ON THE SYNTHESIS OF UNSATURATED 4(5H)-IMIDAZOLONES

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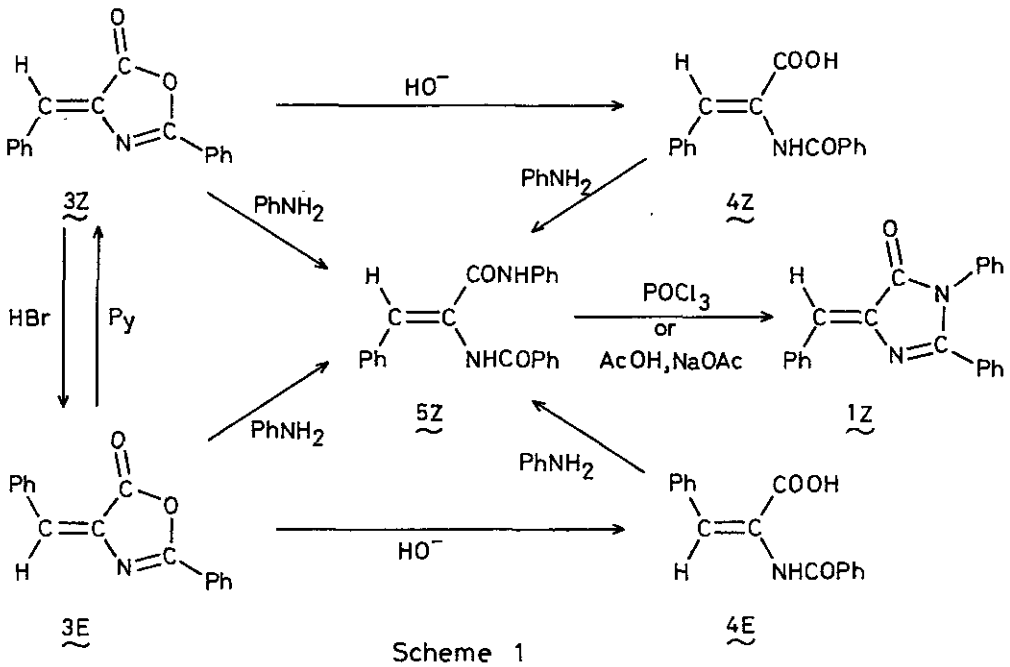
Abstract ——— (Z)-2,3-Diphenyl-5-benzylidene-4(5H)-imidazolone and (Z)-2,3-diphenyl-5-(α-phenylethylidene)-4(5H)-imidazolone were obtained from the corresponding (Z)-2-phenyl-4-benzylidene-5(4H)-oxazolone and (Z)-2-phenyl-4-(α-phenylethylidene)-5(4H)-oxazolone and aniline. (Z)-2,3--Diphenyl-5-benzylidene-4(5H)-imidazolone reacted with diazomethane to afford a mixture of stereoisomeric spirocyclopropanes and (Z)-2,3-diphenyl-5-(α-phenylethylidene)-4(5H)-imidazolone, the product ratios being modified with the appropriate solvent. Anilide of 1-phenyl-4-methyl-3-isoquinolincarboxylic acid or (Z)-2,3-diphenyl-5-(α-phenylethylidene)-4(5H)-imidazolone were obtained from anilide of (Z)-2-benzamidocinnamic acid depending upon the reaction conditions.

It has been reported that interaction of arylamines with 2-aryl-4-arylmethylene-5(4H)-oxazolones generally leads to ring opening to give the arylamides of α-aryl-carboxamido-β-arylacrylic acids which may recyclize, in some cases, to the corresponding 2,3-diaryl-4-arylmethylene-4(5H)-imidazolones by heating at 200ºC in vacuo or in the presence of acetic acid and sodium acetate[1], but in no case was the stereochemistry considered. We now wish to report our findings on the synthesis of (Z)-2,3-diphenyl-5-benzylidene-4(5H)-imidazolone(1Z) and (Z)-2,3-diphenyl-5-(α-phenylethylidene)-4(5H)-imidazolone(2Z).

