Flash Vacuum Pyrolysis of 1-Azolyl-1-phenylhydrazono-2-propanones

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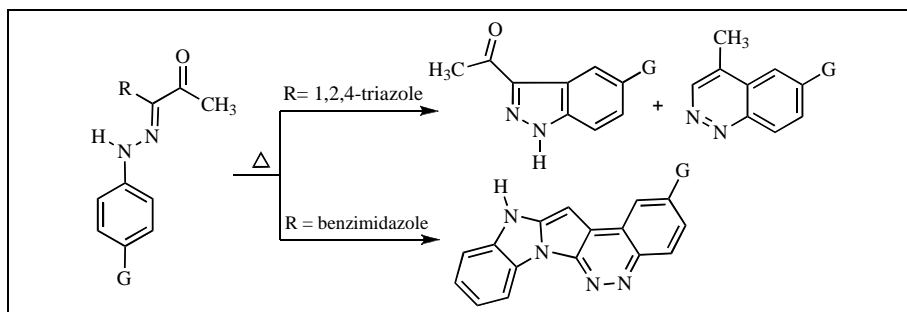
Flash vacuum pyrolysis (FVP) of 1-(2-arylhydrazono)-1-(1*H*-1,2,4-triazol-1-yl)acetone **8a-c** at 650°C and 2.67 Pa yielded 5-substituted 1-(1*H*-indazol-3-yl)ethanone **14a-c** and 4,6-disubstituted cinnoline **18a-c**. Similarly FVP of 1-(1*H*-benzo[*d*]imidazol-1-yl)-1-(2-phenylhydrazono)acetone **9a-c** gave 8*H*-benzo[4',5']imidazo[2',1':5,1]pyrrolo[2,3-*c*]cinnoline derivatives **23a-c**. A plausible mechanism is suggested to account for their transformation based on the kinetics and products of reaction.

INTRODUCTION

We have recently reported efficient procedures for the synthesis of 3-acylcinnolines starting with 3-oxo-3-aryl-2-arylhydrazonopropanal **1**, where it underwent preferential cyclization in acid medium to give only the corresponding 3-acylcinnolines **2** (Scheme 1) [1].
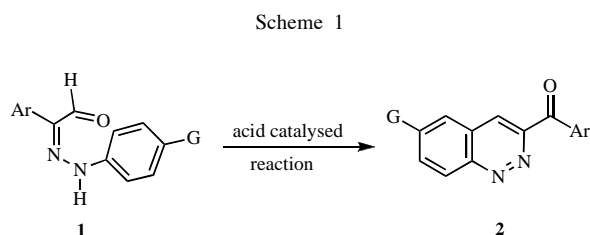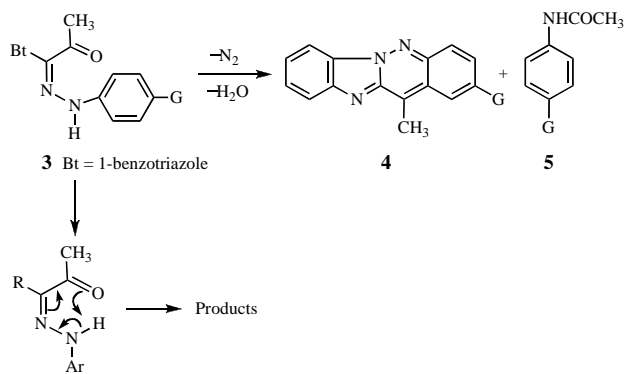
Scheme 1

We have also reported the result of efficient utilization of the preparative power of FVP in synthesis of benzimidazo[1,2-*b*]cinnoline derivatives **4** and several novel condensed heterocycles (Scheme 2) [2-4].
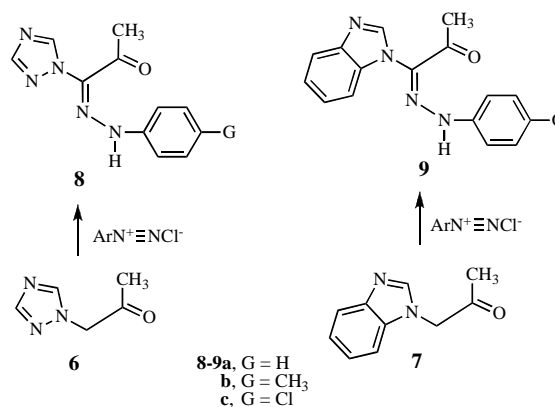
RESULTS AND DISCUSSION

