SYNTHESIS OF SOME 1H- OR -2H,4H-BENZO[4,5]CYCLOHEPTA[1,2-c]PYRAZOL-4-ONE DERIVATIVES

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Abstract---- Synthesis of some 1H- or -2H,4H-benzo[4,5]cyclohepta[1,2-c]pyrazol-4-one derivatives from 4-ethoxycarbonyl-1-substituted-5 or 3-styrylpyrazoles is described.

Benzoheterocycloheptadienes (heterocyclic analogs of dibenzosuberone) are useful intermediates in the synthesis of biologically active compounds[1-6]. Although a variety of heterocycles such as furan[8], thiophene[2], pyridine[3-5], oxazole[6,7], thiazole[6] and imidazole[6] have been reported, there is no example of a pyrazole ring as the heterocycle moiety[9]. We describe here the synthesis of some 1H- or -2H,4H-benzo[4,5]cyclohepta[1,2-c]pyrazol-4-one derivatives from the isomeric 4-ethoxycarbonyl-1-substituted-5 and 3-styrylpyrazoles (1 and 3).

In a previous work from this laboratory, we described the synthesis of 4-ethoxycarbonyl-1-substituted-5 and 3-styrylpyrazoles (1 and 3)[10,11]. These products are suitably functionalized to give rise to the fused-pyrazole derivatives (7, 8 and 9).

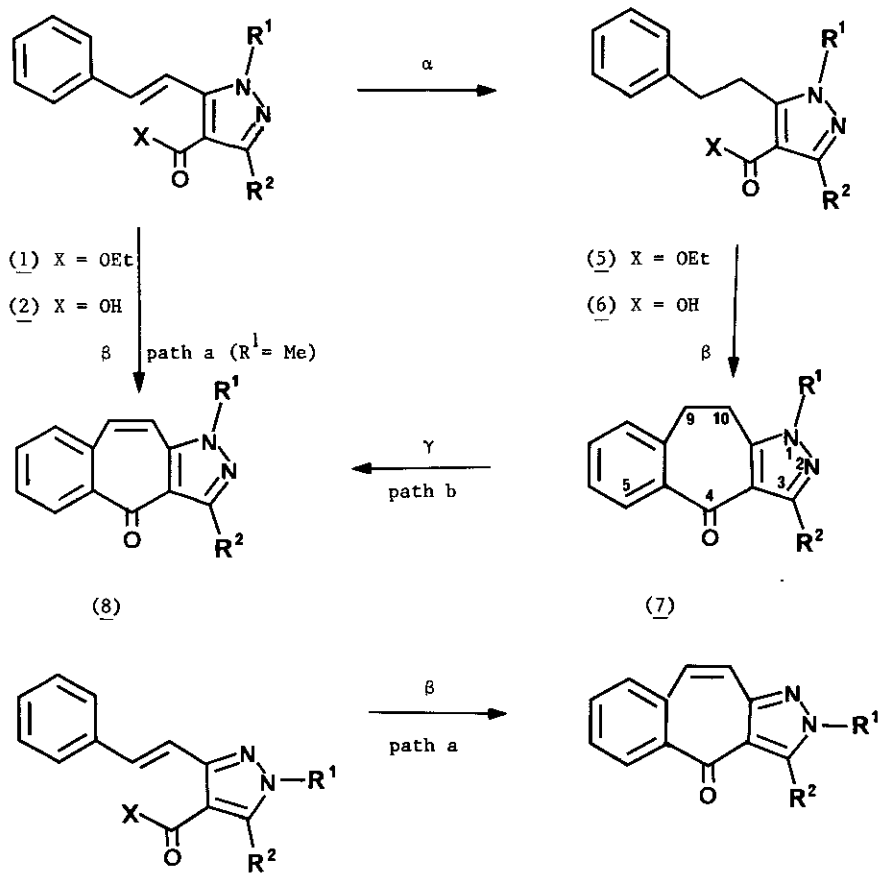
9,10-Dihydro-1H,4H-benzo[4,5]cyclohepta[1,2-c]pyrazol-4-ones (7) were obtained from the styrylpyrazoles (1) by a sequence involving classical methods (catalytic hydrogenation, basic hydrolysis and cyclization of the β-phenethylpyrazolecarboxylic acid (6) in polyphosphoric acid), as outlined in scheme.

