Reaction of Hydrazidic Halides with Cyanoacetic Acid Derivatives

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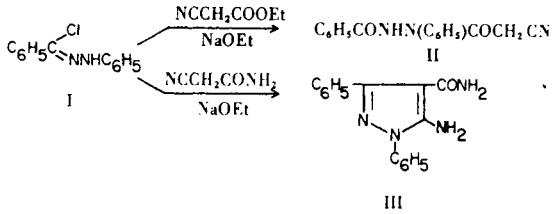
Received June 2, 1976

Ethyl cyanoacetate reacts with the hydrazidic halides IV-VI in presence of sodium ethoxide in ethanol at room temperature to give the pyrazole derivatives VIII-X respectively. Similar treatment of IV-VIII with cyanoacetanilide gives the substituted pyrazoles XI-XIV respectively. The results show that IV to VIII, unlike I, follow one and the same sequence in their reactions with cyanoacetic acid derivatives. The structure assignments of the products VIII-XIV were based on elemental analysis and spectral evidence.

J. Heterocyclic Chem., 13, 1137 (1976).

Some time ago Justoni (2) reported that benzphenylhydrazidic chloride (I) reacts with ethyl cyanoacetate and cyanoacetamide in different ways to give the products II and III respectively (Scheme 1). This result is surprising as

Scheme I



I

III

it is contrary to current findings that β-keto esters and β-keto amides follow the same reaction sequence in their reactions with hydrazidic halides to give in both cases the corresponding pyrazole derivatives (3,4). To examine the extent to which the modification of the ester by an amide group causes such a change in the course of the reactions of I with cyanoacetic acid derivatives, we have investigated reactions of four series of hydrazidic halides (IV-VII) with ethyl cyanoacetate and cyanoacetanilide. To our knowledge compound I has been the only hydrazidic halide which has been treated with cyanoacetic acid derivatives.

p-$RC_6H_4C(Br)$:$NNHC_6H_4NO_2$-p

IV

$EtOOCC(Cl)$:$NNHC_6H_4R$-p

V

R-C(Br):NNHC6H4NO2-p

VI

C6H5NHCOC(Cl):NNHC6H4R-p

VII

a, R = H
b, R = Cl
c, R = CH3O
d, R = NO2
e, R = CH3
f, R = CH3CH2
g, R = (CH3)2CH
h, R = o-Cl

Results and Discussion.

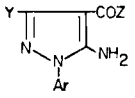
Treatment of IV with the sodium salt of ethyl cyanoacetate in ethanol in a manner similar to that described by Justoni (2) yielded 1,3-diaryl-4-carbethoxy-5-aminopyrazoles (VIII). Similar reactions of V and VI with the same salt afforded the pyrazoles IX and X respectively. The structures of the products VIII-X were indicated by the elemental analyses (Table I) and the spectral (nmr, uv and ir) data (Table II). Thus, the ir spectra displayed the characteristic NH_2 and the ester CO absorptions associated with the 4-carboethoxy-5-aminopyrazole structure. Compounds of series IX showed in addition an extra ester CO band near 1730 cm^{-1} assignable to the 3-COOEt group. The nmr spectra of VIII-X in deuteriochloroform showed the expected signals for the 4-$COOCH_2CH_3$ and the 5-NH_2 protons (Table II). The disappearance of the NH_2 proton signal upon exchange of VIII-X with deuterium oxide confirmed its assignment. The electronic absorption spectra of VIII-X were also in accordance with the assigned structures, each exhibits a characteristic pyrazole maximum in the 260-310 nm region (log $\epsilon > 4$). The spectral data of the compounds prepared are summarized in Table II.

Table I

1,3-Disubstituted 5-Aminopyrazole-4-carboxylic Acid Derivatives, VIII-XIV (a)

