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A NOVEL ANNULATION METHOD FOR THE SYNTHESIS OF SOME NITROGEN-CONTAINING HETEROCYCLES: THE SYNTHESIS OF (±)-HELIOTRIDANE AND (±)-NUPHAR INDOLIZIDINE

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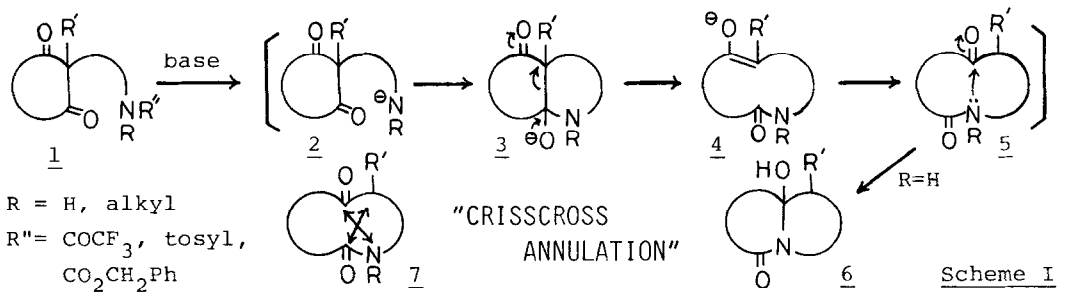
(Dedicated to Dr. Arnold Brossi on the occasion of his sixtieth birthday)

Abstract: The synthesis of the nuclei of pyrrolizidine and indolizidine could be readily achieved by use of the one pot reaction named as "crisscross annulation", which was extended to the synthesis of (±)-heliotridane(16) and (±)-nuphar indolizidine(20), a minor component of dried scent glands of the Canadian beaver.

The great development over the past decades has been made in the array of synthetic methods available for construction of the nitrogen-containing ring system such as pyrrolizidine, indolizidine, quinolizidine, and so on. We wish to report here a new type of annulation suitable to the efficient synthesis of various heterocycles. As shown in a general Scheme I, 1,3-diketone 1 bearing the appropriate protected amino side chain is readily converted into 6 in one pot from 1 under base-catalysed conditions.[1] This sequential process involves a formation of carbinolamine 3 via 2, followed by a retroaldol type of ring-opening to give 4, and finally a transannular cyclization of 5(R = H). With an another point of view this sequence could be briefly depicted by a crisscross sign indicating reaction sites in formula 7, and thereby named as the *crisscross annulation*.[2] Moreover, when the protected secondary amine(1, R = alkyl) is used as a substrate in this versatile annulation, it is of great significance to be able to obtain the strained medium-sized ketolactam 5,[3] controlling the *crisscross annulation*.