In the present work we describe our results on the FVP of **8a-c** and **9a-c** prepared *via* coupling of **6** and **7** with aromatic diazonium salts following literature procedures (Scheme 3) [5,6].
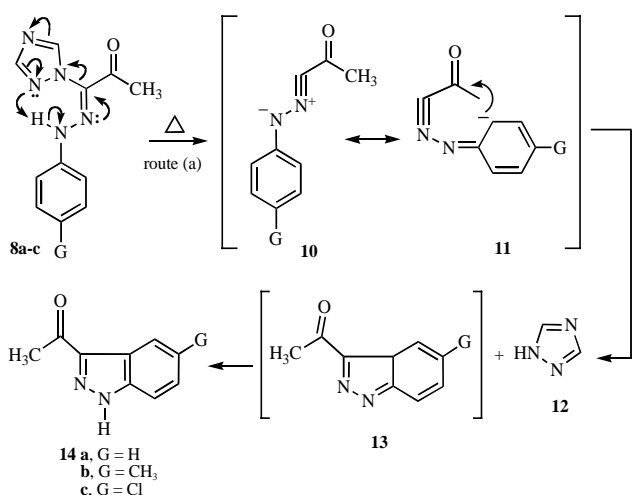
Scheme 2

Scheme 3

8-9a, G = H
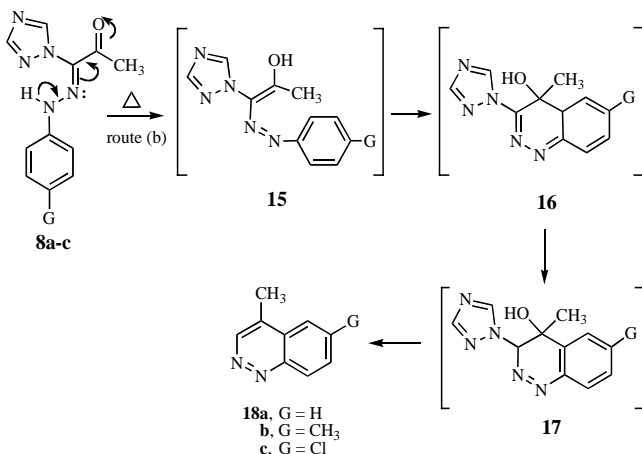**b**, G = CH$_3$
c, G = Cl

FVP of **8a-c** afforded a mixture of 3-acetylindazoles **14a-c** and cinnolines **18a-c** in 2:1 ratio determined by integration of the singlet signal at $\delta_H \approx 8$ ppm in the ^{1}H NMR spectrum of **18a-c**. The indazole derivatives **14a-c** are believed to be formed *via* 1,2,4-triazole elimination from **8a-c** *via* a quazi-aromatic six-membered transition state to yield nitrile imine which can be represented as resonance hybrid **10-11**. Form **11** readily cyclised into **13** then rearranged into fully aromatic **14a-c** (Scheme 4). Alternately initial enolization of **8a-c** would yield enol **15** that then undergoes 6 π-electrocyclization into **16**. The latter then eliminates 1,2,4-triazolium ion and hydroxide ion to yield **18a-c** *via* **17** (Scheme 5).

Scheme 4

8a-c   **10**   **11**

14 a, G = H
b, G = CH$_3$
c, G = Cl

13   **12**

Scheme 5

8a-c   **15**   **16**

18a, G = H
b, G = CH$_3$
c, G = Cl

17

FVP of **9a-c** results in a single product of m/z 258 (M$^+$), 272 (M^{+1}) and 292 (M^{+1}) respectively. Full characterization of the products suggested the formation of 8*H*-benzo[4',5']imidazo[2',1':5,1]pyrrolo[2,3-*c*]cinnoline derivatives **23a-c** which is believed to be formed through

initial formation of an eneazo derivative **19** that undergoes electrocyclization to yield **20** that would then aromatize into **21**, the nucleophilic methyl function in **21** adds to the π-deficient center of the benzimidazole ring to yield **22** that will then further aromatize yielding the final product **23a-c** (Scheme 6).