Compound No.	M.p., °C	Molecular Formula	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	N, % Calcd.	N, % Found
VIIIa	159	$C_{18}H_{16}N_4O_4$	61.36	61.55	4.58	4.73	15.90	15.87
VIIIb	211	$C_{18}H_{15}ClN_4O_4$	55.89	55.79	4.17	4.15	14.48	14.39
VIIId	235	$C_{18}H_{15}N_5O_6$	53.60	53.13	3.80	3.81	17.62	17.70
VIIIe	177	$C_{19}H_{18}N_4O_4$	62.29	62.28	4.95	4.94	15.29	15.35
VIIIh	209	$C_{18}H_{15}ClN_4O_4$	55.89	55.52	4.17	4.20	14.48	14.72
IXd	165	$C_{15}H_{16}N_4O_6$	51.72	52.00	4.63	4.71	16.08	16.00
Xe	184	$C_{13}H_{14}N_4O_4$	53.79	53.49	4.86	4.74	19.30	19.52
Xg	164	$C_{15}H_{18}N_4O_4$	56.59	56.62	5.70	5.59	17.60	17.70
XIa	230	$C_{22}H_{17}N_5O_3$	66.15	65.99	4.29	4.34	17.53	17.47
XIb	228	$C_{22}H_{16}ClN_5O_3$	60.90	60.80	3.71	3.64	16.14	16.24
XIIa	177	$C_{19}H_{18}N_4O_3$	65.13	65.00	5.18	5.20	15.99	16.01
XIIc	176	$C_{20}H_{20}N_4O_4$	63.14	63.01	5.30	5.22	14.73	14.63
XIIIa	206	$C_{17}H_{15}N_5O_3$	60.53	60.39	4.48	4.58	20.76	20.80
XIIIf	165	$C_{18}H_{17}N_5O_3$	61.53	61.49	4.88	5.00	19.93	19.89
XIVa	201	$C_{23}H_{19}N_5O_2$	69.50	69.48	4.82	5.00	17.62	17.51
XIVe	205	$C_{24}H_{21}N_5O_2$	70.05	69.89	5.14	5.19	17.02	16.91

(a) All compounds were crystallized from ethanol except VIIIe and XIVa, e which were crystallized from acetic acid.



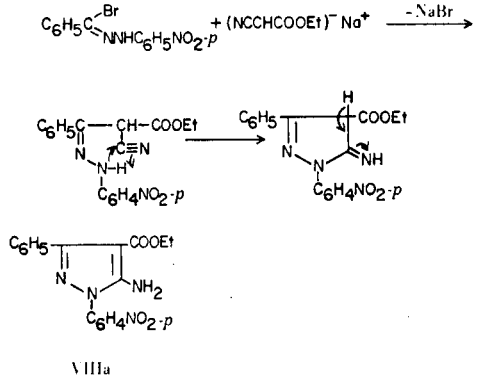
VIII,	Y = RC_6H_4;	Ar = p-$NO_2C_6H_4$;	Z = OEt
IX,	Y = EtOOC;	Ar = p-RC_6H_4;	Z = OEt
X,	Y = R;	Ar = p-$O_2NC_6H_4$;	Z = OEt
XI,	Y = RC_6H_4;	Ar = p-$O_2NC_6H_4$;	Z = NHC_6H_5
XII,	Y = EtOOC;	Ar = p-RC_6H_4;	Z = NHC_6H_5
XIII,	Y = R;	Ar = p-$O_2NC_6H_4$;	Z = NHC_6H_5
XIV,	Y = PhNHCO;	Ar = p-RC_6H_4;	Z = NHC_6H_5

The formation of VIII-X may be rationalized in terms of a carbanion attack at the α-carbon atom in IV-VI with displacement of the halogen atom, examplified in Scheme 2 with IVa and ethyl cyanoacetate, to give a hydrazone intermediate, which undergoes ring closure; addition on C≡N, followed by tautomerization, then afforded VIIIa.

Next the reactions of IV-VII with cyanoacetanilide were examined. In each case, the corresponding 5-amino-1,3-disubstituted pyrazole-4-carboxanilides (XI-XIV) were obtained in good yield. The formation of the latter products may be interpreted in terms of a sequence similar to that in Scheme 2. Both elemental analyses (Table I) and spectral data (Table II) were compatible with the assigned structures.

This work provides a convenient method for the preparation of 5-aminopyrazole-4-carboxylic acid derivatives.

Scheme 2



VIIIa

EXPERIMENTAL

All melting points are uncorrected. Nmr (deuteriochloroform) spectra were recorded on a Varian T-60A spectrometer using TMS as internal standard. Ir (potassium bromide) and uv (ethanol) spectra were reocrded on Unicam SP1000 and SP8000 spectrophotometers respectively. Elemental analyses were carried out by Alfred Bernhardt Mikroanalytisches Laboratorium, West Germany.

The hydrazidic halides IV and VI were prepared by bromination of the corresponding aldehyde p-nitrophenylhydrazone (2,3), whereas V and VII by coupling α-chloro derivatives of ethyl acetoacetate and acetoacetanilide respectively with the appropriate diazotized aniline (6,7) as previsouly described. The physical constants of the compounds prepared agreed with those in literature (2,5-7).