Scheme I

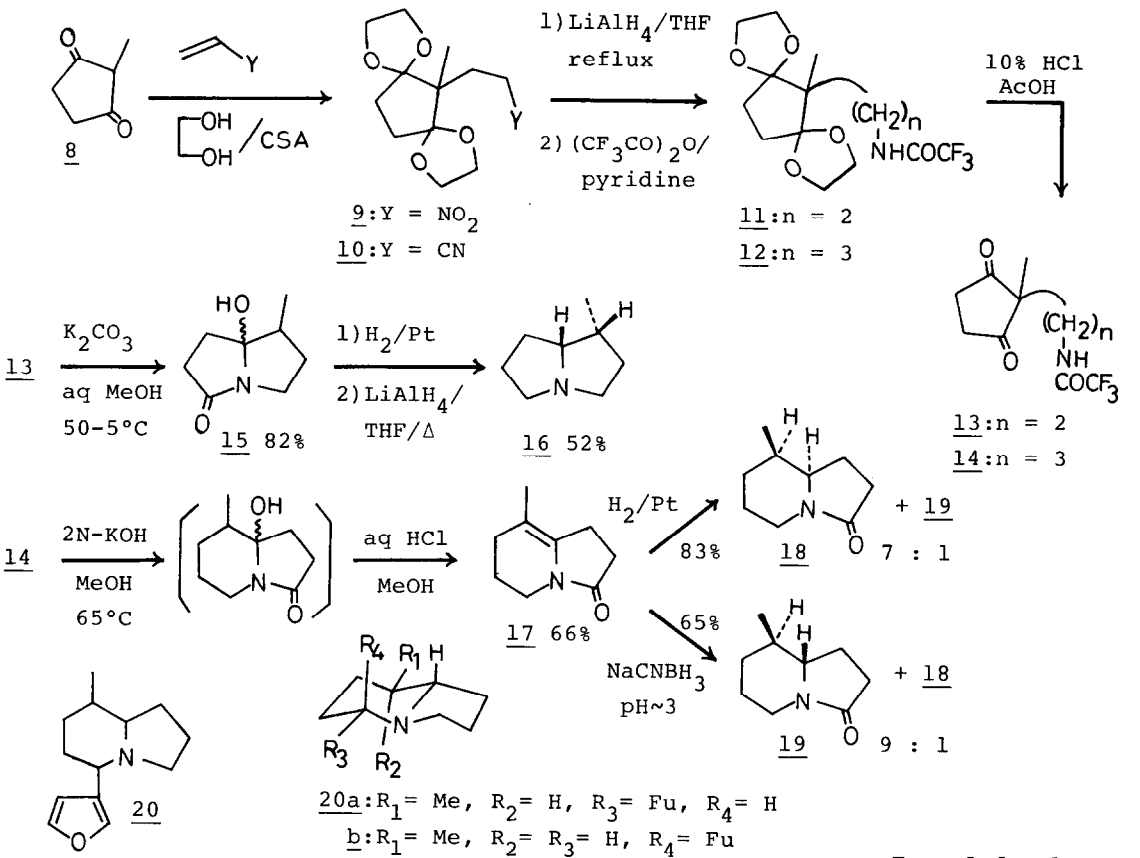
For preparation of the substrates of this *annulation*, the compounds(13, 14) were provided as follows(Scheme II). The Michael addition of 2-methylcyclopentane-1,3-dione(8) with nitroethylene(1.2 equiv KF,[4] catalytic 18-crown-6, THF, reflux) followed by ketalization gave the diketal 9(88% from 8), which in turn was submitted to reduction, acylation, and finally deketalization to afford 13(95% from 9) through the amide 11. Likewise, the diketal 10(51%) prepared in two steps from 8 with acrylonitrile,[5] was converted into 14(85% from 10) via the amide 12.

First, the *crisscross annulation* of 13 was carried out with potassium carbonate[4 equiv, 7% conc in MeOH-H_2O(5:2), 50-5°C for 4.5 h], affording the expected pyrrolizidine 15 as a diastereomeric mixture in a good yield. In order to confirm this structure, the stereoselective hydrogenation and subsequent hydride reduction were easily converted into (±)-heliotridane(16).[6]

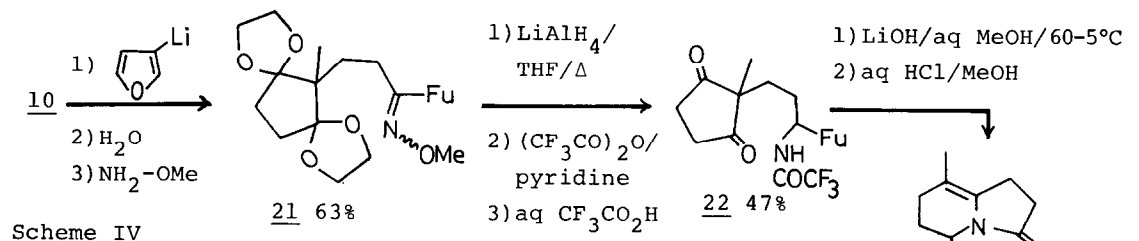
Secondly, the *annulation* of 14 was effected with aqueous KOH[7] in MeOH at 65°C, yielding the indolizidine 17 after acid-treatment, which was reduced by catalytic hydrogenation to give mainly the cis isomer 18. On the contrary, the sodium cyanoborohydride reduction of 17 under acidic condition gave the trans isomer 19 as a major product. This procedure was extended to the synthesis of the nuphar indolizidine, 5-(3-furyl)-8-methyloctahydroindolizine(20) proposed only by a plane formula, the amount of which is extremely small as the minimum component(<0.0002%) in the fourteen nitrogen-containing compounds isolated so far from castoreum(dried scent glands of the Canadian beaver), an article of commerce used in perfumery.[8] Recently, LaLonde and co-workers[9] have stereoselectively synthesized the isomer 20a with equatorial substituents of the four possible stereoisomers(20a-d). We also planned the stereoselective synthesis of the remaining isomers 20b and 20c except 20d possessing all axial substituents to obtain an important clue to the stereochemical research of the natural product 20.

