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Base-Catalyzed Rearrangement of 2-Vinylpyrazolium Salts into 1,2-Dihydropyrimidines

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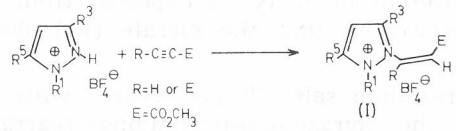
The ring transformation of 2-vinylpyrazolium salts into dihydropyrimidines is the last step of a process which starts from neutral pyrazoles. Globally, it results in the insertion of a >CE—CHOH—E (E = CO_2Me) fragment between the two nitrogen atoms of a 1-substituted pyrazole. The dihydropyrimidines formed were identified spectroscopically (^1H and ^{13}C NMR) and the relative configuration of the two chiral centres established by the X-ray structure analysis of a picrate. Finally, a plausible mechanism for the formation and epimerization of dihydropyrimidines is proposed.

INTRODUCTION

In a recent report[1] on the non-aromatic behaviour of aromatic azoles, we described the reaction between *N*-substituted pyrazolium fluoroborates and acetylenic esters. The reaction yields 2-vinylpyrazolium fluroborates by the Michael addition of the corresponding pyrazole to the activated triple bond.



These vinylpyrazolium salts (*I*) were unknown. In an attempt to study their reactivity, this paper describes the reaction of salts (*I*) with nucleophiles (aqueous potassium carbonate and alcohols).

RESULTS AND DISCUSSION

When (*Ia*), (*Ib*) and (Ic) are treated with an aqueous solution of potassium carbonate they undergo a rearrangement leading to a mixture of two compounds, one being slightly predominant. They have been identified as the

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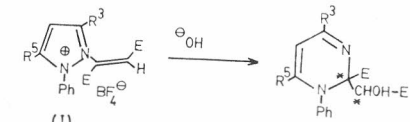
two diastereoisomers of the dihydropyrimidine (*II*). We were not able to separate the diastereoisomers either by chromatography (column or HPLC) or by fractional crystallization.



(I)
a; R^3=H, R^5=CH_3
b; R^3=CH_3, R^5=H
c; R^3=R^5=CH_3

(II)
*chiral centres

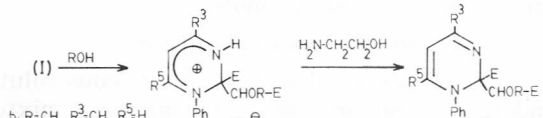
The structure of the dihydropyrimidines (*II*) was established by analytical and spectroscopic data. Thus, both microanalysis and mass, spectrometry indicate that (*II*) have a molecular formula resulting from the addition of an OH^- to the cation (*I*). Moreover, in the mass spectra fragments appear corresponding to the loss of CHOH—CO_2Me (base peak) and CO_2Me from the molecular ion.

The IR spectra of (*II*), recorded in KBr, present bands at 2080—3600 cm^{-1} (ν_{OH} strongly associated) and at 1735—1740 and 1715—1720 cm^{-1} (non-conjugated ester groups).

Proton NMR spectra of (*II*) and of some of their salts are summarized in Table I. One of the diastereoisomers (the less abundant one) shows the methoxy signal of one of the ester groups clearly shielded with regard to the other three methoxy signals (one of the same diastereoisomer and two of the other). At the same time, the mixture of diastereoisomers shows the *ortho* protons of the more abundant compound deshielded comparatively with the remaining protons of the phenyl groups. Signals corresponding to the exocyclic CH appear as broad singlets due to residual ^3J coupling with the OH (addition of trifluoroacetic acid or deuterium oxide causes disappearance of the OH signals and the narrowing of the CH singlets).

Table II contains the carbon-13 chemical shifts of compounds (*IIa*), (*IIb*) and (*IIc*) (*IIb* decomposes partialy in deuteriochloroform solution) and those of the picrate (*Vc*) of the last compound. The signals of the pyrimidine ring are consistent with literature values for similar compounds.[2] Most signals are »doublets« of different intensity, as expected from a mixture of diastereoisomers. It is noteworthy that the picrate (*Vc*) shows only one signal for each carbon.