Scheme 6

9a-c   **19**

21   **20**

22   **23 a**, G = H
b, G = 4-CH$_3$
c, G = 4-Cl
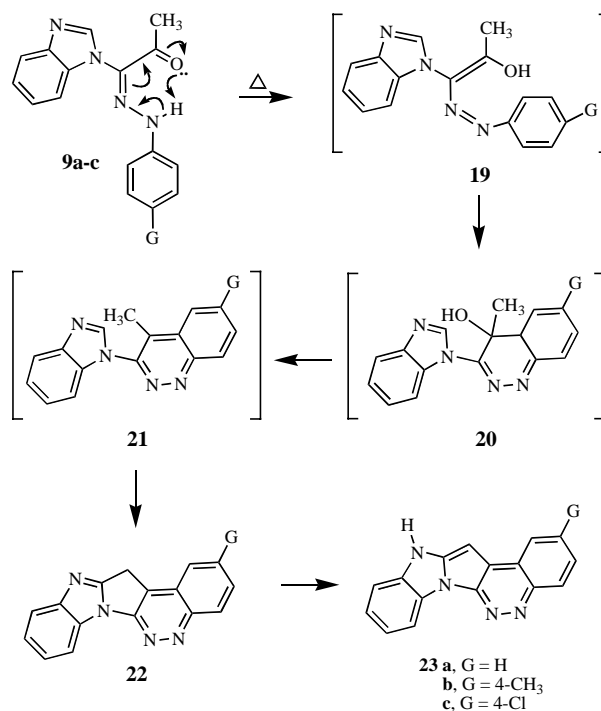
Kinetic Study. The rate coefficients $k/(s^{-1})$ are used to determine the E_a (kJ mol^{-1}) values of compounds (Table I). Each rate coefficient represents the mean from three kinetic runs in agreement to within ±2%. The reactions were ascertained to be homogeneous, unimolecular, and free of reactor surface effects. The Arrhenius plots were linear up to ≥95% reaction. The homogeneous nature of the reaction was tested by comparing rates using a normal reactor with those obtained when the reaction vessel is packed with helices. Absence of a free radical pathway in the elimination reaction is confirmed using established procedures [7,8]. The relative rates of gas-phase pyrolysis of the substrates **8a-c** and **9a-c** at 500 K are recorded in (Table 1) for the gas-phase cyclization of **8a-c** and **9a-c** show no significant effect of the substituent on the reaction rate. The absence of substituent effect suggests that the 6-π electrocyclization of intermediates **11** and **15** generated from **8a-c** are the rate-determining steps that aromatize yielding indazoles **14a-c** (route a) or followed by dehydration process to produce cinnolines **18a-c** (route b).

Table 1

Rate coeffecients (k/s⁻¹), Arrhenius parameters of compounds **8a-c, 9a-c**

Cpd.	T /K	$10^4 k$ /s⁻¹	log A /s⁻¹	Ea / k J mol⁻¹	k_{500K}/s⁻¹
8a	523.05	1.489	11.31 ± 0.10	153.45 ± 3.45	7.998 x 10⁻⁴
	532.85	2.750			
	543.65	5.274			
	553.75	9.877			
	563.15	16.90			
	574.45	34.20			
8b	518.45	1.373	10.55 ± 0.09	144.83 ± 0.90	9.065 x 10⁻⁴
	529.25	2.647			
	538.85	4.669			
	549.15	8.529			
	558.75	14.80			
	569.35	26.68			
8c	518.65	1.742	10.97 ± 0.32	148.29 ± 3.41	11.36 x 10⁻⁴
	529.05	3.135			
	539.75	5.857			
	549.85	10.56			
	559.95	21.02			
	570.25	36.59			
9a	452.75	2.658	2.68 ± 0.20	54.282 ± 1.94	1.0338 x 10⁻³
	478.65	6.248			
	491.95	8.203			
	505.45	10.90			
	519.15	16.10			
	532.95	22.29			
	545.55	34.01			
9b	460.85	6.883	1.423 ± 0.11	40.462 ± 1.03	1.573 x 10⁻³
	470.85	8.807			
	491.15	13.09			
	506.55	17.15			
	537.25	31.68			
9c	443.45	0.927	9.633 ± 1.00	115.83 ± 8.98	3.428 x 10⁻³
	456.25	2.122			
	469.05	6.905			
	481.95	13.61			
	494.75	21.19			

Similarly, enolization followed by 6-π electrocyclization of intermediates **19-20** is also believed to be the rate-determining step generated from **9a-c** that aromatize yielding **23a-c**.