(Z)-2-Phenyl-4-benzylidene-5(4H)-oxazolone(3Z) was prepared from hippuric acid and benzaldehyde in the presence of acetic anhydride and anhydrous sodium acetate according to the Erlenmeyer method[2]. It has been reported that the Erlenmeyer method usually gives the thermodynamically more stable Z-isomer[3], while (E)-2-phenyl-4-benzylidene-5(4H)-oxazolone(3E) can be obtained by isomerization of 3Z with hydrobromic acid[2,3]. These compounds were stereospecifically hydrolyzed to the corresponding (Z- or E)-2-benzamidocinnamic acids(4Z or 4E) without any difficulty. The geometry of all these compounds has been unambiguously determined[4] by

^{13}C-NMR spectroscopy[5].

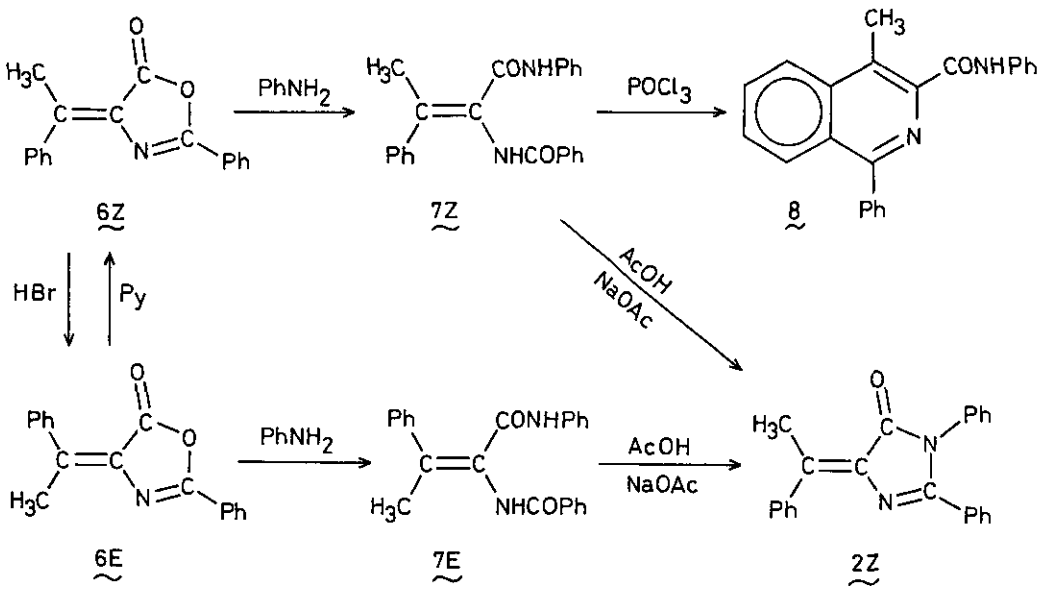
The interaction of aniline with both(Z or E)-5(4H)-oxazolones(3Z or 3E) afforded the anilide of Z-2-benzamidocinnamic acid(5Z) (that is to say the reaction of 3E occurs with isomerization) which recyclized in the presence of acetic acid and sodium acetate or phosphorus oxychloride to the desired (Z)-2,3-diphenyl-5-benzylidene-4(5H)-imidazolone (1Z) (Scheme 1). The spectral data of 5Z and 1Z [the coupling constants of the ^{1}H-C=C-^{13}CON- were in the appropriate range(J=5.3Hz for 1Z and J=2.8Hz for 5Z)] are consistent with a "cis" arrangement of the coupled nuclei and the assignment of the Z configuration was established. All attempts to obtain 5E from 3E or 4E were unsuccessful.