When 2-vinylpyrazolium salts (*I*) are treated with methanol or ethanol at room temperature, the »pyrazolium-pyrimidine« rearrangement takes place. The tetrafluoroborate (*IIIc*), on treatment with an aqueous solution of ethanolamine, yields the free dihydropyrimidine (*IVc*).



b; R=CH_3, R^3=CH_3, R^5=H
c; R=CH_3, R^3=R^5=CH_3
d; R=CH_2CH_3, R^3=R^5=CH_3

(III)

(IV)

TABLE I

Proton NMR Spectra of the Dihydropyrimidines (II); δ (ppm from TMS), J (Hz)

Compound	Solvent	isomer	R^3	H-5	R^5	OCH_3	CHOH	OH	Ph	$J_{R^3=H(5)}$	$J_{R^5=H(5)}$	$J_{R^3=R^5}$
IIa	$DCCl_3$	major	7.75	5.27	1.66	3.71, 3.72	4.40	—	7.10—7.54(3H), 8.0(2H)	3.5	0.7	0.5
		minor	7.64	5.19	1.63	3.41, 3.68	4.95	—	7.10—7.54(5H)	3.6	0.7	0.5
IIb	$DCCl_3$	major	2.13	5.20	6.60	3.71, 3.71	4.73	—	7.20—7.64(5H)	—	7.0	—
		minor	2.11	5.16	6.60	3.44, 3.65	4.99	—	7.20—7.64(5H)	—	7.0	—
IIb	TFAA	—	2.53	5.85	under Ph	3.77, 3.83	5.23	—	7.55(6H)	—	7.0	—
IIc	$DCCl_3$	major	2.10	5.18	1.62	3.64, 3.68	4.40	3.84	7.20—7.66(3H), 7.92(2H)	—	0.7	—
		minor	2.06	5.10	1.59	3.39, 3.66	4.95	4.10	7.20—7.66(5H)	—	0.7	—
IIc	DMSO-d_6	major	1.95	5.19	1.52	3.55, 3.58	4.27	—	7.25—7.50(3H), 7.75(2H)	—	0.7	—
		minor	1.92	5.10	1.49	3.32, 3.53	4.62	—	7.25—7.50(5H)	—	0.7	—
IIc	TFAA	—	2.48	5.80	2.08	3.77, 3.82	5.18	—	7.20—7.87(5H)	—	—	—
Vc	DMSO-d_6	—	2.33	5.80	1.87	3.47, 3.65	4.78	—	7.50(5H)	—	—	—
VIc	DMSO-d_6	—	2.35	5.78	1.88	3.47, 3.63	4.82	—	7.48(5H)	—	—	—
VIIc	$DCCl_3$	—	2.37	5.45	1.90	3.28, 3.87	5.20	—	7.47(5H)	—	—	—

TABLE II

Carbon-13 NMR Spectra of the Dihydropyrimidines (II): δ (ppm from TMS)

Compound	Solvent	isomer	C-2	C-4	C-5	C-6	R^3	R^5	OCH_3	CHOH	C=O	Ph
IIa	$DCCl_3$	major	84.7	159.4	97.6	152.6	—	20.8	52.5	71.8	171.3	128.9, 129.0, 131.8,
		minor	84.0	158.7	96.8	153.5	—	20.6	52.4, 52.8	72.9	170.3	131.9 132.1, Ci:139.4
IIb[a]	$DCCl_3$	major	84.7	168.2	98.2	143.2	26.5	—	53.1, 53.5	72.2	171.6	
		minor	85.1	167.5	97.0	143.2	26.0	—	52.7	72.2	170.9	128.7, 129.3, 129.6
IIc	$DCCl_3$	major	84.2	167.1	98.8	151.6	23.8	20.6	52.2, 52.4	72.1	171.1, 171.5	128.6, 128.9, 129.0, 131.7, 131.8, 132.1,
		minor	85.1	166.9	97.6	152.5	23.8	20.5	52.4, 52.6	73.0	170.4, 172.5	Ci:139.6
Vc	DMSO-d_6	—	80.5	166.3[b]	97.9	165.0[b]	21.0	19.2	54.1, 52.6	69.0	169.4	c

[a] This compound decomposes on standing, some signals are tentatively assigned.

[b] The assignement of these signals may be inverted.

[c] Complex group of signals which includes those of the picryl group.

