Reaction of β-Acylarylhydrazines with Dimethylformamide in the Presence of Calcium Hydride. A Novel Route to 3-Pyrazolin-5-ones.

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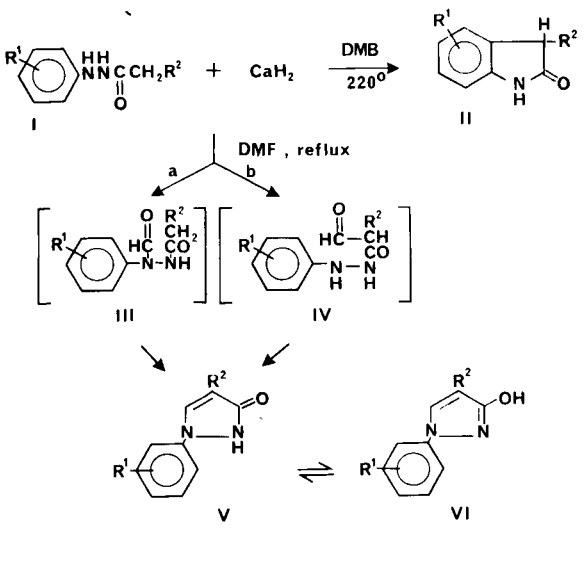
Reaction of β-acylarylhydrazines with calcium hydride in refluxing dimethylformamide (DMF) was found to lead to the formation of 2-aryl-3-pyrazolin-5-ones (V). Application of this novel synthetic method resulted in fair to good yields of a series of 2,4-diaryl-3-pyrazolin-5-ones. The infrared spectra (potassium bromide) of the products (V) showed that these compounds exist as the lactim tautomer (VI). An oxindole (IIc) was obtained when dimethylbenzamide was substituted for DMF under similar reaction conditions.

In the course of other work we became interested in the Brunner reaction (1) as a pathway to the synthesis of substituted oxindoles. A well-documented example of the reaction is the preparation of 3-methyloxindole by heating a mixture of β-propionylphenylhydrazine and calcium hydride (CaH_2) at 210-220° (2). With the objective of working out milder reaction conditions, we modified the procedure by introducing dimethylformamide (DMF) as the solvent. Surprisingly, the isolated product proved to be not the expected 3-methyloxindole, but a blue-fluorescent compound melting at 216.5-218°. Spectral (mass, ultraviolet, infrared, and nuclear magnetic resonance) and elemental analysis indicated the product to be 2-phenyl-4-methyl-3-pyrazolin-5-one (Vb) (3). To remove any doubt concerning the course of this novel transformation, the process was repeated with β-acetylphenylhydrazine as the starting material; this should analogously result in the formation of 2-phenyl-3-pyrazolin-5-one (Va), for which more literature data is available (3a,4,5). The outcome confirmed our expectation: the blue-fluorescent product, m.p. 156-157°, was identical with Va that was prepared *via* an unambiguous route (*vide infra*) and showed spectral characteristics (mass, infrared, and nuclear magnetic resonance) that were in agreement with the assigned structure (*vide infra*).

SCHEME I



a: R^1 R^2 H
b: R^1 H; R^2 CH_3
c: R^1 H; R^2 C_6H_5
d: R^1 H; R^2 o-$CH_3C_6H_4$
e: R^1 H; R^2 m-$CH_3C_6H_4$
f: R^1 H; R^2 p-$CH_3C_6H_4$
g: R^1 H; R^2 p-$CH_3OC_6H_4$
h: R^1 H; R^2 p-ClC_6H_4
i: R^1 p-CH_3; R^2 C_6H_5
j: R^1 p-CH_3; R^2 o-$CH_3C_6H_4$
k: R^1 p-CH_3; R^2 p-$CH_3C_6H_4$
l: R^1 p-Cl; R^2 C_6H_5
m: R^1 p-Cl; R^2 m-$CH_3C_6H_4$
n: R^1 p-Cl; R^2 p-ClC_6H_4

