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THE AZA-ACHMATOWICZ REARRANGEMENT: A ROUTE TO USEFUL BUILDING BLOCKS FOR N- CONTAINING STRUCTURES

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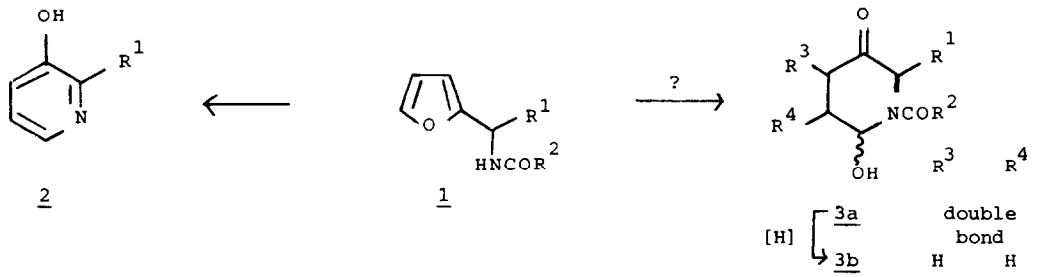
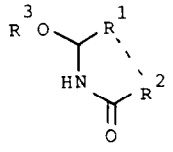
Abstract: N-Acyl 2-furylamines were transformed into 2-alkyl-6-methoxy-hexahydropyridin-3-ones. The rearranged products are useful building blocks for the total synthesis of alkaloids and unusual aminoacids.

In connection with various projects, we needed to develop an expeditious route to indolizidine and quinolizidine building blocks[1]. A method was sought whereby versatile starting materials could be produced under mild conditions. It was surmised that ketones of the type 3b may become available through the aza analog of the Achmatowicz rearrangement[2], using substrates such as 1 (cf. 1→3a). Similar transformations had previously been accomplished only in a format wherein fully aromatic pyridines result[3] (cf. 1→2). This limitation restricts the usefulness of the process to a considerable extent, because potential chirality present at the furfurylic methine of 1 would be lost. It was observed that the subtarget enones 3a cannot be made directly from 1, by either the Achmatowicz[2] or the Lefebvre[4] methods. Apparently, the double bond present in compounds of the type 3a causes their rapid destruction under the conditions of the rearrangement. Success was finally achieved as described below.

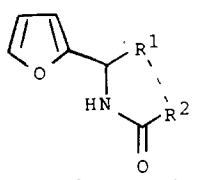


Starting materials 7-11 were prepared by Ben-Ishai[5] or Speckamp[6] reactions, in good yields (77-91%)[7]. Dimethoxy derivatives 12-15 were obtained in excellent yields (chromatographed[8]) upon subjection of crude 8-11 to the action of Br_2 in methanol[9]. Each dihydrofuran was produced as a mixture of four diastereomers, as evident by NMR. These were not separated.



	R^1	R^2	R^3
4	COOMe	OBn	Me
5	CH_2	CH_2	Et
6	CH_2	$(CH_2)_2$	Et

a

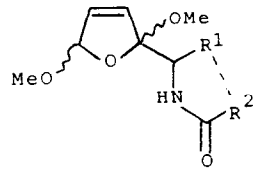


	R^1	R^2
7	COOMe	OBn
8	CH_2	CH_2
9	CH_2	$(CH_2)_2$
10	CH_2	O
11	CH_2OAc	OBn

b,c

b,d

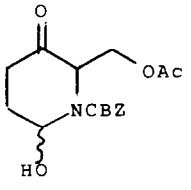
e



	R^1	R^2
12	CH_2	CH_2
13	CH_2	$(CH_2)_2$
14	CH_2	O
15	CH_2OAc	OBn

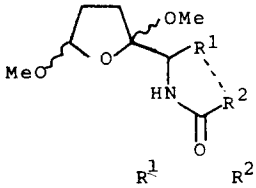
a. Furan, ether, BF_3OEt_2, RT, 75-80%; b. $LiBH_4$, EtOH, THF, 0°C, 90%[15e]; c. NaH, THF, RT, 80%; d. Ac_2O, pyridine, RT, 97%; e. Br_2, MeOH, ether, -40°C, then $NH_{3(g)}$, -40°C to RT, 85-95%.