Addition of 10 with 3-furyllithium furnished the ketone, which was then converted into the diketone 22 through the methyloxime 21. In a similar manner, the *annulation* of 22 in the presence of LiOH[7] produced the desired indolizidine 23[10] in a good yield after acid-treatment(Scheme III). Reduction of the olefinic bond in 23 was performed stereoselectively, as aforementioned, with sodium cyanoborohydride at pH ~3,[11] affording the major trans isomer 24 and minor 25 after separation by silica gel chromatography. This selective reduction process could be explained as follows. The axial protonation to the more preferred conformation 23A than 23B according to the severe $A^{(1,3)}$ interaction[12] between a furyl and lactam carbonyl group would give exclusively the N-acyliminium 26. Subsequently, the hydride attack to this iminium occurs preferentially from the β-side at C-8a to afford the more stable 24 again based on the concept of $A^{(1,3)}$ strain(Scheme IV). This consideration was further supported by ^1H NMR analysis, that each proton at C-5 in 23A and 24 appears at δ 5.30 ($CDCl_3$) respectively under the influence of the down field effect of lactam carbonyl group, and that the C-5 proton in 25 without its effect is situated

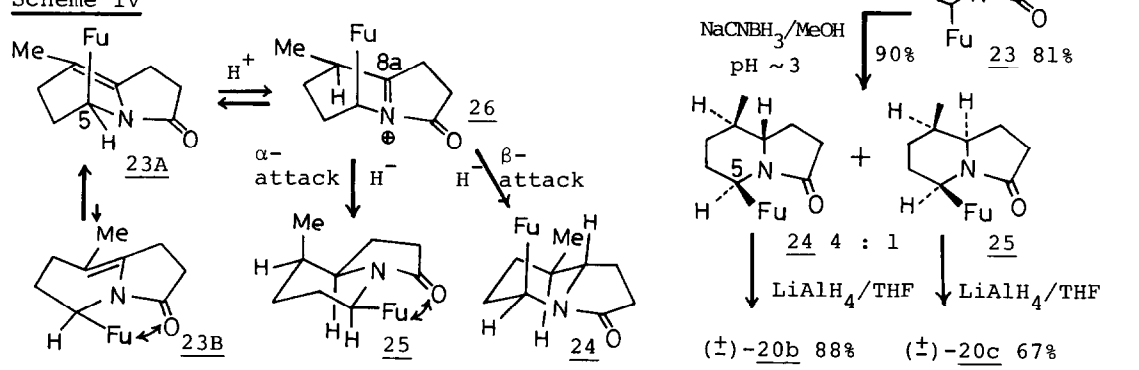
Scheme II



Scheme III



Scheme IV



at δ 4.40. Reduction of 24 and 25 with $LiAlH_4$ was led to (±)-20b and (±)-20c,[13] respectively, and each Mass spectrum was almost identical with that of 20 reported by Ohloff.[8] Further to confirm the stereochemical feature of our synthetic 20b, it was established by X-ray analysis of the picrate 20b[mp 87-9°C(decomp)].

Studies are in progress to investigate the scope and limitation of this useful *annulation*.

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References and Notes

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2. As for the naming of this reaction, we acknowledge the valuable suggestion by Professor B. M. Trost, University of Wisconsin.
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6. Compound (±)-16: ^{1}H NMR($CDCl_3$) δ 0.99(d, J = 7 Hz, 3H), 1.2-1.9(m, 6H), 2.0-2.7(m, 3H), 2.9-3.7(m, 3H); picrate, mp 242-4°C(lit mp 242-3°C). N. J. Leonard, D. L. Felly, J. Am. Chem. Soc., 72, 2537(1950).
7. The following bases to improve this yield were used in this annulation, but these gave no satisfied results: K_2CO_3, $KHCO_3$, Na_2CO_3, NaOH, n-Bu_4NF.
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10. Compound 23(oil): ^{1}H NMR($CDCl_3$) δ 1.63(broad s, 3H), 1.9-2.1(m, 4H), 2.4-2.8(m. 4H), 6.25(m, 1H), 7.20(m, 1H), 7.32(m, 1H); IR(Neat) 1680 cm^{-1}; Mass m/e 217(M^+).
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13. Compound 20b(oil): ^{1}H NMR($CDCl_3$) δ 0.96(d, J = 6 Hz, 3H), 4.23(broad s, 1H), 6.38(broad s, 1H), 7.39(s, 1H), 7.40(s, 1H); IR($CHCl_3$) 2920, 865 cm^{-1}; no Bohlmann band; Mass m/e 205(M^+). Compound 20c: ^{1}H NMR($CDCl_3$) δ 0.91(d, J = 6 Hz, 3H), 2.7-3.1(m, 2H), 6.46(s, 1H), 7.35(s, 1H), 7.36(s, 1H): IR($CHCl_3$) 2920, 2775(Bohlmann band), 880 cm^{-1}; Mass m/e 205(M^+).

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