Regiospecific Synthesis of 1-Arylpyrazoles

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A new regiospecific synthesis of 1-aryl-substituted pyrazoles by reaction of aryl-hydrazines with β-amino-enones is reported.

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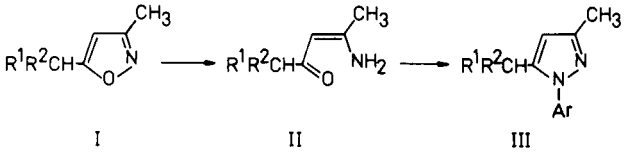
A recent report by Lemke and Sawhney [1] on the regiospecific synthesis of 1- and 2-substituted indeno[1,2-*c*]pyrazol-4(1*H*)-ones prompts us to report our preliminary results in a similar area.

The classical pyrazole synthesis, consisting of the addition of a hydrazine derivative to α,β-ethynyl ketones or β-chlorovinyl ketones often results in the formation of mixtures of isomers since there can be direct competition between the process leading to hydrazone function and that in which a preliminary Michael-type addition of the hydrazine to the electron-deficient unsaturated linkage occurs [2]. On the other hand, β-aminoenones allow us to prepare isoxazole derivatives regiospecifically [3], but the reaction fails when they were treated with *N*-substituted-ureas, leading to mixtures of both isomeric 2(1*H*)-pyrimidinones [4].

We now wish to report a very simple regiospecific synthesis of 1-aryl-substituted pyrazoles III by reaction of arylhydrazines with β-aminoenones II, which were obtained by hydrogenolytic fission of the labile N-O linkage of isoxazoles [5]. Some other publications [6] deal with the preparation of pyrazole derivatives *via* β-oxovinylamines.



I II III

I, II

a. $R^1 = R^2 = H$
b. $R^1 = Me$, $R^2 = H$
c. $R^1 = R^2 = Me$
d. $R^1 = n\text{-}Pr$, $R^2 = H$
e. $R^1 = n\text{-}Bu$, $R^2 = H$
f. $R^1 = R^2 = n\text{-}Bu$
g. $R^1 = Bz$, $R^2 = H$
h. $R^1 = R^2 = Bz$

III

a. $R^1 = R^2 = H$, Ar = Ph
b. $R^1 = Me$, $R^2 = H$ Ar = 2,4-DNPH
c. $R^1 = R^2 = Me$, Ar = 2,4-DNPH
d. $R^1 = n\text{-}Pr$, $R^2 = H$, Ar = Ph
e. $R^1 = n\text{-}Bu$, $R^2 = H$, Ar = Ph
f. $R^1 = R^2 = n\text{-}Bu$, Ar = Ph
g. $R^1 = Bz$, $R^2 = H$, Ar = Ph
h. $R^1 = R^2 = Bz$, Ar = Ph

Catalytic reductions of I (Pd-C or Ra-Ni W-2) afforded unequivocally β-aminoenones II in good yields (Table 1). Treatment of IIa,d-h (0.1 mole) with phenylhydrazine hydrochloride (0.1 mole) and potassium acetate (0.1 mole) in ethanol-water, and of IIb,c (0.01 mole) with 2,4-dinitrophenylhydrazine (0.01 mole) and 4 ml of sulfuric acid in aqueous methanol, at room temperature during 0.5 hour yielded 1-arylpyrazoles III. These products were extracted with methylene chloride and purified by distillation followed by column chromatography (silicagel and benzene-ethyl acetate, 15:1), or recrystallisation (from benzene-hexane, 5:1). Yields reported in Table I refer to isolated purified compounds.

Table I

Regiospecific Synthesis of 1-Aryl-substituted Pyrazoles

Isoxazole	β-Aminoenone (%)	Pyrazole (%)
Ia	IIa (85)	IIIa (70)
Ib	IIb (80)	IIIb (75)
Ic	IIc (83)	IIIc (80)
Id	IId (73)	IIId (66)
Ie	IIe (75)	IIIe (77)
If	IIf (75)	IIIf (80)
Ig	IIg (95)	IIIg (60)
Ih	IIh (77)	IIIh (66)

The formation of only one of the two possible *N*-substituted pyrazoles was confirmed by glc and pmr. The identity of the isomer produced was first determined by comparison of IIIb and IIIc with authentic specimens. In order to verify the generality of the reaction pathway and hence to establish the structure of the remaining products, 3-methyl-5-phenylisoxazole was converted into the 3-methyl-1,5-diphenylpyrazole by the same method. The ir and pmr spectra found for the latter compound are identical with those published [7].

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Table II

Physical Constants and Analytical Data of Compounds II and III

Compound No.	Molecular Formula	Mp or (Bp/torr) Lit Mp or Bp	Derivative (Mp)	Elemental Analyses Found (Calcd.) C	H	N
IIa	C_5H_9NO	43-44° lit. 43° [8]	—	—	—	—
IIb	$C_6H_{11}NO$	60-62° lit. 62-63° [9]	—	—	—	—
IIc	$C_7H_{13}NO$	85-86°	—	65.93 (66.14)	10.41 (10.23)	10.85 (11.02)
IId	$C_8H_{15}NO$	(64-66°/0.4)	—	69.30 (69.06)	10.52 (10.79)	10.23 (10.07)
IIe	$C_9H_{17}NO$	(86-89°/0.7)	—	69.35 (69.67)	11.03 (10.96)	9.22 (9.03)
IIf	$C_{13}H_{25}NO$	31-32°	—	73.71 (73.93)	11.96 (11.84)	6.81 (6.63)
IIg	$C_{12}H_{15}NO$	100-101° lit 103° [10]	—	—	—	—
IIh	$C_{19}H_{21}NO$	75-76°	—	81.83 (81.72)	7.40 (7.52)	5.22 (5.01)
IIIa	$C_{11}H_{12}N_2$	(144-145°/12) lit 273°/754 [11]	Hydrochloric acid (158-159°)	—	—	—
IIIb	$C_{12}H_{12}N_4O_4$	132-133° lit 133-134° [12]	—	—	—	—
IIIc	$C_{13}H_{14}N_4O_4$	76-77° lit 76-77° [12]	—	—	—	—
IIId	$C_{14}H_{16}N_2$	(95-98°/0.2)	Picrate (89-90°)	78.32 (78.50)	8.48 (8.41)	13.20 (13.08)
IIIe	$C_{15}H_{20}N_2$	(94-95°/0.1)	Picrate (55-56°)	78.72 (78.94)	8.60 (8.77)	12.46 (12.28)
IIIf	$C_{19}H_{28}N_2$	(108-110°/0.4)	—	80.50 (80.28)	9.98 (9.85)	9.62 (9.85)
IIIg	$C_{18}H_{16}N_2$	oil	Picrate (98-99°)	82.36 (82.44)	6.61 (6.87)	10.91 (10.86)
IIIh	$C_{25}H_{24}N_2$	40-41°	Picrate (154-155°)	85.38 (85.22)	6.65 (6.81)	8.19 (7.95)

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