The double bond in compounds of the type 12 was readily removed with 5% $Rh(Al_2O_3)$ under 1500 psi of H_2 (25°C)[10]. The complete survival of a CBZ group (entry 19) demonstrates that these seemingly harsh conditions are in fact quite mild. Tetrahydrofurans 16-19 were thus obtained in quantitative yield. Rearrangement of crude 16-18 to the desired heterocycles occurred smoothly upon exposure to 15 mol% trifluoromethane sulfonic acid in THF (freshly distilled from Na-benzophenone) containing two molar equivalents of water (25°C, 2-3h)[11]. Compounds 21-23 were formed stereospecifically, the methoxy group emerging with the axial orientation in each case. Chromatography (Baker 60-200 mesh silica gel, EtOAc/hexanes in various proportions depending on the sample) provided pure products (74-91%). Monocyclic compound 19 was rearranged under slightly different conditions, leading to hemiamidal 20[12] (95% crude). This unstable compound was not purified.



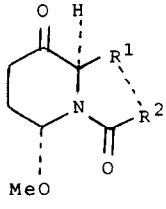
20

see text



	R^1	R^2
16	CH_2	CH_2
17	CH_2	$(CH_2)_2$
18	CH_2	O
19	CH_2OAc	OBn

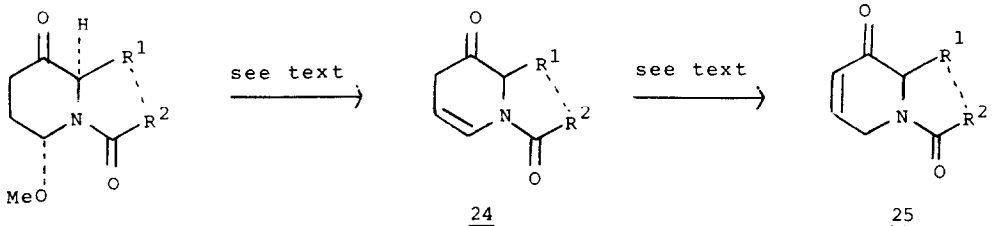
see text



	R^1	R^2
21	CH_2	CH_2
22	CH_2	$(CH_2)_2$
23	CH_2	O

While a full picture of the chemistry of the rearranged products awaits completion of on-

going investigations, we report that elimination of methanol from 21-23 is readily induced by refluxing in benzene in the presence of 15 mol% quinolinium camphorsulfonate (QCS)[13]. For instance, enamide 24 (R^1=R^2=CH_2) may be obtained from 21 in 88% yield. Further rearrangement of 24 to enone 25 (R^1=R^2=CH_2) may be achieved with 15 mol% DBU in dry THF (RT, 85%)[14].



24 25

It is recognized that optically active alkaloid synthons could be obtained from optically active 8-11. Clearly, these could be made from optically active, N-protected furylglycines, using established methods for aminoacid manipulation[15]. Efficient resolution of (±)-methyl-N-acyl furylglycinates is in fact readily achieved by the use of esterase enzymes[16]. We are actively pursuing the ramifications of the newly uncovered methodology in connection with the total synthesis of various alkaloids and unusual aminoacids. Developments in these areas will be reported in due course[17].

Acknowledgement. Support for this work by the Robert A. Welch Foundation (C-1007) is gratefully acknowledged.

References and notes.

