STUDY OF THE MECHANISM OF CYCLIZATION AND DECOMPOSITION OF METHYLKETONES OXINDOLES IN ACIDIC MEDIUM

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Résumé:
La stechiométrie de l'acide para toluène sulfonique est un facteur déterminant dans la réaction de cyclisation du méthyle cétone oxindole **1** .
En effet, le méthyle cétone oxindole **1** est cyclisé en composé pentacyclique **2** en présence d'une quantité adequate d'acide para toluène sulfonique avec un bon rendement. L'obtention des deux épimères **3a** et **3b** nous aide à expliquer le mécanisme de cette réaction .

Summary: The stechiometry of the paratoluene sulphonic acid is a determining factor of the reaction of cyclization of the oxindolic methylketone 1.
Indeed, the oxindolic methylketone 1 is cyclized in pentacyclic compound 2 in the presence of an adequate quantity of paratoluene sulphonic acid in good yield. Obtaining the tow epimeric indolenines 3a and 3b enabled us to explain the mechanism of this reaction.

Keywords: Cyclization, methylketone oxindoles, acidic medium, indolenine.

The pentacyclic ketolactam 1 has been first synthesized by Ban [1] who has employed an intra – molecular cyclization of the methylketone 1 via his iminoether in basic area (NaH/DMSO).
A convergent access to this compound, starting from 2-hydroxytryptamine yielded the major isomer 1 (50%) [2], which had the natural stereochemistry [3].
Treatment of the methyl ketone 1 with poliphosphoric acid gives the pentacyclic ketolactam 2 in few yields (scheme 1) [4].
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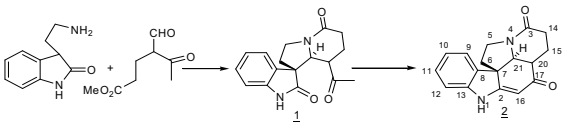
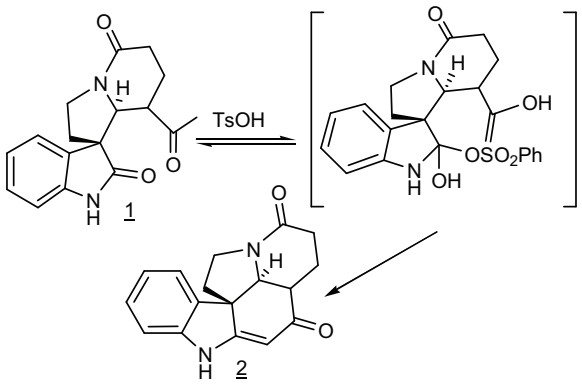


Scheme 1

At the time of the first synthesis of aspidofractinine, the para-toluene-sulphonic acid (TsOH) was used like agent of cyclization [5].
Indeed, the compound 1, treated by para-toluene-sulphonic acid (TsOH) gave, in more of two epimeric indolenines (3a, 3b), the traces of made up pentacyclic ketolactam2.
In improving the output of this cyclization, a modification of the procedure was undertaken.
Indeed, the treatment of 1 by tosylic acid (3 equivalents) in toluene with backward flow by using an apparatus of Dean-Stark would lead to the compound 2 with an output of 65% starting from the most polar isomer of the compound 1 , prepared according to the method described in scheme 1.
This result allows us to suppose that the reaction proceeds according to the mechanism described in scheme 2.