One plausible explanation for the formation of V in the above reaction involves formylation by DMF of the phenylhydrazide at the α-nitrogen (6), followed by ring-closure of the resulting α-formyl-β-acylphenylhydrazine (IIIa or IIIb) (Scheme I, path a) (7). Alternatively, one may assume initial formylation by DMF to take place at the carbon atom adjacent to the carbonyl group to form IV (IVa or IVb) (8), with subsequent nucleophilic attack by the α-nitrogen on the formyl carbonyl group to form the product V (Va or Vb) (9) (Scheme I, path b). Both postulated pathways show that this novel method for the synthesis of V (10) should succeed more readily when applied to β-acylarylhydrazines in which the active hydrogen on the α-carbon is

TABLE I

β-(Arylacyl)arylhydrazines (I).

Number	Method	M.p., °C	Molecular Formula	% Yield	Analysis (a) C	H	N
Ic	A	174-175 (b)	$C_{14}H_{14}N_2O$	75	----	---	----
Id	A	184.5-185.5	$C_{15}H_{16}N_2O$	70	74.97	6.71	11.66
					75.16	6.58	11.82
Ie	A	121-122	$C_{15}H_{16}N_2O$	58	74.97	6.71	11.66
					75.14	6.60	11.83
If	A	177-178	$C_{15}H_{16}N_2O$	66	74.97	6.71	11.66
					75.10	6.62	11.62
Ig	A	186-187	$C_{15}H_{16}N_2O_2$	59	70.29	6.29	10.93
					70.53	6.39	10.98
Ih	A	168-169 (c)	$C_{14}H_{13}ClN_2O$	80	----	---	----
Ii	B	176-177	$C_{15}H_{16}N_2O$	53	74.97	6.71	11.66
					75.17	6.79	11.78
Ij	B	167-168	$C_{16}H_{18}N_2O$	50	75.56	7.13	11.01
					75.54	6.89	11.03
Ik	B	175-176	$C_{16}H_{18}N_2O$	59	75.56	7.13	11.01
					75.60	7.13	10.98
Il	B	188-189	$C_{14}H_{13}ClN_2O$	65	64.50	5.02	10.75
					64.78	5.14	10.79
Im	B	134-135	$C_{15}H_{15}ClN_2O$	46	65.57	5.50	10.20
					65.70	5.47	10.38
In	B	185-186	$C_{14}H_{12}Cl_2N_2O$	64	56.96	4.10	9.49
					57.35	4.45	9.66

(a) Top numbers are analyses calculated, bottom are analyses found. (b) Literature, m.p. 175° (20). (c) Literature, m.p. 167° (20).

more easily removed. Consequently, to explore the preparative value of our procedure, a number of β-(arylacetyl)arylhydrazines (Table I) (11) was reacted with refluxing DMF in the presence of calcium hydride. The results (Table II) show that this method can be used to prepare members of the heretofore unknown class of 2,4-diaryl-3-pyrazolin-5-ones (V, R^2 = aryl) in fair to good yields.

The synthesized compounds are colorless, high-melting solids which show a blue fluorescence and can be easily purified by sublimation under reduced pressure. The infrared spectra (potassium bromide) of these materials do not show absorption in the C=O stretching region (12); on the other hand, all spectra exhibit a strong absorption band at around 6.25 μ due to C=N stretching and also a broad absorption band in the 3.6-3.9 μ region which may be attributed to strongly hydrogen-bonded O-H stretching. It can therefore be concluded that under such conditions the compounds actually exist as 1,4-diaryl-3-hydroxypyrazoles (VI), the lactim tautomer of V (13). However, in order to conform with established practice (14,15), the 3-pyrazolin-5-one nomenclature has been retained in this paper.

While our results indicate that this reaction affords a general route to compounds of type V or VI, it is of interest to note that no analogous transformation occurred when *N,N*-dimethylbenzamide (DMB) was substituted for DMF. Thus heating of β-(phenylacetyl)phenylhydrazine (Ic) and calcium hydride in liquified DMB in the expectation of obtaining 2,3,4-triphenyl-3-pyrazolin-5-one, yielded instead the Brunner reaction product 3-phenyloxindole (IIc) (16).