1. Alternative synthetic methods: see, e.g.: a. Chamberlin, A. R.; Nguyen, H. D.; Chung, J. Y. L. J. Org. Chem. 1984, 49, 1682; b. Hart, D. J.; Kanai, K. J. Am. Chem. Soc. 1983, 105, 1255; c. Danishefsky, S.; Taniyama, E.; Webb, R. R. Tetrahedron Lett. 1983, 24, 11, and references cited therein. See also ref. 6.
2. a. Achmatowicz, O.; Bukowsky, P.; Szechner, B.; Zwierzchowska, Z.; Zamojski, A. Tetrahedron 1971, 27, 1973; b. Achmatowicz, O. in "Organic Synthesis Today and Tomorrow", Trost, B. M.; Hutchinson, C. R., Eds.; Pergamon Press: Oxford, U.K., 1981, p.307; c. Zamojsky, A.; Grynkiewicz, G. in "The Total Synthesis of Natural Products", ApSimon, J., Ed.; John Wiley & Sons: New York, N.Y., 1984, p.141. See also d. Georgiadis, M. P.; Couladouros, E. A. J. Org. Chem. 1986, 51, 2725.
3. a. McKillop, A.; Boulton, A. J. in "Comprehensive Heterocyclic Chemistry", Katritzsky, A. R.; Rees, C. W., Eds.; Pergamon Press: Oxford, U.K. 1984; v. 2A, p.90 ff.; b. Shono, T.; Matsumura, Y.; Tsubata, K.; Inoue, K.; Nishida, R. Chem. Lett. 1983, 21; c. Shono, T.; Matsumura, Y.; Tsubata, K.; Tanaka, J. Chem. Lett. 1981, 1121, and references cited therein.
4. a. Lefebvre, Y.; Tetrahedron Lett. 1972, 133; b. Laliberte, R.; Medawar, G.; Lefebvre, Y. J. Med. Chem. 1973, 16, 1084.
5. a. Ben-Ishai, D.; Sataty, I.; Bernstein, Z. Tetrahedron 1976, 32, 1571; b. Zoller, U.; Ben-Ishai, D. Tetrahedron 1975, 31, 863.
6. Speckamp, W. N.; Hiemstra, H. Tetrahedron 1985, 41, 4367.
7. All new compounds produced spectra in full accord with the proposed structure. Several physical data are listed in ref. 17.
8. Chromatography (Baker 60-200 mesh silica, EtOAc/Hexanes in various proportions depending on the sample) removed contaminants that would poison the hydrogenation catalyst (vide infra).