Scheme 1

2-phenyl-4-(α-phenylethylidene)-5(4H)-oxazolone(6) was prepared from hippuric acid and acetophenone in the presence of acetic anhydride and anhydrous lead acetate in THF[6], giving a mixture of geometric isomers which were isolated by appropriate isomerization procedures; treatment with pyridine at room temperature or with hydrobromic acid at 0ºC afforded the Z-isomer(6Z) or the E-isomer(6E), respectively. In this case the opening of the oxazolidinone ring with aniline to an anilide of 2-benzamido-3-phenylbutenoic acid(7) was stereospecific when refluxed in ben-

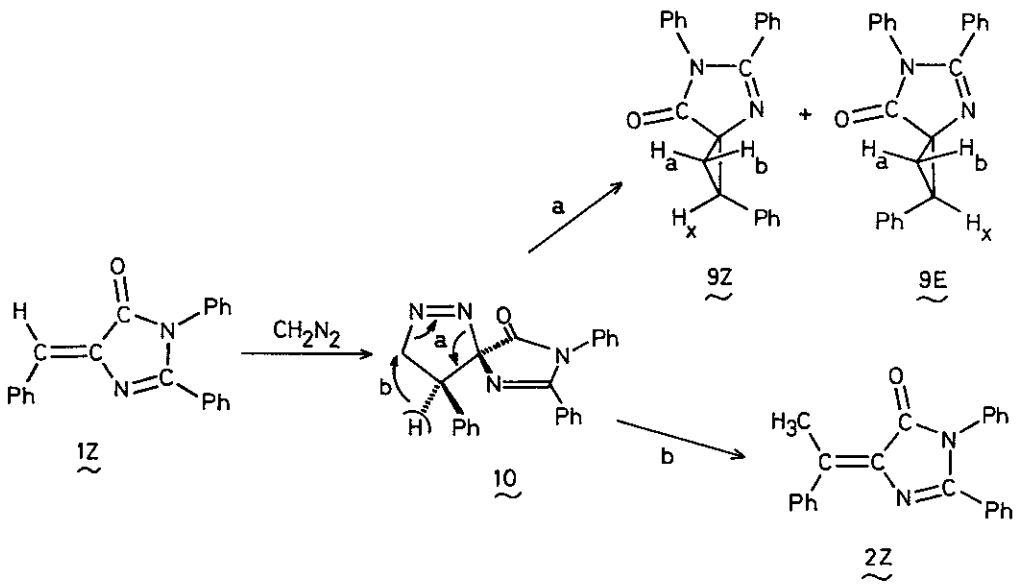
zene. The geometric isomers, 7Z and 7E, were unambiguously assigned by ^{1}H-NMR spectroscopy[7]. But different results were obtained when different conditions of cyclodehydration were employed. Thus, (Z)-2-benzamido-3-phenylbutenoic acid(7Z) gave anilide of 1-phenyl-4-methyl-3-isoquinolincarboxylic acid(8) which constitutes an interesting new procedure for the synthesis of functionalized isoquinolines and both isomers(7Z and 7E) gave with acetic acid and sodium acetate the desired (Z)-2,3-diphenyl-5-(α-phenylethylidene)-4(5H)-imidazolone(2Z)in low yield(Scheme 2).



Scheme 2

It is known that the addition of diazomethane to double bonds activated by a suitable electron-withdrawing group, followed by thermal decomposition of the resulting pyrazolines, is an established route to cyclopropanes[8], although the synthetic utility of the method is hampered by extensive formation of unsaturated compounds. In this case, the action of diazomethane on (Z)-2,3-diphenyl-5-benzylidene-4(5H)-imidazolone(1Z) gave a three-compound mixture, two stereoisomeric spirocyclopropanes(9) and (Z)-2,3-diphenyl-5-(α-phenylethylidene)-4(5H)-imidazolone(2Z), which retained its initial imidazolinone geometry. That is to say, the cyclopropanation proceeds with loss of geometry, although there is a high degree of stereoselectivity, and the unsaturated compound was obtained with retention of the geo-

metry, as we have previously reported[9] with related oxazolinones. However, the selectivity of decomposition can be modified by changing the solvent polarity, since we were able to obtain 9% of 2Z and 70% of 9 with CCl_4 but 52% of 2Z and 28% of 9 when DMF was used. 2Z and 9Z were separated by column chromatography, but a pure sample of 9E could not be isolated, since the proportion in the mixture is too small and the separation too poor. Structural assignment of 9Z was made on the basis of the ^{1}H-NMR spectral data by comparisons of their vicinal coupling constants and chemical shifts as previously reported on similar spiroazalactones[2,9].