EXPERIMENTAL (17)

Arylacetyl Chlorides.

o-, *m*-, *p*- Tolyl-, *p*-methoxyphenyl-, and *p*-chlorophenylacetyl chloride were prepared by a modification of the method described for the preparation of mesitoyl chloride (18). A magnetically stirred mixture of 0.5 mole of the appropriate carboxylic acid and 57 ml. (0.75 mole) of thionyl chloride was heated gently in an oil bath at 50-60° until evolution of sulfur dioxide and hydrogen chloride gases ceased to be noticeable. The mixture was refluxed for 2 additional hours, and subjected to evaporation under reduced pressure (rotary evaporator) to remove the excess thionyl chloride. Distillation under reduced pressure of the residue yielded the desired acyl chloride.

TABLE II

2-Aryl-3-pyrazolin-5-one (V) (a)

Number	M.p., °C	Molecular Formula	% Yield	Analysis (b) C	H	N
Va (c)	156-157 (d)	$C_9H_8N_2O$	10	67.49 67.47	5.03 5.09	17.49 17.52
Vb (e)	216.5-218 (f)	$C_{10}H_{10}N_2O$	18	68.95 68.95	5.79 5.94	16.08 15.97
Vc (g)	202-203	$C_{15}H_{12}N_2O$	76	76.25 76.37	5.12 5.31	11.86 11.84
Vd	159-160	$C_{16}H_{14}N_2O$	58	76.78 76.84	5.64 5.70	11.19 11.15
Ve	221-222	$C_{16}H_{14}N_2O$	47	76.78 76.86	5.64 5.69	11.19 11.28
Vf	205-206	$C_{16}H_{14}N_2O$	54	76.78 76.82	5.64 5.48	11.19 11.12
Vg (h)	196-197	$C_{16}H_{14}N_2O_2$	58	72.17 72.41	5.30 5.24	10.52 10.50
Vh (h)	249-250	$C_{15}H_{11}ClN_2O$	76	66.55 66.83	4.10 4.12	10.35 10.55
Vi	258-259	$C_{16}H_{14}N_2O$	54	76.78 76.82	5.64 5.61	11.19 11.18
Vj	191-192	$C_{17}H_{16}N_2O$	38	77.25 77.45	6.10 5.95	10.60 10.53
Vk	257-258	$C_{17}H_{16}N_2O$	54	77.25 77.40	6.10 6.09	10.60 10.61
Vl	251-252	$C_{15}H_{11}ClN_2O$	54	66.55 66.81	4.10 4.21	10.35 10.52
Vm	217-219	$C_{16}H_{13}ClN_2O$	31	67.49 67.53	4.60 4.60	9.84 9.80
Vn	298-299	$C_{15}H_{10}Cl_2N_2O$	40	59.04 59.13	3.30 3.41	9.18 9.12

(a) All exhibited ir (potassium bromide) absorption maxima at about 6.25 μ (lactim C=N). (b) Top numbers are analyses calculated, bottom are analyses found. (c) Mass spectrum (70 eV) m/e (rel. intensity) 161 (39), 160 (100), 144 (4), 131 (33), 116 (5), 104 (43), 91 (16), 78 (30), 77 (93), 63 (9), 54 (13), 51 (38), 39 (9), 26 (8). (d) Lit. (4a) 155°. (e) Uv (methanol) max 277 nm (ϵ 1.89 x 10^{-4}); mass spectrum (70 eV) m/e (rel. intensity) 175 (39), 174 (100), 173 (12), 149 (5), 145 (13), 130 (9), 118 (10), 104 (14), 91 (5), 81 (5), 78 (13), 77 (52), 72 (5), 69 (11), 57 (9), 55 (11), 51 (9), 45 (6), 43 (10), 41 (11), 39 (11). (f) Lit. (3a) 213-215°. (g) Ir ($CHCl_3$) 5.82 (weak, lactam C=O) and 6.23 (strong, lactim C=N). (h) The ir (potassium bromide) spectra of these compounds showed a very weak shoulder-like absorption band at 5.9 μ.