EXPERIMENTAL

Melting points were determined on a Shimadzu-Gallenkamp apparatus and are uncorrected. Elemental analysis was by means of a LECO CHNS-932 Elemental Analyzer. NMR spectra were measured using a Bruker DPX 400 MHz superconducting spectrometer, and FT-IR measurements were from a Perkin Elmer 2000 FT-IR system. Mass spectrometric analysis was carried out on a VG-Autospec-Q high performance tri-sector GC/MS/MS, and the instrument for HPLC was an Agilent 1100 series LC/MSD with an API-ES/APCI ionization mode.

General Procedure for Pyrolysis of 8a-c and 9a-c. Each of compounds **8a-c** and **9a-c** was introduced in the reaction tube (1.5x12 cm Pyrex), cooled in liquid nitrogen, sealed under vacuum (0.06 mbar) and placed in the pyrolyser for 900 s at a temperature comparable to that used for complete pyrolysis in the kinetic studies. The pyrolysate was then separated into its constituents by preparative TLC (MERCK, 12 PSC-Platten 20x20 cm, Silica gel 60 F_{254} 2mm) using chloroform: petroleum ether (40:60) in 80:20 ratio as eluent, and each constituent was collected, analyzed and characterized. The techniques used include ¹H NMR, ¹³C NMR, and GC/MS. Temperatures of analytical pyrolysis, Arrhenius parameters, and rates of compounds **8a-c** and **9a-c** are given in Table 1.

MS and NMR Characterization. **1-(1H-Indazol-3-yl)-ethanone (14a)**. MS: m/z = 160 (M⁺), $C_9H_8N_2O$ (160.18). ¹H NMR (CDCl₃): δ = 2.50 (s, 3H, CH₃), 7.33 (t, J = 8.4 Hz, 1H), 7.42 (t, J = 8.4 Hz, 1H), 7.46 (d, J = 8.4 Hz, 1H), 8.19 (d, J = 8.4 Hz, 1H), 13.08 (br s, 1H, NH).

1-(5-Methyl-1H-indazol-3-yl)-ethanone (14b). MS: m/z = 174 (M⁺), $C_{10}H_{10}N_2O$ (174.20). ¹H NMR (CDCl₃): δ = 2.66 (s, 3H, CH₃), 7.75 (s, 3H, CH₃), 7.22 (d, J = 8.4 Hz, 1H), 7.27 (d, J = 8.4 Hz, 1H), 8.33 (s, 1H), 7.66 (br s, 1H, NH).

1-(5-Chloro-1H-indazol-3-yl)-ethanone (14c). MS: m/z = 194 (M⁺), $C_9H_7ClN_2O$ (194.62). ¹H NMR (CDCl₃): δ = 2.66 (s, 3H, CH₃), 7.56 (d, J = 8.3 Hz, 1H), 7.65 (d, J = 8.3 Hz, 1H), 8.29 (s, 1H), 13.23 (br s, 1H, NH).

4-Methylcinnoline (18a). MS: m/z = 145 (M^{+1}), $C_9H_8N_2$ (144.18). ^{1}H NMR (CDCl$_3$): δ = 2.64 (s, 3H, CH$_3$), 7.10 (t, J = 8.3 Hz, 1H), 7.33 (t, J = 8.3 Hz, 1H), 7.53 (d, J = 8.1 Hz, 1H), 7.75 (d, J = 8.1 Hz, 1H), 8.06 (s, 1H).