Scheme 3

Cyclopropane formation is in accordance with the ionic mechanism(a) of the decomposition of 1-pyrazolines, proposed by van Auken and later by others[10]. The stereospecificity of the cleavage of 1-pyrazoline(10) is lacking, although stereoselectivity does exist as cyclization to 9Z would be favored over rotation and cyclization. Hydride shift in the 1-pyrazoline intermediate(10) with loss of nitrogen would give 2Z.

EXPERIMENTAL

Melting points were determined on a Mettler FP 61 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer Infrared Spectrophotometer Model 283. NMR spectra were measured on a Perkin-Elmer R-12 B Spectrophotometer and Varian FT-80 with tetramethylsilane as the internal standard. Microanalyses were measured

on a Perkin-Elmer 240-B analyzer and were in satisfactory agreement with the calculated values.

The acids 4Z and 4E were prepared by stereospecific hydrolysis of 3Z and 3E respectively as previously described[11].

Preparation of 5Z, 7Z and 7E(General Method): 6 mmole of respective (Z)- or (E)-5(4H)-oxazolone and 18 mmole of freshly distilled aniline were refluxed in anhyd. benzene for the appropriate time(10 h in the case of 5Z and 20 h for 7Z and 7E). The solution was then cooled and the precipitate filtered, washed with anhyd. benzene and dried. One recrystallization from ethanol/water gave analytically pure samples. The yield was about 75% in all three cases.

5Z: mp 234-235ºC(dec); colorless needless; ir(nujol)3280,1650 cm^{-1}; ^{1}H-NMR (DMSO,d_6) δ 6.9-8.2(16H,m), 10.1(1H,s), 10.15(1H,s).

7Z: mp 259-260ºC(dec); colorless needless; ir(nujol)3270,1670,1650 cm^{-1}; ^{1}H-NMR (DMSO,d_6) δ 2.2(3H,s), 7-7,8(15H,m), 9.4(1H,s), 10.8(1H,s).

7E: mp 210-211ºC(dec); colorless needless; ir(nujol)3270,1650 cm^{-1}; ^{1}H-NMR (DMSO,d_6) δ 2.1(3H,s), 6.7-8.0(15H,m), 9.2(1H,s), 9.8(1H,s).

Preparation of 1Z

Method A: 1.03 g(3 mmole) of 5Z, 0.84 g(9 mmole) of freshly distilled aniline and 0.25 g(3 mmole) of anhyd. AcONa were refluxed in glacial AcOH(10 ml) for 5 h. The solution was then cooled and poured on crushed ice. The precipitate was extracted with CH_2Cl_2, the extract washed with aq. $NaHCO_3$ and dried over anhyd. $MgSO_4$. The solvent was distilled off, and the residue was recrystallyzed from ethanol/water (70%).

Method B: 1.03 g(3 mmole) of 5Z were refluxed in $POCl_3$(4 ml) for 4 h. The solution was then cooled, poured on crushed ice, and the precipitate was extracted with CH_2Cl_2. The extract was washed with aq. $NaHCO_3$ and then dried over anhyd. $MgSO_4$. The solvent was distilled off and the residue was recrystallized from ethanol/water(80%).

1Z: mp 178-179ºC; yellow needless; ir(nujol)1720 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 7.0-7.9 (14H,m), 8.4-8.6(2H,m).

Preparation of 2Z: 1.07 g(3 mmole) of 7Z, 0.84 g(9 mmole) of freshly distilled aniline and 0.25 g(3 mmole) of anhyd. AcONa were refluxed in glacial AcOH(10 ml) for 10 h. The solution was then cooled, poured on crushed ice, and the precipitate was extracted with CH_2Cl_2. The extract was washed with aq. $NaHCO_3$ and then dried over anhyd. $MgSO_4$. The solvent was distilled off and the residue recrystallized

from ethanol/water(30%).