β-(Arylacetyl)arylhydrazines (I).

Method A.

A solution of 0.1 mole of the acyl chloride in 200 ml. of anhydrous ether was added dropwise, with mechanical stirring and cooling in an ice water bath, to a solution of 0.2 mole of the arylhydrazine in 200 ml. of anhydrous ether. After completion of the addition, the mixture was stirred at room temperature for another 2 hours and allowed to settle overnight. The precipitated solid was collected by filtration and triturated with 300 ml. of water. The insoluble material was filtered, washed with water, air-dried, and recrystallized from 70-95% ethanol to give Ic-h. Additional quantities of products were obtained by evaporation of the ethereal filtrate of the reaction mixture and recrystallization of the solid residue. The results are compiled in Table I.

Method B.

A hydrochloride salt of the arylhydrazine (0.10 mole) was added to a solution of 0.22 mole of triethylamine in 200 ml. of anhydrous ether. The resulting mixture was treated dropwise, with mechanical stirring and ice-water bath cooling, with a solution of 0.1 mole of the acyl chloride, and was subsequently allowed to remain at room temperature overnight, with stirring, before undergoing a work-up similar to that described under Method A. The results are compiled in Table I.

2-Aryl-3-pyrazolin-5-one (Va-n).

A mixture of 0.05 mole of the β-acylarylhydrazine and 40 ml. of dry DMF was placed in a 250 ml. round-bottom flask equipped with a magnetic stirrer and a water-cooled condenser connected to a Hg-filled bubbler tube. To this magnetically stirred mixture

TABLE III

Proton Nmr Spectra of 2-Aryl-3-pyrazolin-5-ones (V).

Compound Number	Chemical shift and multiplicity (a) 3-H	Aromatic-H	Other
Va (b)	7.61 (d)	6.86-7.47 (m)	5.85 (d) (4-H)
Vb (b)	7.91 (s)	7.18-7.85 (m)	2.21 (s) (CH_3)
Vc (b)	8.20 (s)	7.27-7.95 (m)	
Vd (c)	8.45 (s)	7.07-8.00 (m)	2.39 (s) (CH_3)
Ve (b)	8.15 (s)	7.10-7.85 (m)	2.39 (s) (CH_3)
Vf (b)	8.21 (s)	7.18-7.90 (m)	2.38 (s) (CH_3)
Vg (c)	8.72 (s)	6.89-8.07 (m)	3.82 (s) OCH_3)
Vh (c)	8.90 (s)	7.10-8.11 (m)	
Vi (b)	8.21 (s)	7.16-7.91 (m)	2.51 (s) (CH_3)
Vj (b)	8.30 (s)	7.32-7.70 (m)	2.40 (s) (CH_3); 2.53 (s) (CH_3)
Vk (b)	8.12 (s)	7.15-7.78 (m)	2.38 (s) (CH_3); 2.48 (s) (CH_3)
Vl (c)	8.85 (s)	6.93-8.13 (m)	
Vm (c)	8.87 (s)	6.98-8.04 (m)	2.38 (s) (CH_3)
Vn (c)	8.95 (s)	7.40-8.05 (m)	

(a) Chemical shifts given in δ, ppm, units. Multiplicity reported as: s = singlet, d = doublet, m = multiplet. Integrated intensities were consistent with the proposed structure. (b) Determined in approximately 10% solution in TFA with TMS as internal reference. (c) Determined in approximately 10% solution in DMSO-d_6 with TMS as internal reference.