4,6-Dimethylcinnoline (18b). MS: m/z = 159 (M^{+1}), $C_{10}H_{10}N_2$ (158.20). ^{1}H NMR (CDCl$_3$): δ = 2.39 (s, 3H, CH$_3$), 2.50 (s, 3H, CH$_3$), 7.15 (d, J = 8.3 Hz, 1H), 7.43 (d, J = 8.3 Hz, 1H), 7.53 (s, 1H), 7.94 (s, 1H).

6-Chloro-4-methylcinnoline (18c). MS: m/z = 179 (M^{+1}), $C_9H_7ClN_2$ (178.62). ^{1}H NMR (CDCl$_3$): δ = 2.50 (s, 3H, CH$_3$), 7.33 (d, J = 8.5 Hz, 1H), 7.83 (s, 1H), 8.00 (d, J = 8.5 Hz, 1H), 8.44 (s, 1H).

8H-benzo[4',5']imidazo[2',1':5,1]pyrrolo[2,3-c]cinnoline (23a). MS: m/z = 258 (M$^+$), $C_{16}H_{10}N_4$ (258.28). ^{1}H NMR (CDCl$_3$): δ = 6.70 (m, 2H), 7.18 (t, J = 7.5 Hz, 1H), 7.48-7.57 (m, 4H, aromatic H and NH), 7.69 (d, J = 7.8 Hz, 1H), 7.90 (d, J = 7.8 Hz, 1H), 8.19 (s, 1H).

5-Methyl-8H-benzo[4',5']imidazo[2',1':5,1]pyrrolo[2,3-c]-cinnoline (23b). MS: m/z = 273 (M^{+1}), $C_{17}H_{12}N_4$ (272.31). ^{1}H NMR (CDCl$_3$): δ = 2.23 (s, 3H, CH$_3$), 6.68-6.70 (m, 1H), 6.92-7.00 (m, 1H), 7.44-7.55 (m, 4H, aromatic H and NH), 7.70 (d, J = 8.0 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H), 8.19 (s, 1H).

5-Chloro-8H-benzo[4',5']imidazo[2',1':5,1]pyrrolo[2,3-c]-cinnoline (23c). MS: m/z = 293 (M^{+1}), $C_{16}H_9ClN_4$ (292.73). ^{1}H NMR (CDCl$_3$): δ = 6.63 (d, J = 8.0 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 7.49-7.57 (m, 4H, aromatic H and NH), 7.70 (d, J = 7.64 Hz, 1H), 7.91 (d, J = 7.64 Hz, 1H), 8.19 (s, 1H).

Kinetic Studies. For each substrate, first-order rate coefficients were obtained at regular temperature intervals. Each rate constant is an average of at least three independent measurements in agreement to within ± 2%. The reactions for which the kinetic data were obtained have been ascertained to be homogeneous, unimolecular, non-catalytic and non-radical processes. These were carried out in the manner and apparatus previously described [9]. Arrhenius plots of the data using first order rate equation: log k (s^{-1}) = log A – E$_a$ kJ mol^{-1} (2.303 RT)$^{-1}$ were strictly linear over ≥ 95% reaction with correlation coefficient in the 0.99 ± 0.005 range. The log A, E$_a$ values and the first order-rate constants at 500 K of the six compounds under investigation are given in Table 1.

Pyrolysis. Flash Vacuum Pyrolysis (FVP). The apparatus used was similar to the one which has been described in our recent publications [10,11]. The sample was volatilized from a tube in a Büchi Kugelrohr oven through a 30 x 2.5 cm horizontal fused quartz tube. This was heated externally by a Carbolite Eurotherm tube furnace MTF-12/38A to a temperature of 650 °C, the temperature being monitored by a Pt/Pt-13%Rh thermocouple situated at the center of the furnace. The products were collected in a U-shaped trap cooled in liquid nitrogen. The whole system was maintained at a pressure of 2.67 Pa by an Edwards Model E2M5 high capacity rotary oil pump, the pressure being measured by a Pirani gauge situated between the cold trap and the pump. Under these conditions the contact time in the hot zone was estimated to be ≅ 10 ms. The different zones of the products collected in the U-shaped trap were analyzed by 1H NMR, LCMS and GC-MS. Relative and percent yields were determined from 1H NMR. Identities of compounds obtained were confirmed by comparison of their 1H NMR with data of products separated from preparative HPLC.

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