2Z: mp 156-157ºC; yellow needless; ir(nujol)1700 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 2.9(3H,s), 7.2-7.9(13H,m), 8.0-8.2(2H,m).

Action of diazomethane over 1Z

Method A: 1.00 g(3 mmole) of 1Z was dissolved in DMF(10 ml) and an ethereal solution of CH_2N_2 was added with stirring until no 1Z was noticed by TLC. Water was then added to the solution to precipitate a solid. The solid was dissolved in the minimum amount of warm benzene and the components of the mixture separated by column chromatography on silica gel, using benzene/hexane 3:2 as an eluting agent, to afford analytically pure samples of two compounds in this order: first 2Z(52%), later 9Z(20%).

Method B: 1 g(3 mmole) of 1Z was dissolved in CCl_4(10 ml) and an ethereal solution of CH_2N_2 was added with stirring until no 1Z was noticed by TLC. The solvent was then removed by distillation, and the resulting solid was purified in the same way as Method A. Yield was 9% of 2Z and 62% of 9Z.

9Z: mp 164-165ºC; white powder; ir(nujol)1725 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 2.2($1H_a$, dd, J_{ab}=13Hz, J_{ax}=10Hz), 2.4($1H_b$, dd, J_{ab}=13Hz, J_{bx}=8Hz), 3.3($1H_x$, dd, J_{ax}=10Hz, J_{bx}=8Hz), 7.0-7.6(15H,m).

Preparation of 8: 1.07 g(3 mmole) of 7Z were refluxed in $POCl_3$(4 ml) for 6 h. The solution was then cooled, poured on crushed ice, and the precipitate was extracted with CH_2Cl_2. The extract was washed with aq. $NaHCO_3$ and then dried over $MgSO_4$. The solvent was distilled off and the residue was recrystallized from ethanol/water(64%).

8: mp 183-184ºC; yellowish powder; ir(nujol)3280,1700,1650 cm^{-1}; ^{1}H-NMR(DMSO-d_6) δ 2.25(3H,s), 6.7-8.0(14H,m), 9.2(1H,s).

REFERENCES

1. A.H. Harhash, N.A.L. Kassab and A.A.A. Elbanani, Ind.J.Chem., 1971, 9, 789; A.F.M. Fahmy and M.O.A. Orabi, Ind.J.Chem., 1972, 10, 961; A.M. Islam, A.M. Khalil and I.I. Abd El-Gawad, Aust.J.Chem., 1973, 26, 827; A.M. Islam, A.M. Khalil and M.S. El-Houseni, Aust.J.Chem., 1973, 26, 1701.
2. S.W. King, J.M. Riordan, E.M. Holt and C.H. Stammer, J.Org.Chem., 1982, 47, 3270.
3. Y.S. Rao and R. Filler, Synthesis, 1975, 749.
4. E.P. Prokof'ev and E.I. Karpeiskaya, Tetrahedron Lett., 1979, 737; M. Cutolo, V. Fiandanese, F. Naso and O. Sciacovelli, Tetrahedron Lett., 1983, 4603.

5. S. Braun, Org.Magn.Reson., 1978, 11, 197; U. Vogeli and W. von Philipsbron, ibid., 1975, 7, 617.

6. C. Cativiela and E. Meléndez, Synthesis, 1978, 832.

7. C. Cativiela, J.I. García and E. Meléndez, Synthesis, 1982, 763.

8. A.I. Meyers, "Heterocycles in Organic Synthesis", Wiley, New York, 1974, pp. 28-33.

9. C. Cativiela, M.D. Díaz de Villegas, J.A. Mayoral and E. Meléndez, J.Org.Chem., 1984, 49, 1436.

10. T.V. van Auken and K.L. Rinehart, J.Am.Chem.Soc., 1962, 84, 3736; E. Nagai and Y. Hirata, J.Org.Chem., 1978, 43, 626; P.S. Engel, Chem.Rev., 1980, 80, 99.

11. C. Cativiela and E. Meléndez, Synthesis, 1980, 901.

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