was added 3.47 g. (0.0825 mole) of finely powdered calcium hydride. The system was purged with nitrogen and the flask was immersed in an oil bath which was heated cautiously. In the range of 130-150°, a vigorous reaction accompanied with much gas evolution was observed. After the reaction abated, the bath temperature was raised to around 180° and the mixture was kept at reflux overnight. After cooling the flask in an ice-water bath, a mixture of 12 ml. of methanol and 5 ml. of water was added to the dark reaction mixture in order to decompose the excess of calcium hydride. The resulting greenish paste was adjusted to *p*H 2-3 by the cautious addition of concentrated hydrochloric acid and poured into 400 ml. of ice-cold water; a light-brown precipitate separated out. After readjustment of the acidity of the mixture to *p*H 6 by the addition of a 20% aqueous solution of sodium hydroxide, the precipitate was collected by filtration, washed with water and dried overnight in a vacuum desiccator over phosphorus pentoxide. All compounds of this series were recrystallized from benzene, with the exception of Va, Vb and Vn which were recrystallized from benzene/hexane, absolute ethanol and acetone, respectively. The results are recorded in Table II; nmr spectral data are collected in Table III.

3-Phenyloxindole (IIc).

The procedure described for the synthesis of Vc was modified by the substitution of 0.5 mole of liquified DMB for the 40 ml. of dry DMF. The crude product, a brown liquid, was extracted into chloroform. Evaporation of the dried (magnesium sulfate) chloroform solution under reduced pressure (rotary evaporator) gave a liquid residue which was dissolved in 200 ml. of ether. When this ethereal solution was extracted several times with water to remove the excess of DMB, a solid separated out. The precipitate was collected by filtration and recrystallized from 95% ethanol to afford 4.0 g. (38% yield) of IIc, m.p. 185-187° (lit. (18a) 183°, (18b) 185-187°); ir (potassium bromide) 5.86 (oxindole C=O) and 6.18 μ (ring); nmr ($CDCl_3$) δ 4.64 (s, 1, 3-H), 6.82-7.66 (m, 9, aromatic CH), and 9.25 ppm (broad s, 1, lactam N-H).

Unambiguous Synthesis of 2-Phenyl-3-pyrazolin-5-one (Va) (19).

To a warm solution of 3.24 g. (0.02 mole) of 1-phenyl-3-pyrazolidinone in 75 ml. of 95% ethanol was added dropwise a solution of 11.9 g. (0.044 mole) of ferric chloride·hexahydrate in 50 ml. of water until the brown-red coloration, which was observed upon the addition of the oxidant, ceased to disappear. The resulting mixture was poured into 50 ml. of water and immediately extracted three times with 50 ml. portions of chloroform. The dried (magnesium sulfate) chloroform extract was subjected to evaporation under reduced pressure in a rotary evaporator and the solid residue was recrystallized from benzene/hexane to afford 2.5 g. (78% yield) of Va, m.p. 154.5-155.5° (lit. (4a) 155°). The ir spectrum of this material proved to be identical to that of compound Va which was previously synthesized *via* our novel method.

REFERENCES

(1) For leading references see: R. J. Sundberg, "The Chemistry of Indoles", Academic Press, New York, 1970, pp. 362-363.

(2) A. S. Endler and E. I. Becker, *Org. Syn.*, Coll. Vol. IV, 657 (1963).

(3a) F. Effenberger and W. Hartmann, *Chem. Ber.*, **102**, 3260 (1969); (b) F. Fichter and R. Vortisch, *J. Prakt. Chem.*, **74**, 303 (1906); (c) F. Stolz, *Ber.*, **38**, 3273 (1905).

(4a) Six references are cited by R. H. Wiley and P. Wiley in "Pyrazoles, Pyrazolidones, and Derivatives," Interscience Publishers, New York, 1964, p. 247; (b) C. Harries and G. Loth,

Ber., 29, 519 (1896); (c) F. Stolz, *ibid.*, 27, 407 (1894).

(5) The structure and spectra of this compound has been discussed: (a) E. Moczar and L. Mester, *Bull. Soc. Chim. France*, 1707 (1962); (b) S. Kikuchi and H. Yoshida, *Bull. Chem. Soc. Japan*, 35, 747 (1962).