Direct access to 1H,4H-benzo[4,5]cyclohepta[1,2-c]pyrazol-4-ones (8), from the styrylpyrazolecarboxylic acids (2), by cyclization in polyphosphoric acid can be accomplished only when R^1= Me (path a). A previous report of such a treatment of compounds (1 b-d) showed the formation of 4,5-dihydropyrazolo[1,5-a]quinolines (R^1= Ph) or 4,5-dihydro-10H-pyrazolo[1,5-b][2]benzazepine (R^1= CH_2-Ph)[11]. The synthesis of compounds (8 b-d)was achieved by bromination of the fused-pyrazoles (7 b-d) and subsequent dehydrobromination (path b).

Synthesis of 2*H*,4*H*-benzo[4,5]cyclohepta[1,2-c]pyrazol-4-ones (9), according to path a, was also realized from 1-substituted 4-ethoxycarbonyl-3-styrylpyrazole derivatives (4).

The structures of compounds (7, 8 and 9) were all consistent with the microanalyses and spectral data summarized in the table.

Scheme



α : H_2/Pd ; β : PPA ; γ : NBS then t-C_4H_9OK/t-C_4H_9OH

	a	b	c	d	e
R^1	Me	Ph	CH_2-Ph	Ph	CH_2-Ph
R^2	Me	Me	Me	H	H

Table Physical constants and spectral data of compounds (7,8 and 9)

Compound	Yield[a] %	MP °C	Molecular Formula[b]	UV (C_2H_5OH) λ nm (ε)	^{1}H-NMR (δ ppm, $CDCl_3$) H_5(m)	H_9 and H_{10}
7a	75	88	$C_{14}H_{14}N_2O$	277 (12300)	7.93-8.08	2.90-3.33(m)
7b	55	140	$C_{19}H_{16}N_2O$	282 (16500)	7.92-8.10	3.10(s)
7c	63	132	$C_{20}H_{18}N_2O$	278 (13500)	7.84-8.02	2.80-3.33(m)
7d	62	oil	$C_{18}H_{14}N_2O$	280 (15000)	7.91-8.09	3.11(s)
8a	65[c] 70[d]	133	$C_{14}H_{12}N_2O$	255 (28500) 306 (8400)[sh] 318 (10400)	8.55-8.75	6.95 and 7.15[e]
8b	90[d]	105	$C_{19}H_{14}N_2O$	259 (26000) 319 (12000)	8.57-8.82	6.96 and 7.02[e]
8c	50[d]	142	$C_{20}H_{16}N_2O$	255 (30800) 304 (8400)[sh] 318 (10600)	8.67-8.87	6.92 and 7.09[e]
8d	65[d]	189	$C_{18}H_{12}N_2O$	257 (34600) 306 (11400)[sh] 318 (12700)	8.73-8.99	7.11 and 7.17[e]
9c	55[c]	124	$C_{20}H_{16}N_2O$	254 (36400) 297 (10000)[sh] 311 (9000)	8.50-8.70	7.02 and 7.17[e]
9e	50[c]	175	$C_{19}H_{14}N_2O$	254 (39100) 298 (8400) 312 (8100)	8.73-8.91	7.16 and 7.28[e]

IR ($CHCl_3$) ν_{CO} : 1630 cm^{-1} for 7 ; 1610-1615 cm^{-1} for 8 and 9.

[a] Isolated yield of pure materials. [b] The microanalyses were in satisfactory agreement with the calculated values (C, ± 0.37 ; H, ± 0.20 ; N, ± 0.22); exception 9c (C, -0.61).

[c] Path a. [d] Path b. [e] 2d, 2H, AB system, J_{AB}=12 Hz.

