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COUPLING OF ß-ACETAMIDO RADICALS WITH α-CHLORO ACRYLONITRILE — A NEW ACCESS TO DISUBSTITUTED PROLINE DERIVATIVES

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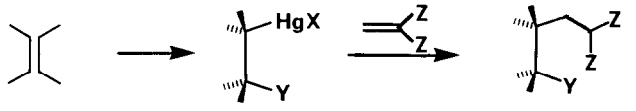
Summary: ß-Acetamido radicals are prepared by reduction of organomercurials and coupled with α-chloro-acrylonitrile. The coupling products are further converted to proline derivatives.

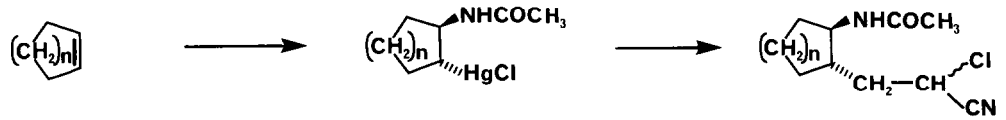
A recent publication by Kozikowski and Scripko [1] on the successful reductive coupling of acetamidomercurials with electron deficient olefins as well as related work by Danishefsky and coworkers [2] prompted us to communicate our own results in this field.
In connection with our synthetic effort in the area of angiotensin converting enzyme inhibitors we intended to make use of the reductive activation of organomercurials containing heteroatoms in the ß-position which had been pioneered by Giese and coworkers (equation (1)) [3] and which allows vicinal introduction of a carbon chain and a hetero functionality into an olefin substrate.



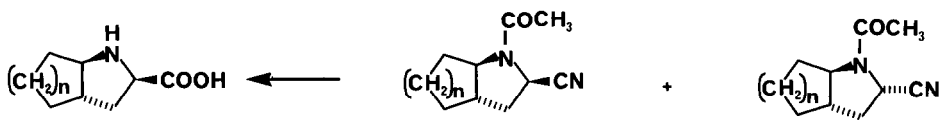
(1)

Our synthetic approach is illustrated below by the preparation of octahydroindole-2-carboxylic acid (4a) and octahydrocyclopenta [b] pyrrol-2-carboxylic acid (4b). Reaction of cyclohexene and cyclopentene with acetonitrile and mercuric nitrate followed by ligand exchange with sodium chloride according to the procedure of Beger and Vogel [4] gave the crystalline acetamideomercurials 1a and 1b in 98 and 75 % yield, respectively. 1a was dissolved in ethanol together with 4 equiv. of α-chloro-acrylonitrile and cooled to -15°C. One equiv. of sodium borohydride was added as quickly as possible, which caused the temperature to rise to +15°C. Filtration of precipitated mercury through Celite followed by concentration, treatment with NaOH and extraction with CH_2Cl_2 gave 2a, which was cyclized without purification

to indole-derivative 3a (1.6 equiv. NaH, DMF, 0°C). This was obtained as an 18.5 : 1-mixture of two isomers, which proved to have the configurations 3aa and 3ab shown below [5,6] in 49 % total yield. Under the same conditions we obtained 2b from 1b as a crystalline mixture of diastereomers (mp. 114 - 117°C) at the carbon atom bearing the chlorine, in 44 % yield after chromatography. Cyclization gave a separable mixture (4:1) of isomers 3ba and 3bb[7]. Finally, the major isomers were hydrolysed to the amino acids 4a (mp. 286 - 288°C (dec.)) and 4b (mp. 250°C (dec.)) in 85 and 74 % yield, respectively by refluxing with 5 N HCl.

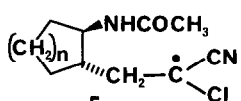


n = 1,2 | 1a: n = 2; 1b: n = 1 | 2a: n = 2; 2b: n = 1



4a: n = 2; 4b: n = 1 | 3aa: n = 2; 3ba: n = 1 | 3ab: n = 2; 3bb: n = 1

Interestingly, no cis-isomer of compounds 3 could be detected under our conditions; the stereochemical integrity of 1 is fully conserved (The only other products found were demercurated cycloalkyl acetamides and polymeric material). This is not the case under Kozikowski's conditions where partial isomerization is observed [1]. We can only speculate on the cause of the stereochemical outcome of our sequence. The preservation of the trans stereochemistry of mercurials 1 in compounds 3 seems to rely on the very fast reaction under the above conditions. The intermediate radical [8] probably does not have enough time to equilibrate before the addition to the activated olefin. A very surprising result is the highly preferential formation of one isomer over the other at the chloro nitrile carbon in 2. According to Giese[3], chain propagation results from transfer of a hydrogen atom of an initially formed R-Hg-H species to radical 5.



