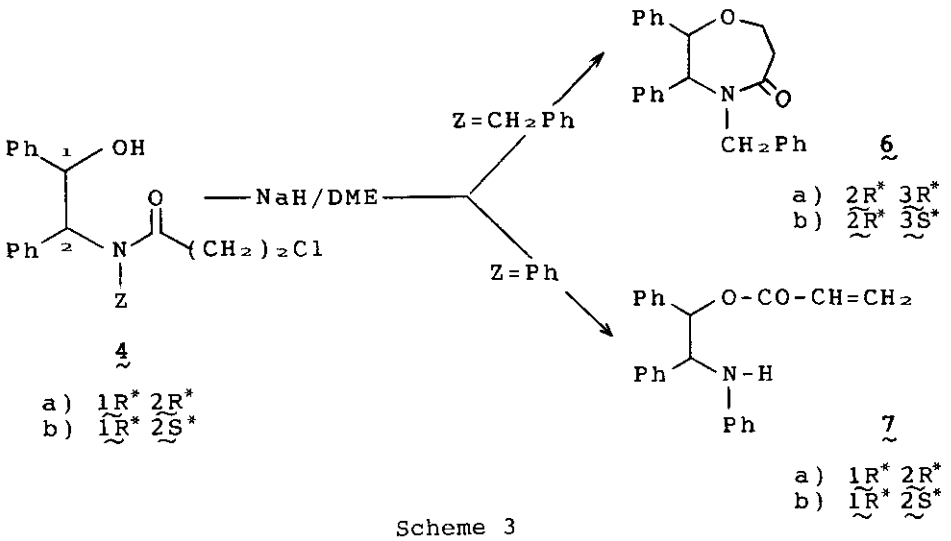


3 4 5

a) Z = Ph, 1R* 2R*
b) Z = Ph, 1R* 2S*
c) Z = CH_2Ph, 1R* 2R*
d) Z = CH_2Ph, 1R* 2S*

Scheme 2

The reaction of compound (4) with NaH/DME gave different results depending on the nature of Z (Scheme 3). In the case of Z=CH_2Ph, the 1,4-oxazepines (6) were obtained, whereas when Z=Ph acrylates (7) are the only isolated products (Scheme 3).[5]



Scheme 3

In this case an alcoholysis of the amide[6] moiety followed by base-induced dehydrohalogenation competes with the expected intramolecular substitution reaction.

Some of the compounds (4-6) show significant in vitro antitumour activity against L-1210 cells (ascitic fluid from DBA/2 mouse). Results are indicated in the Table.

Table

Compound	4a	5a	5b	5d	6b
IC_{50}(μg/ml)	3.8	1.9	1.3	4.6	8.3

In summary, the result of the reaction between chloroamides (4) and base appears to be dependent on the nature of the substituent attached to the nitrogen atom. An aromatic substituent induces the alcoholysis of the amide moiety whereas an aliphatic substituent gives cyclization to the oxazepine derivative.

ACKNOWLEDGEMENTS

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REFERENCES AND NOTES

1. See, inter alia: a) F.H. Clarke, J. Org. Chem., 1962, 27, 3251; b) A. Balsamo, P. Crotti, A. Lapucci, B. Macchia, and F. Macchia, J. Med. Chem., 1979, 22, 738; c) L. Nedelec, A. Pierdet, P. Fauveau, C. Euvrad, L. Proulx-Ferland, C. Dumont, F. Labrie, and J.R. Boissier, J. Med. Chem., 1983, 26, 522; d) G.R. Brown, A.J. Foubister, and B. Wright, J. Chem. Soc., Perkin Trans. 1, 1985, 2577; e) G. Bettoni, C. Celluci, S. Ferorelli, R. Perrone, and V. Tortorella, Tetrahedron, 1986, 42, 2117; f) C. Kashima and K. Harada, J. Chem. Soc., Perkin Trans 1, 1988, 1522; g) J. Danklmaier and H. Hönig, Liebigs Ann. Chem., 1988, 815.

2. The 5-oxoperhydro-1,4-oxazepines have been synthesized by reaction of 1,3-amino alcohols with chloroacetyl chloride, followed by cyclodehydrohalogenation. See: a) R.M. Bowman, U.S. Patent n°. 40.101.166. (Chem. Abstr., 1977, 87, 53414r); b) H.J. Treiber, German Patent n°. 3.242.933 (Chem.Abstr., 1984, 101, 211187h).

3. For the synthesis of both diastereomers of 3 see: B. Alcaide, C. L. Mardomingo, R. P. Ossorio, and J. Plumet, J. Chem. Soc., Perkin Trans 2, 1983, 1649 and references therein.

4. Isolated yields: Compound 4a, 73%; Compound 4b, 89%; Compound 4c, 83%; Compound 4d, 75%; Compound 5a, 6%; Compound 5b, 9%; Compound 5c, 8% and Compound 5d, 17%.

5. Isolated yields and selected spectroscopic data: Compound 6a : mp>240°C, (66%). ^{1}H-nmr(200 MHz, $CDCl_3$) δ 1.9-2.0 (m, 1H); 2.6-2.7 (m, 1H); 3.1-3.2 (m, 1H); 4.65 (1H, d, J=11.0 Hz); 4.7 (1H, d, J=18.7 Hz); 5.0 (1H, d, J=18.7 Hz); 6.7 (1H, d, J=11.0 Hz); 7.0-7.3 (m, 15H) ppm. Compound 6b : mp= 103-104°C, (80%). ^{1}H-nmr(200 MHz, $CDCl_3$) δ 2.6-2.8 (m, 1H); 2.9-3.1 (m, 1H); 3.8 (1H, d, J=14.0 Hz); 3.8-3.9 (m, 1H); 4.1-4.2 (m, 1H); 4.7 (s, 1H); 4.8 (s, 1H); 5.9 (1H, d, J=14.0 Hz); 6.8-7.5 (m, 15H) ppm. Compound 7a : mp= 103-105°C, (51%). ^{1}H-nmr(200 MHz, $CDCl_3$) δ 4.55 (broad, 1H); 4.75 (1H, d, J=6.6 Hz); 5.8 (1H, dd, J=1.6, 10.2 Hz); 6.09 (1H, d, J=6.6 Hz); 6.15 (1H, dd, J=10.2, 17.2 Hz); 6.4 (1H, dd, J=1.6, 17.2 Hz); 6.5 (2H, dd, J=1.0, 8.2 Hz); 6.64 (1H, tt, J=1.0, 7.4 Hz); 7.0-7.2 (m, 12H) ppm. Compound 7b : mp= 143-145°C, (70%). ^{1}H-nmr(200 MHz, $CDCl_3$) δ 4.3 (broad, 1H); 4.85 (1H, d, J=4.7 Hz); 5.8 (1H, dd, J=1.6, 10.2 Hz); 6.1 (1H, dd, J=10.2, 17.3 Hz); 6.20 (1H, d, J=4.7 Hz); 6.38 (1H, dd, J=1.6, 17.3 Hz); 6.45 (2H, d, J=7.6 Hz); 6.6 (1H, t, J=7.3 Hz); 7.0-7.3 (m, 12H) ppm.

6. Probably this reaction constitutes a rare case of base-catalyzed nitrogen-to-oxygen migration. Usually this kind of process is acid-catalyzed. See J. March, "Advanced Organic Chemistry. Reactions, Mechanism and Structure". McGraw-Hill, New York. 3th ed, p. 353 and references therein.

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