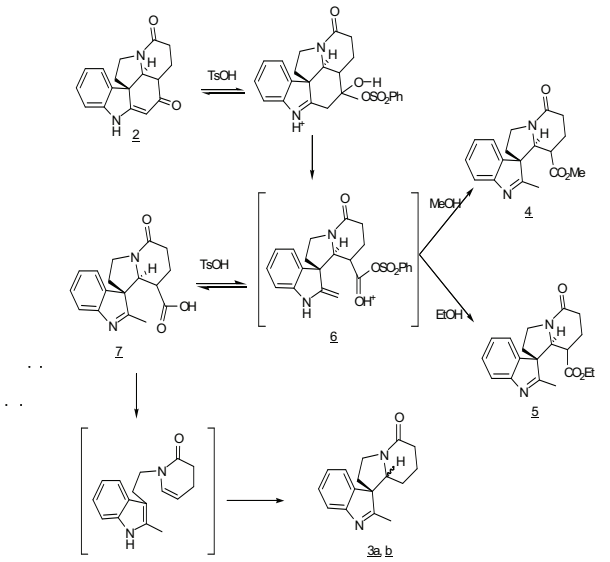
Scheme 2

On the other hand, treatment of the oxindolic methylketone 1 by an excess of para-toluene-sulphonic acid (10 equivalents) in toluene with backward flow exclusively gives to both epimeric indolenines (3a ,b) with a total output of 60% starting from the most polar isomer of oxindolic methyl 1 .
It would be thus interesting to follow the process of degradation to end to clear up mechanism of this reaction.
Obtaining methyl ester 4 in work of Lévy and All [4,5] proves that the reaction passes by an intermediate 6 which evolves then, by methanolic treatment towards the compound 4 (scheme 3).
Indeed, treatment of oxindolic methylketone 1 by TsOH (5 equiv.) in toluene with backward flow, followed of a methanoic treatment gives methyl ester 4 with an output of 65%.
However, the ethanoic treatment under the same conditions gives the ethyl ester 5 with an output of 45%.
From these results, we can deduce that the general mechanism of this reaction passes probably initially by

an activation of the lactam carbonyl group of compound 2.

The ketal 6 obtained evolves then, according to the treatment undergone to the methyl ester 4 or to the ethyl ester 5.

With an excess of para-toluene-sulphonic acid, the intermediate ketal 6 evolves to the acidic compound 7 which undergones aninternal rearrangement to give the epimeric indolenines 3a or 3b. (Scheme 3).



Scheme 3

Experimental section.

Pentacyclic compound 2.

A 100-mL, one-necked, round-bottomed flask is equipped with a magnetic stirrer, Dean-Stark trap, and a reflux condenser. The flask is charged with 1.0 g (3.35 mmol) of methyl ketone 1, 1.9g (10 mmol) of p-toluenesulfonic acid monohydrate, and 40 mL of toluene.

The mixture is heated under reflux in an oil bath (about 130°C) for 13 hrs. The reaction mixture is allowed to cool to ambient temperature, diluted with CH_2Cl_2, and poured onto 50 mL of aqueous, saturated sodium bicarbonate.

The organic phase is separated and the aqueous phase is extracted twice with 20 mL of CH_2Cl_2. The combined organic phases are dried over sodium sulfate and concentrated on a rotary evaporator. The residue is purified by flash column chromatography on silica gel using methylene chloride-methanol (50:1) as eluent to afford 0.61 g (65%) of Pentacyclic compound 2.

IR (CH_2Cl_2): 3200, 2875, 1650, 1630, 1600, 1350cm^{-1}.
UV (MeOH): 204, 235, 290, 340 nm.
NMR ($CDCl_3$, 300 MHz): δ 8.30 (s, 1H, NH), 7.30-6.95 (m, 4H, aromatic)
5.6(s, 1H, H_{16}),4.27(d, 1H, j=9Hz, H_{21}), 4.12(dd, j=6.7, j=12.5Hz , 1H, H_5) 3.40(dt,j=12.5, j=5.4Hz , $H_{5'}$) 290(m,1H, H_{20}).
MS. m/e (rel. intensity): 280(M^+, 38), 183(90), 170(100), 156(20).

Indolenine 3a and 3b.

A 100-mL, round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser is charged with 0.5g (1.67mmol) of oxindolic methylketone 1 , 25 mL of toluene and 3.17 g (16.7mmol) of para-toluene-sulfonic acid.

The mixture is refluxed for 15 hr, and then the reaction is quenched with 10 g of solid sodium bicarbonate and allowed to stir for 15 min at 25°C. The mixture is filtered to remove the sodium bicarbonate and the volatile components are removed under reduced pressure. The residue is dissolved in 50 mL of methylene chloride, placed in a separatory funnel and washed with 100 mL of water.

The aqueous layers are collected and extracted with methylene chloride (2 × 100 mL). The organic layers are combined, dried over 10 g of sodium sulfate for 1 hr, filtered into a 100-mL, round-bottomed flask, and concentrated under reduced pressure.

The residue is purified by flash column chromatography on silica gel using methylene chloride - methanol (50:1) as eluent yielding 100mg (23.6 %) for less polar isomer 3a and 150 mg (36.4 %) for more polar isomer 3b.

Indolenine 3a.
IR (CH_2Cl_2):3420, 2940, 1630, 1570, 1450, 1400, 1250, 1060cm^{-1}.
UV (MeOH): 220, 260 nm.
NMR ($CDCl_3$, 300 MHz): δ7.55 (d, 1H,j=7.6Hz), 7.37(m,1H), 7.25(m,2H), 4.08(m,1H), 3.96(dd, 1H, j_1=4.5,j_2=11Hz), 2.5-2.3(m, 3H), 2.25(s,3H, CH_3) 2.15(m, 1H), 1.9(m,1H,), 1.63 (m,1H), 1.40(m, 1H,) 1.05(dt, 1H, j_1=4.5, j_2=11Hz).
MS. m/e (rel.intensity):254(M^+ 14), 157(100), 144(75), 105(15), 111(34).