TABLE III

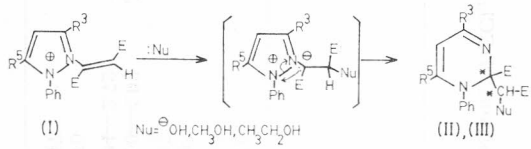
Proton NMR Spectra of the Dihydropyirimidines (III) and (IV); solvent: $DCCl_3$, δ (ppm from TMS)

Compound	isomer	R^3	H-5	R^5	CHOR	OCH_3	R	Ph
IIIb	major	2.55	5.86[a]	under Ph	4.47	3.72, 3.92	3.10	7.12—7.70(6H)
	minor	2.50	5.69[a]	under Ph	4.68	3.40, 3.87	3.55	7.12—7.70(6H)
IIIc	major	2.50	5.88	2.03	4.23	3.77, 3.87	3.03	7.07—8.07(5H)
	minor	2.43	5.73	1.93	4.60	3.47, 3.83	3.47	7.07—8.07(5H)
IIId	major	2.42	5.79	1.94	4.22	3.68, 3.80	1.13[b], 3.10—4.02	7.01—7.73(3H), 7.85(2H)
	minor	2.37	5.62	1.85	4.60	3.35, 3.76	0.96[b], 2.04—2.72	7.01—7.73(5H)
IVc	major	2.10	5.20	1.60	4.18	3.68, 3.72	2.70	7.00—8.10(5H)
	minor	2.05	5.08	1.60	4.37	3.28, 3.72	3.47	7.00—8.10(5H)

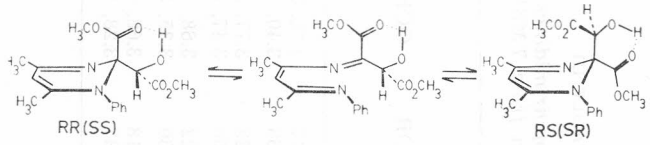
[a] $^3J_{R^5-H(5)} = 7.0$ Hz; [b] $^3J_{CH_3-CH_2} = 7.0$ Hz.

The salts (*III*) and the free base (*IVc*) are oily mixtures of the two diastereoisomers, whose characteristic proton NMR spectra are given in Table III. When (*IVc*) is dissolved in 32% tetrafluoroboric acid and the solution is evaporated to dryness, salt (*IIIc*) is recovered.

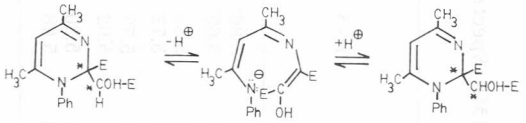
Transformation of *N*-vinylpyrazolium salts (*I*) into the corresponding 1,2-dihydropyrimidines (*II*) and (*III*) is due to expansion of the pyrazole ring. Probably this expansion starts from the intermediate carbanion, formed by nucleophilic addition to the exocyclic double bond, according to the following scheme.



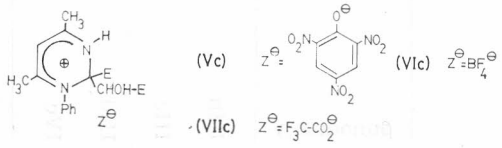
Two chiral centres are created in the reaction. As a consequence, the dihydropyrimidines (*II*) and (*III*) are a mixture of RR(SS) and RS(SR) diastereoisomers. Both diastereoisomers are in equilibrium through an open-chain valence tautomer. This explains why it is impossible to separate the mixture or even modify the proportions.



Using deuterium oxide, either in the basic or neutral conditions, the exocyclic CH proton of (*IIc*) or its salts does not exchange. This observation is in favour of the open-chain intermediate and against another possible epimerization mechanism (see below) which would begin with the loss of the aforementioned proton.



When the dihydropyrimidine (*IIc*) is protonated (trifluoroacetic, tetrafluoroboric or picric acid) only one diastereoisomeric salt, (*Vc*)—(*VIIc*), is obtained (see Tables I and II). The great effect observed on C-6 in the carbon-13 NMR spectra indicates that the salt has the delocalized structure corresponding to protonation on N-3.



Molecular models shown that the salt is likely to have the RS(SR) diastereoisomeric structure*, since only in this case can two stabilizing hydrogen bonds be formed (Figure 1).

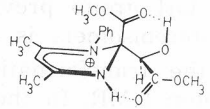


Figure 1. Molecular model of salts (*Vc*)—(*VIIc*) showing the two intramolecular hydrogen bonds.