Table II

Spectral Data for the Pyrazole Derivatives VIII-XIV

Compound	Nmr Chemical Shift, δ (Deuteriochloroform) (a) ppm	λ max (Ethanol) (log ε)	ν (Potassium bromide) cm^{-1}
VIIIa	1.21 (3H, t, J = 7 Hz); 4.25 (2H, q, J = 7 Hz); 5.68 (2H, s); 7.0-8.6 (9H, m).	310 (4.047)	3480, 3360, 1675
VIIIb	1.20 (3H, t, J = 7 Hz); 4.20 (2H, q, J = 7 Hz); 6.07 (2H, s); 7.0-8.2 (8H, m).	305 (4.240)	3400, 3340, 1680
VIIIe	1.28 (3H, t, J = 7 Hz); 2.45 (3H, s); 4.31 (2H, q, J = 7 Hz); 5.72 (2H, s); 7.0-8.6 (8H, m).	265 (4.314)	3390, 3335, 1678
VIIIh	1.05 (3H, t, J = 7 Hz); 4.19 (2H, q, J = 7 Hz); 5.68 (2H, s); 7.3-8.8 (8H, m).	300 (4.191)	3400, 3335, 1682
IXd	1.30 (6H, two t, J = 6, 7 Hz); 4.32 (4H, two q, J = 6, 7 Hz); 5.2 (2H, s); 7.2-8.4 (4H, two d).	270 (4.263)	3400, 3310, 1730, 1680
Xe	1.40 (3H, t, J = 7 Hz); 2.43 (3H, s); 4.37 (2H, q, J = 7 Hz); 5.57 (2H, s); 7.7-8.4 (2H, two d).	295 (4.146)	3400, 3350, 1680
Xg	1.30 (9H, d + t, J = 6, 7 Hz); 3.43 (1H, h, J = 6 Hz); 4.33 (2H, q, J = 7 Hz); 5.53 (2H, s); 7.0-8.4 (4H, m).	300 (4.676)	3425, 3320, 1675
XIa	5.95 (2H, s); 7.0-8.4 (15H, m).	288 (4.452)	3500, 3420, 3350, 1660, 1545
XIb	5.90 (2H, s); 7.0-8.5 (14H, m).	288 (4.486)	3500, 3410, 3300, 1655, 1550
XIIa	1.43 (3H, t, J = 7 Hz); 4.43 (2H, q, J = 7 Hz); 5.93 (2H, s); 6.7-7.8 (11H, m).	307 (4.111)	3450, 3340, 1700, 1660, 1545
XIIe	1.43 (3H, t, J = 7 Hz); 3.65 (3H, s); 4.42 (2H, q, J = 7 Hz); 5.85 (2H, s); 6.7-7.8 (10H, m).	307 (4.188)	3440, 3310, 1700, 1660, 1545
XIIIe	2.63 (3H, s); 5.96 (2H, s); 7.0-8.5 (10H, m).	282 (4.415)	3450, 3320, 1650, 1550
XIIIf	1.50 (3H, t, J = 6.5 Hz); 3.0 (2H, q, J = 6.5 Hz); 5.93 (2H, s); 7.0-8.5 (10H, m).	310 (4.290)	3450, 3320, 1650, 1550
XIVa	6.00 (2H, s); 7.0-8.0 (17H, m).	295 (4.335)	3440, 3380, 1660, 1673, 1560
XIVe	2.60 (3H, s); 6.0 (2H, s); 7.0-8.0 (16H, m).	295 (4.405)	3450, 3320, 1670, 1660, 1560

(a) The signal at δ 5.2-6.0 ppm in the spectra of all compounds disappeared upon shaking their solutions in deuteriochloroform with deuterium oxide, and a new signal appeared at δ 4.50 ppm due to DOH resonance.

Pyrazole Derivatives (VIII-XIV). General Procedure.

The appropriate cyanoacetic acid derivative (0.01 mole) was added to an ethanolic sodium ethoxide solution (prepared from 0.01 g.-atom of sodium metal and 50 ml. of absolute ethanol). After stirring for 10 minutes, an equivalent of the appropriate hydrazidic halide was added, and stirring continued for 2 hours, then the mixture was left overnight at room temperature. During this period, the hydrazidic halide went into solution and the crude pyrazole derivative precipitated. The latter was collected, washed with water and recrystallized from ethanol or acetic acid (Table I). The compounds prepared and their physical constants are listed in Table I.

REFERENCES AND NOTES

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