EXPERIMENTAL SECTION

All melting points were determined on a Kofler block. Infrared and ultraviolet spectra were obtained with Beckman Model Acculab 2 and DB spectrometers. NMR spectra were recorded on a Brucker WP 80 spectrometer, with respect to TMS. Elemental analyses were performed by Microanalytical laboratory, Centre National de la Recherche Scientifique, 69390 Vernaison, France.

Compounds (1b,c and 3c)[10] and (1d)[11] were prepared as previously described. Compound (1a) was synthesized according to the procedure described for (1b), from 4-ethoxycarbonyl-5-hydroxymethyl-1,3-dimethylpyrazole[12] (yield 65%).

1-Benzyl-4-ethoxycarbonyl-3-styrylpyrazole (3e)

A solution of hydrazine hydrate (10 mmol) in acetic acid (50 ml) was added to crude ethyl 2-dimethylaminomethylene-3-oxo-5-phenyl-4-pentenoate[11] (10 mmol). After standing for a night at room temperature, water was added. Extractive work up with chloroform and purification of the residue by column chromatography on silica gel, using ethyl acetate as eluent, left 4-ethoxy-carbonyl-3(or 5)-styrylpyrazole (yield 74%), which was benzylated using potassium carbonate as base and dimethylsulfoxide as solvent, following the procedure described in ref.[12]; recrystallization of the crude material from hexane afforded the pure compound (3e) (yield 60% ; mp 105°C).

9,10-Dihydro-1H,4H-benzo[4,5]cyclohepta[1,2-c]pyrazol-4-ones (7)

A solution of (1) (20 mmol) in ethyl acetate (60 ml) was hydrogenated with 5% palladium on carbon (1 g) at room temperature using a low pressure (*ca. 1 atm.*) hydrogenation apparatus. After uptake of the calculated amount of hydrogen, the catalyst was filtered off and the solvent evaporated under reduced pressure. The crude product (5) was dissolved in a solution of potassium hydroxide (2 g) in ethanol (50 ml) and refluxed for 4 h. After evaporation of the solvent, water was added. The aqueous layer was extracted with ethyl ether and then acidified with concentrated hydrochloric acid and the acid (6) was collected by filtration. A mixture of the crude acid (6) (5 mmol) and polyphosphoric acid (H_3PO_4/P_2O_5 = 1/1, 35 g) was stirred at 130°C for 40 min (a,b,c) or 4 h (d). The resultant mixture was poured into crushed ice followed by filtration (7a,b,c) or extractive work up with chloroform (7d). Pure compounds were obtained by recrystallization from cyclohexane (7a,c), acetonitrile (7b) or column chromatography on silica gel using hexane/ethyl acetate (1:1) as eluent (7d).

1H- or -2H,4H-Benzo[4,5]cyclohepta[1,2-c]pyrazol-4-ones (8a) and (9) (path a)

A mixture of acid (5 mmol) and polyphosphoric acid (H_3PO_4/P_2O_5 = 1/1, 35 g) was stirred at 130°C for 10 min (4c,e) or 40 min (2a). The resultant mixture was poured into crushed ice followed by filtration (9e) or extractive work up with ethyl acetate (8a and 9c). Pure compounds were obtained by recrystallization from acetonitrile (9e) or column chromatography on silica gel,

using ethyl acetate (8a) or ethyl ether (9c) as eluent.

1H,4H-Benzo[4,5]cyclohepta[1,2-c]pyrazol-4-ones (8) (path b)

A mixture of (7) (5 mmol), N-bromosuccinimide (5 mmol), benzoyl peroxide (0.05 mmol) and carbon tetrachloride (80 ml) was refluxed for 4 h. The succinimide was filtered off and the solvent evaporated. To the residue was added anhydrous *tert*-butyl alcohol (50 ml) and potassium *tert*-butoxide (5 mmol) and the solution was refluxed for 4 h under nitrogen. The solvent was evaporated and water was added. After extractive work up with ethyl acetate, pure compounds (8) were obtained by column chromatography on silica gel using ethyl acetate (8a) or ethyl ether (8b,c,d) as eluent.

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