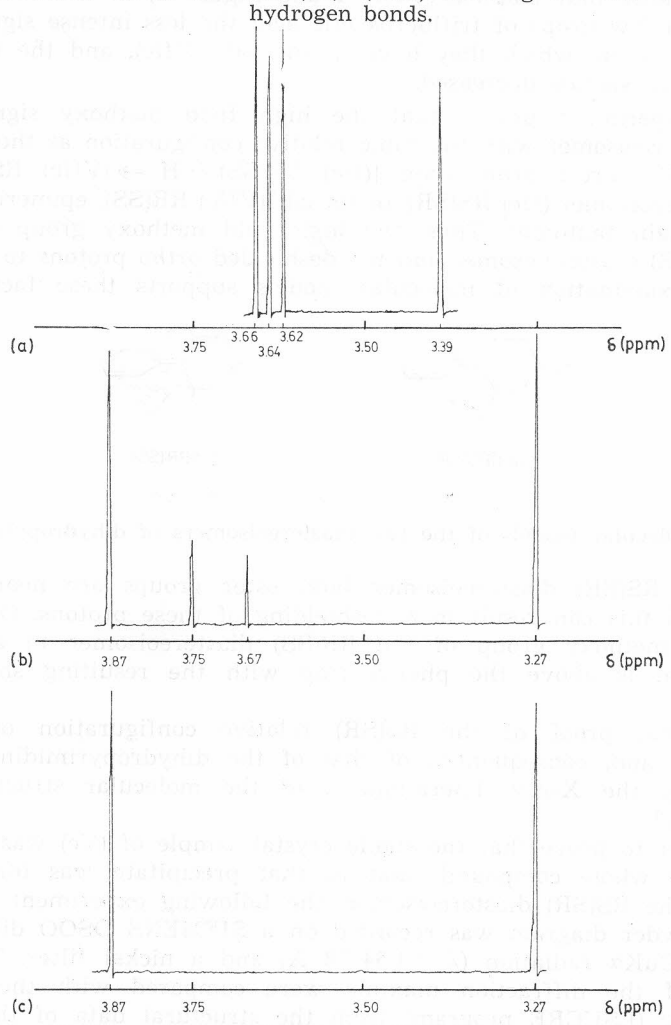


Figure 2. Proton NMR spectra of (*IIc*): a) in $DCCl_3$; b) in $DCCl_3$ + a small quantity of CF_3CO_2H; c) in $DCCl_3$ + a large quantity of CF_3CO_2H (or of *VIIc* in $DCCl_3$).

* The protonation of N-3 changes the absolute configuration as a consequence of the Cahn-Ingold-Prelog rules. However, (*IIc*) RR(SS) and (*VIIc*) RS(SR), on one the hand, and (*IIc*) RS(SR) and (*VIIc*) RR(SS), on the other hand, have an identical disposition of the substituents.

When the picrate (*Vc*) is treated with ethanolamine, the free base (*IIc*) is recovered. A proton NMR spectrum shows that both diastereoisomers are present in the proportions identical to those in the starting compound. In salts (*III*), the absence of the OH group prevents the formation of double chelate and a mixture of diastereoisomers is observed.

It is possible to follow the transformation of the dihydropyrimidine (*IIc*) into its salt (*VIIc*) by proton NMR. In the zone of methoxy signals the free base shows four singlets (Table I and Figure 2) in deuteriochloroform. By adding a few drops of trifluoroacetic acid the less intense signals shifted to a new position, which they have in the salt (*VIIc*), and the intensity of the two other signals decreased.

This experiment proves that the high field methoxy signal belongs to the diastereoisomer with the same relative configuration as the salt which is formed by direct protonation [(*IIc*) RR(SS) + $H^+ \rightarrow$ (*VIIc*) RS(SR)]. The other diastereoisomer (*IIc*) RS(SR), or its salt (*VIIc*) RR(SS), epimerizes through the open-chain tautomer. Thus, the high field methoxy group corresponds to the RR(SS) diastereoisomer and the deshielded *ortho* protons to the RS(SR) one. The examination of molecular models supports these facts.

(II c)RS(SR) (II c)RR(SS)

Major isomer Minor isomer

Figure 3. Molecular models of the two diastereoisomers of dihydropyrimidine (*IIc*).

In the RS(SR) diastereoisomer both ester groups are near the *ortho* protons and this can result in a deshielding of these protons. On the other hand, one methoxy group of the RR(SS) diastereoisomer in a particular conformation is above the phenyl ring with the resulting shift to high fields.