(6) *Cf.* (a) The formylation of anilines by DMF in the presence of sodium hydride or sodium amide: G. R. Pettit, M. V. Kalnins, T. M. H. Liu, E. G. Thomas, and K. Parent, *J. Org. Chem.*, 26, 2563 (1961); (b) The reaction of β-acyl arylhydrazines with carboxylic acid amides to form 1,2,4-triazoles (Pellizari reaction): E. Enders in "Methoden der organischen Chemie", Vol. X/2, R. Stroh, Ed., G. Thieme Verlag, Stuttgart, 1967, pp. 362, 541.

(7) No comparable precedent for this ring-closure could be found in the literature.

(8) No reports of α-formylation by DMF of carboxylic acid amides seem to have been published.

(9) *Cf.* the synthesis of 2-phenyl-3-methyl-3-pyrazolin-5-one from phenylhydrazine and diketene: A. B. Boese, Jr., *Ind. Eng. Chem.*, 32, 18 (1940); H. Henecka in "Chemie der Beta-Dicarbonylverbindungen", Springer-Verlag, Berlin, 1950, p. 352.

(10a) The synthesis of 3-pyrazolin-5-ones has been reviewed by Wiley and Wiley (ref. 4a, pp. 46-48); a recent method is reported by Effenberger and Hartmann (ref. 3a). (b) Ring-closure reactions of phenylhydrazine derivatives have been reviewed by Enders (ref. 6b, pp. 539-545). (c) In the literature only one reaction could be found which may be comparable to our synthesis: the formation of 3-methyl-2-phenyl-3-pyrazolin-5-one when β-acetylphenylhydrazine was heated at 300-320° with magnesium oxide and potassium acetate (K. Brunner and H. Moser, *Monatsh. Chem.*, 53 & 54, 682 (1929)). By assuming β-acetylphenylhydrazine to act as acetylating agent, similar reaction pathways and intermediates as advanced in this paper may be used to account for this reaction.

(11) These materials were prepared from the appropriate acyl halides and arylhydrazines. Details are given in the experimental section.

(12) A very weak shoulder-like absorption band at 5.9 μ is observable in the spectra of Vg and Vh.

(13) This is in agreement with the findings in refs. 5a-b for the actual structure of "2-phenyl-3-pyrazolin-5-one".

(14) The ir spectrum of Vc in chloroform did show a very weak C=O band at 5.85 μ. This is somewhat surprising, because Moczar and Mester (ref. 5a) reported that no such band was found in the ir spectrum of Va in chloroform. On the other hand, a similar difference in the ir spectra of potassium bromide pellet and of chloroform solution was noticed in the case of 1-phenyl-3-pyrazolin-5-ones; see W. Pelz, W. Püschel, H. Schellenberger, and K. Löffler, *Angew. Chem.*, 72, 967 (1960).

(15) *Cf.* ref. 4a, p. 4.

(16) K. Brunner, *Monatsh. Chem.*, 18, 547 (1897); (b) J. Meisenheimer and H. Meis, *Ber.*, 57, 297 (1924).

(17) Microanalysis was performed by Dr. Kurt Eder, Geneva, Switzerland. Nmr spectra were obtained using a Varian A-60 A spectrometer with tetramethylsilane as the internal reference; uv spectra were recorded on a Beckman DK-2A; ir spectra were taken on a Beckman IR-8; and mass spectra were measured using a RMU-7 double focusing mass spectrometer by Hitachi/Perkin Elmer. Melting points were taken on a Mel-Temp capillary melting point apparatus and are uncorrected.

(18) E. C. Horning, *Org. Syn.*, Coll. Vol. III, 556 (1955).

(19) This procedure was adapted from the preparation of 3-methyl-2-phenyl-3-pyrazolin-5-one as described by L. Lederer, *J. Prakt. Chem.* [2], 45, 83 (1892).

(20) L. Cononica and A. M. Maderna, *Gazz. Chim. Ital.*, 80, 412 (1950).