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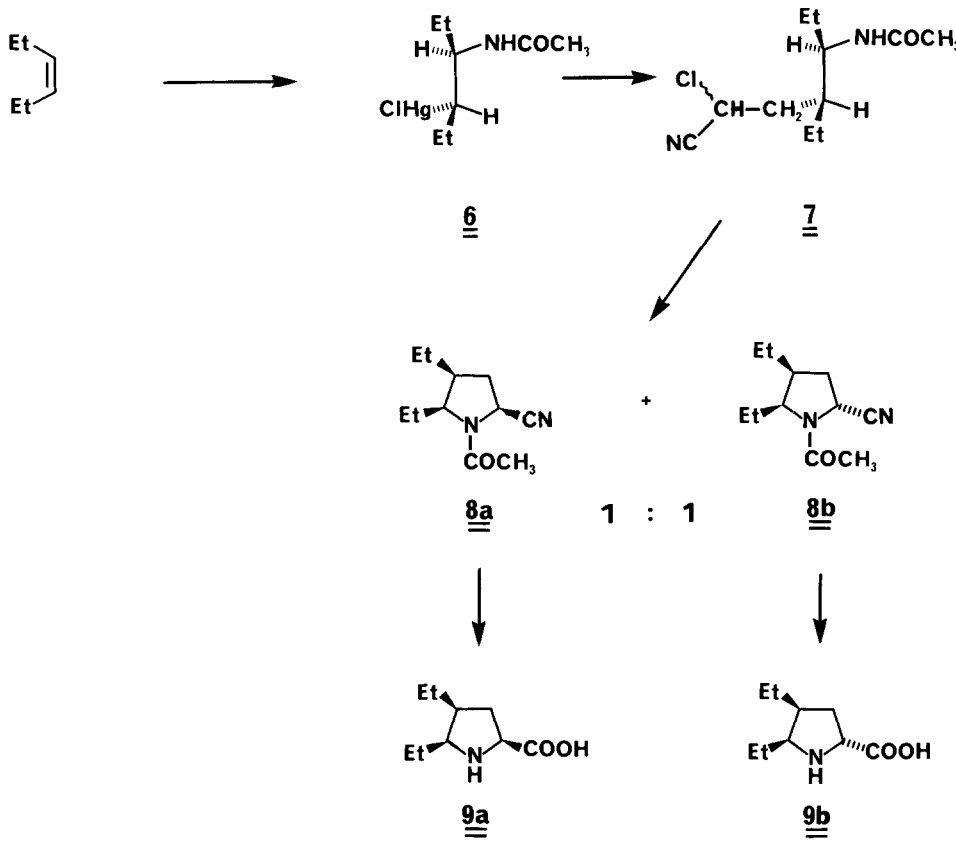
It is entirely possible that radical 5 is stable enough to react with the bulky R-Hg-H reagent so slowly that the hydrogen atom is delivered from the less hindered face of the molecule.
A close study of Dreiding models of the preferred conformation of 5 suggests that this would lead predominantly to those isomers giving rise to 3aa and 3ba upon cyclization.
This preferential attack is dependant on the existance of constraint due to the carbocyclic ring in 2. Reacting the open chain mercurial 6 obtained from cis-3-hexene under the above conditions gave rise to 7 as a 1 : 1-mixture of isomers, which can be separated by medium pressure chromatography after cyclization to give 8a (oil, R_f (ethyl acetate/cyclohexane = 4:1):0.5) and 8b (mp. 144 - 149°C, R_f: 0.43). Hydrolysis leads to the diastereomeric 4,5-diethylprolines 9a (mp. 230 - 235°C (dec.)) and 9b (mp. 158 - 162°C) [9].



Acknowledgements: We are indebted to Dr. H.-W. Fehlhaber for analytical support.

References and Notes

1) A. P. Kozikowski and J. Scripko, Tetrahedron Lett., 2051 (1983).

2) S. Danishefsky, E. Taniyama and R.R. Webb II, Tetrahedron Lett., 11 (1983); S. Danishefsky and E. Taniyama, ibid., 15 (1983).

3) B. Giese, H. Horler and W. Zwick, Tetrahedron Lett., 931 (1982); B. Giese and K. Heuck, Chem. Ber., 114, 1572 (1981); B. Giese and J. Meixner, ibid., 114, 2138 (1981).

4) V.J. Beger and D. Vogel, J. Prakt. Chem., 311, 737 (1969); R.A. Kretchmer and P. J. Daly, J. Org. Chem., 41, 192 (1976).

5) 3aa crystallizes from the mixture, whereas 3ab is obtained by medium pressure chromatography of the mother liquor.
Physical data: 3aa: mp. 110-113°C; ^{1}H-NMR: δ=4.90(d,J = 7.4HZ,1H); 3.05 (dt,J_1=13Hz, J_2 = 3Hz, 1H); 2.60 (d,1H); 2.17 (d,1H); 2.03(s,3H); 1.95 (br. d, 1H); 1.85-1.6 (m,4H); 1.4-1.0 (m,4H) ppm.
3ab: oil; ^{1}H-NMR: δ=4.66 (t,J = 7Hz, 1H); 3.10-3.0 (m,1H); 2.75-2.6 (m,1H); 2.08 (s,3H); 2.0-1.4 (m,6H); 1.4-1.2 (m,4H) ppm.

6) The determination of the relative stereochemistry of 3aa by NMR spectroscopy, computerized conformational analysis and X-ray crystallography is subject of the following communication in this issue: R. Henning, H. Urbach and E.F.Paulus, Tetrahedron Lett., (1983).

7) Separated by medium pressure chromatography:
Physical data: 3ba: mp. 115-117°C; ^{1}H-NMR ($CDCl_3$, 60 MHz): δ=5.02 (d,J = 7.5Hz, 1H) ppm.
3bb: oil; ^{1}H-NMR ($CDCl_3$, 60MHz): δ=4.80 (t,J = 7Hz,1H)ppm.

8) Concerning the mechanism of reduction of mercurials with borohydride see: C.L. Hill and G. M. Whitesides, J. Amer. Chem. Soc., 96, 87 (1974).

9) The configuration at C-2 of 8a, b and 9a, b could not be assigned unequivocally. However, strong evidence comes from the ^{1}H NMR spectra (60MHz, D_2O) of amino acids 9a and 9b: The proton at C-5 shows up as a doublet of triplets (J_1 = 8Hz, J_2= 6Hz) at 3.2 ppm for 9a and a quartet (J = 6Hz) at 3.6 ppm for 9b.This deshielding of the C-5 proton in 9b is probably due to the carboxyl group's standing on the same side of the pyrrolidine ring, as indicated.

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