The final proof of the RS(SR) relative configuration of the salts (*Vc*)—(*VIIc*) and, consequently, of that of the dihydropyrimidines (*II*), was obtained by the X-ray determination of the molecular structure of the picrate (*Vc*).[3]

In order to prove that the signle crystal sample of (*Vc*) was representative of the whole compound, that is, that precipitate was formed exclusively by the RS(SR) diastereoisomer, the following experiment was carried out.[4] A powder diagram was recorded on a SIEMENS DSOO diffractometer using the CuKα radiation (λ = 1.54178 Å) and a nickel filter. The angular positions of the diffraction maxima were compared with those obtained theoretically (LSUCRE program) from the structural data of the salt (*Vc*). Since all the lines obtained experimentally concide with the theoretical ones, it is possible to conclude that the whole sample is formed exclusively by RS(SR) crystals.

The reaction described here, (*I*) $\rightarrow$ (*II*) or (*III*), is not the first reported example of a pyrazole ring expansion to a pyrimidine derivative. However, literature examples concern quite different reactions, for instance, that of

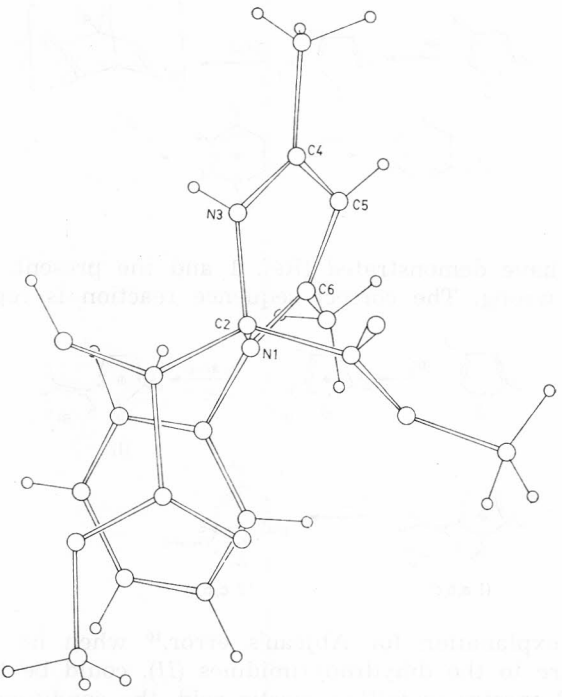
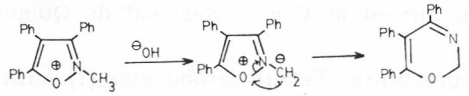
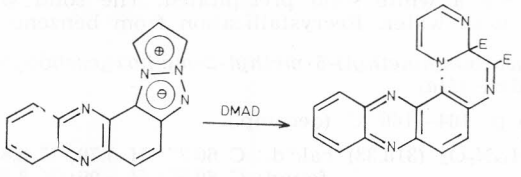


Figure 4. Molecular structure of picrate (*Vc*).

N-benzyl pyrazoles and indazoles with strong bases as amide or hydride at 150 °C;[5] the oxidation of *N*-amino pyrazoles and indazoles with lead tetraacetate,[6] and the insertion of chlorocarbenes into *N*-unsubstituted pyrazoles and indazoles.[7]

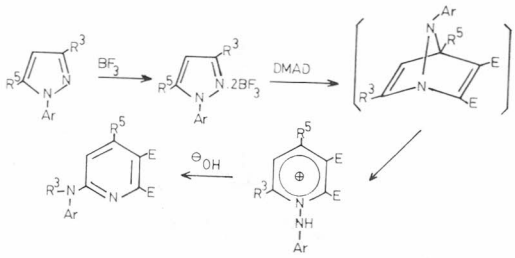


More related to our reaction is the behaviour of isoxazolium salts in diluted basic medium[8] or that of mesoionic pyrazolobenzotriazoles when they are allowed to react with dimethyl acetylenedicarboxylate.[9]

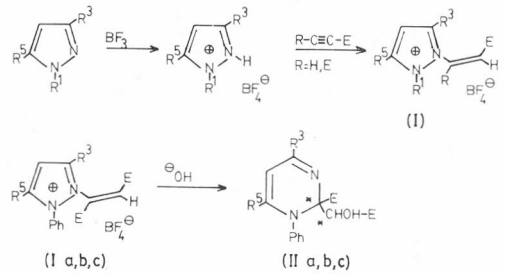


CONCLUSION

In 1974 Abjean[10] described the following sequence of reactions that was remarkable in several aspects: it could be the first and sole xample of dienic behaviour of an aromatic pyrazole and also a rather attractive way of obtaining α-aminopyridines from the easily accesible pyrazoles.