9. Elming, N. Adv. Org. Chem. 1965, 2, 67, and references cited therein.
10. Hydrogenation of compounds of the type 12 is known to require high pressures. See ref. 9. We found $Rh(Al_2O_3)$ (100 mg/g cpd.; EtOAc) more convenient than RaNi (ref. 9).
11. These were the most satisfactory conditions among all those tried.
12. 30 mol% TfOH, 10 mol eq. H_2O, THF, RT, 4h. Subjection of 16-18 to this alternative treatment allows the obtention of the hydroxy analogs of 21-23. Componds in the hydroxy series, however, are rather unstable.
13. QCS is a general catalyst for enamide formation from mixed amidals of the type 21. It was developed by Professor T. Fukuyama of this department (personal communication).
14. Enones of the type 25 are useful building blocks for the synthesis of alkaloids: a. Ziegler, F. E.; Bennett, G. B. Tetrahedron Lett. 1970, 2545; b. Imanishi, T.; Imanishi, I.; Momose, T. Synth. Commun. 1978, 8, 99; c. Imanishi, T.; Shin, H.; Hanaoka, M.; Momose, T.; Imanishi, I. Heterocycles 1980, 14, 1111.
15. Methodology for the conversion of aminoacids into more complex structures: a. Compagnone, R. S.; Rapoport, H. J. Org. Chem. 1986, 51, 1713; b. Cupps, T. L.; Boutin, R. H.; Rapoport, H. J. Org. Chem. 1985, 50, 3972; c. Maurer, P. J.; Knudsen, C. G.; Palkowitz, A. D.; Rapoport, H. J. Org. Chem. 1985, 50, 325; d. Knudsen, C. G.; Rapoport, H. J. Org. Chem. 1983, 48, 2260; e. Hamada, Y.; Shioiri, T. Chem. Pharm. Bull. 1982, 30, 1921.
16. Work underway in collaboration with Professor C.-H. Wong of Texas A&M University.
17. Physical properties of selected compounds (m.p. uncorr.; ^1H NMR @ 300 MHz, $CDCl_3$, δ, ppm; ^{13}C NMR @ 75 MHz, $CDCl_3$, δ, ppm; MS @ 70 eV EI, m/e; IR as films, cm^{-1}): 10b: m.p. 99-100 °C; ^1H: 7.422 (br. s.; 1H), 6.357 (br. m., 2H), 5.000 (dd, 1H, J_1=5.9, J_2=8.6 Hz), 4.647 (t, 1H, J=8.6 Hz), 4.444 (dd, 1H, J_1=5.9, J_2=8.6 Hz); ^{13}C: 159.42, 151.4, 143.25, 110.54, 107.72, 69.12, 49.95; IR: 3285, 3180, 1730, 1490, 1415, 1355, 1300, 1235, 1165, 1105, 1055, 1035, 1020, 975, 945, 915, 815, 760. 20: crude, oil, mixture of stereoisomers, complex NMR as a result of slow interconversion of rotamers of CBZ group; ^1H: 7.30 (br. s., 5H), 5.62 (br. dd, 2H), 5.15 (br. dd, 2H), 4.05-3.80 (br. m., 3H), 2.10-1.60 (br. m., 7H); MS: 321 (M^+), 320, 319, 304, 260, 236, 200, 108, 92, 91 (100%), 85, 79, 77, 71, 65, 57, 43. 21: m.p. 70-72°C; ^1H: 5.378 (t, 1H, J=3.9 Hz), 4.154 (t, 1H, J=7.6 Hz), 3.387 (s, 3H), 2.85-2.05 (br. m., 8H); ^{13}C: 205.63, 174.63, 77.84, 60.21, 55.78, 34.83, 30.07, 29.01, 18.78; MS; 183 (M^+), 152, 125, 84 (100%), 72; IR: 2970, 1710 (br.), 1415, 1360, 1260, 1170, 1095. 22: thick oil; ^1H: 6.040 (t, 1H, J=4.5 Hz), 4.049 (t, 1H, J=6.2 Hz), 3.338 (s, 3H), 2.70-1.70 (compl. m., 10H); ^{13}C: 206.12, 170.58, 78.44, 58.63, 55.56, 34.20, 32.48, 27.60, 22.52 18.46; MS: 197 (M^+), 182, 166, 154, 139, 98, 71, 43 (100%); IR: 2980, 1735, 1655, 1420, 1365, 1345, 1260, 1185, 1085. 23: m.p. 123-125°C; ^1H: 5.163 (t, 1H, J=4.6 Hz), 4.609 (dd, 1H, J_1=5.4, J_2=9.2 Hz), 4.451 (t, 1H, J=9.2 Hz), 4.279 (dd, 1H, J_1=5.4, J_2=9.2 Hz), 3.465 (s, 3H), 2.759 (ddd, 1H, J_1=6.2, J_2=9.5, J_3=16.0 Hz), 2.431 (ddd, 1H, J_1=4.9, J_2=6.9, J_3= 16.0 Hz), 2.314-2.181 (compl. m., 4H); ^{13}C: 204.04, 156.55, 80.82, 63.06, 56.98, 55.94, 34.51, 28.81; MS: 185 (M^+), 154, 99, 82, 72 (100%); IR: 3010, 2950, 1750 (br.), 1415, 1340, 1245, 1205, 1175, 1110, 1095, 1055, 1035, 965, 925, 895. 24 (R^1=R^2=CH_2): ^1H: 6.958 (dt, 1H J_1=2.2, J_2=7.8 Hz), 5.249 (dt, 1H, J_1=3.8, J_2=7.8 Hz), 4.138 (br. t, 1H, J=8.9 Hz), 3.25-2.88 (compl. AB q, 2H, J_{AB}=21 Hz), 2.38-2.25 (compl. m, 2H); MS: 151 (M^+), 123, 94, 68 (100%); IR: 2920, 1685 (br.), 1395, 1250, 1165, 1135. 25 (R^1=R^2=CH_2): ^1H: 7.026 (ddd, 1H, J_1=2.0, J_2=4.6, J_3=10.4 Hz), 6.203 (dt, 1H, J_1=2.3, J_2=10.4 Hz), 4.726 (ddd, 1H, J_1=1.9, J_2= 4.6, J_3=20.7 Hz), 4.30-4.08 (compl. m, 1H), 3.811 (br. d, J=20.7 Hz), 2.60-2.00 (compl. m, 4H); ^{13}C: 194.66, 174.40, 145.76, 127.70, 61.05, 40.15, 29.69, 20.37; MS: 151 (M^+), 123, 109, 68 (100%); IR: 2920, 1675 (br.), 1415, 1375, 1255, 1160.

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