Indolenine 3b.
IR (CH_2Cl_2): 3440, 2940, 1630, 1570, 1450, 1320 cm^{-1}.
UV (MeOH): 204, 262 nm.
NMR ($CDCl_3$, 300 MHz): δ7.58 (d, 1H,j=7.6.Hz), 7.37(t,1H, j=7.6Hz) 7.19(t,1H,j=7.6Hz), 7.04(d,1H,j=7.6Hz,), 4.09(m,1H)
3.97(dd, 1H, j_1=4.5, j_2=11Hz), 3.84(m,1H), 2.40(m,2H)
2.30(s, 3H, CH_3), 2.26(m,1H), 1.80(m,1H), 1.68(m,1H), 1.37(m,1H)
0.75(dt,1H, j_1=4.5, j_2=11Hz).
MS. m/e (rel intensity): 254(M^+, 18), 157(100), 144(70), 105(20), 111(38).

Methyl ester 4 and ethyl ester 5.

In a 100-mL, two-necked, round-bottomed flask equipped with a reflux condenser, septum inlet, and a magnetic stirring bar is fitted to a nitrogen bubbler. The flask is charged with 50 mL of toluene, 1.5g (5mmol) of methyl ketone 1 and 4.75 g (25mmol) of p-toluenesulfonic acid monohydrate . The solution is refluxed for 12 hr and the mixture is cooled to 22°C. 10-mL of Methanol dissolved in
30 mL of toluene , transferred to the flask by cannula and the solution is refluxed for 3 hr. The reaction mixture is cooled and the volatile components are removed under reduced pressure ,washed with saturated

aqueous sodium bicarbonate and the aqueous phase is extracted with methylene chloride and the combined organic extracts are dried over anhydrous magnesium sulfate ($MgSO_4$). The solvents are removed under reduced pressure and the residue is purified by flash column chromatography on silica gel, eluting with 2% methanol/methylene chloride. The methyl ester 4 is obtained with overal yield of 65%.
The ethyl ester 5 is obtained in similar procedure except that the ethanol is replaced by methanol.
Compound 5 is obtained with an overall yield of45%.

Methyl ester 4.
IR (CH_2Cl_2): 3260, 2950, 1720, 1630, 1450cm^{-1}.
UV (MeOH): 216, 262
NMR ($CDCl_3$, 300 MHz): δ7.58 (d, 1H, j=7.6Hz), 7.38(dd, 1H, j=7.6Hz)
7.2(dd, 1H, j=7.6Hz), 7.02(d,1H, j=7.6Hz), 4.25(d,1H, j=9Hz),4.05(m,1H) 3.50(s,3H,CO_2CH_2), 2.52-2.38(m,3H),2.30(s, 3H, CH_3), 1.95-1.84(m, 4H)
1.35(t, 3H, j=Hz, CH_3).
MS. m/e (rel intensity): 312(M^+, 12), 297(20), 226(17), 225 (15).

Ethyl ester 5.
IR (CH_2Cl_2): 3250, 29450, 1720, 1630, 1460cm^{-1}.
UV (MeOH): 215, 260.
NMR ($CDCl_3$, 300 MHz): δ7.70 (d, 1H, j=7.6Hz), 7.40(dd, 1H, j=7.6Hz)
7.35(dd, 1H, j=7.6Hz),7.20(d,1H,j=7.6Hz),4.30(d,1H, j=9Hz)
4.20(m,1H), 3.45(q, 2H, j=Hz, CO_2CH_2), 2.60-2.45(m,3H), 2.40 (s, 3H , CH_3) 1.80-1.60 (m, 4H).
MS. m/e (rel intensity): 326 (M^+, 20), 157(100), 144(60), 105(40), 111(25).

References :

1-Oichi, T.; Nagai, M.; Ban, Y. Tetrahedron Lett.1968, 4, 491-495.
2-Laronze,J.Y.;Cartier,D.;Laronze, J.;Lévy,J.Tetrahedron Lett.1980,46,4441-444.
3-Laronze,J.Y.; Lévy,J.; Le Men,J. ² Tetrahedron Lett.1974, 6, 491-494.
4-Carier, D ; Ouahrani, M.R ; Hugel, G ; Lévy, J. Heterocycles.1988, 27,657-661.
5-Carier, D ; Ouahrani, M.R ; Lévy, J. Tetrahedron Lett.1989, 30,1951-1954.