In fact we have demonstrated (Ref. 1 and the present work) that both conclusions are wrong. The correct sequence reaction is represented below.



A possible explanation for Abjean's error,[10] when he assigned aminopyridine structure to the dihydropyrimidines (*II*), could be that he recorded the proton NMR spectra in trifluoroacetic acid, the conditions in which only one diastereoisomer, (*VIIc*), is observed.

EXPERIMENTAL

M.p.s were determined on a Büchi 510 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 257 spectrometer and the mass spectra on a Varian MAT-711. Proton NMR spectra were recorded on Varian T-60A and HX-100 spectrometers, and the carbon-13 spectra on a Varian FT-80 spectrometer. Microanalyses were performed at Centro Nacional de Química Orgánica (C.S.I.S., Madrid).

Reaction of 2-Vinylpyrazolium Tetrafluoroborates (I) with Aqueous Potassium Carbonate

General procedure. — To a saturated solution of salt (*I*) in water, a 10% aqueous potassium carbonate solution was added dropwise. The mixture became yellow and at pH = 9 a white solid precipitated. The solid was filtered off and thoroughly washed with water. Recrystallization from benzene yield pure (*II*).

2-(Hydroxymethoxycarbonylmethyl)-6-methyl-2-methoxycarbonyl-1-phenyl--1,2-dihydropyrymidine (IIa)

Yield: 27%, m. p. 164—166 °C (decomp.).

Anal. $C_{16}H_{18}N_2O_5$ (318.33) calc'd.: C 60.37; H 5.70; N 8.80%.
found: C 60.57; H 5.99; N 8.64%.

2-(Hydroxymethoxycarbonylmethyl)-4-methyl-2-methoxycarbonyl--1-phenyl-1,2-dihydropyrimidine (IIb)

Yield: 64%, m. p. 118—120 °C.

Anal. $C_{16}H_{18}N_2O_5$ (318.33) calc'd.: C 60.37; H 5.70; N 8.80%.
found: C 60.59; H 5.98; N 8.77%.

2-(Hydroxymethoxycarbonylmethyl)-4,6-dimethyl-2-methoxycarbonyl-1-phenyl--1,2-dihydropyrimidine (IIc)

Yield: 47%, m. p. 160—161 °C (decomp.).

Anal. $C_{17}H_{20}N_2O_5$ (332.36) calc'd.: C 61.43; H 6.06; N 8.43%.
found: C 61.19; H 6.11; N 8.56%.

Reaction of 2-Vinylpyrazolium Tetrafluoroborates (I) with Alcohols

General procedure. — A solution of 1.5 mmol of (*I*) in 50 ml of the anhydrous alcohol was stirred at room temperature for 12 days. After removing the solvent *in vacuo*, compound (*III*) was obtained as an orange oil.

Preparation of picrate (Vc). — A concentrated solution of picric acid in boiling ethanol was added to a concentrated solution of (*IIc*) in boiling ethanol. After filtration of the hot mixture, picrate (*Vc*) crystallized on cooling. M. p. 173—175 °C (ethanol).

Anal. $C_{23}H_{23}N_5O_{12}$ (561.46) calc'd.: C 49.20; H 4.13; N 12.47%
found: C 48.96; H 4.34; N 12.42%

Preparation of 1,2-dihydropyrimidines (IIc) and (IVc) from its salts. — After Weimer and Kaye.[11]

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POVZETEK

Potom baz katalizirana premestitev 2-vinilpirazolijevih soli v 1,2-dihidropirimidine

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Pretvorba 2-vinilpirazolijevih soli v dihidropirimidine je zadnja stopnja postopka, pri katerem izhajamo iz nevtralnih pirazolov. V celoti je posledica vključitve dela >CE—CHON—E (E = COOMe) med dva dušikova atoma pri 1-substituiranem pirazolu. Nastale dihidropirimidine smo identificirali spektroskopsko (^{1}H in ^{13}C NMR) in relativno konfiguracijo dveh kiralnih centrov smo ugotovili s pomočjo rentgenske analize pikrata. Predlagani so tudi ustrezni mehanizmi za nastanek in epimerizacijo dihidropirimidinov.