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Thermolysis of Semicarbazones to the Corresponding Azines Through Reactive N-Substituted Isocyanate Intermediates

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Abstract: Thermolysis of semicarbazones (I) to azines (II) occurs through reactive N-substituted isocyanate intermediates (Ia) which can be converted in situ to carbamates and N-substituted ureas.

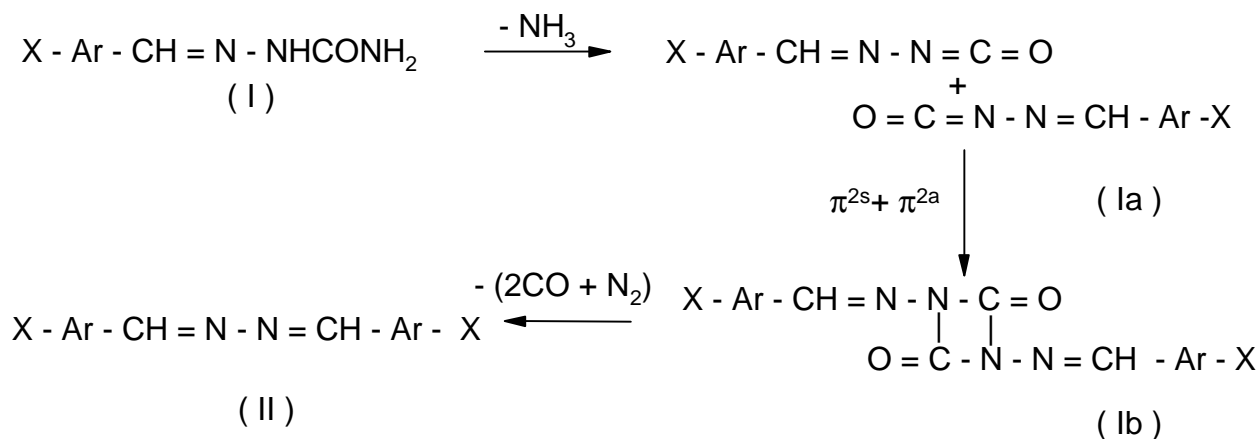
Keywords: Thermolysis, Semicarbazones, Azines, N-substituted isocyanates, Mesogenic compounds.

Introduction

The isocyanate group is one of the most important synthons and intermediates in Organic Chemistry [1]. There are many ways of generating these reactive intermediates, however most of them require the use of hazardous starting materials [2-6]. In the last decade, we have been studying the mesomorphism of semicarbazone [7-10], phenyl hydrazone [11] and 2,4-dinitrosemicarbazone [12] derivatives as well as their biological activity.

Results and Discussion

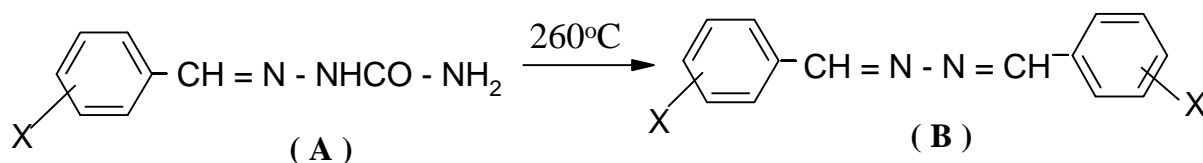
The examination of semicarbazones for mesogenic (liquid crystalline) properties under a polarizing microscope equipped with a heating stage revealed that they undergo transformation to azines at elevated temperature. The proposed mechanism goes through the corresponding N-substituted isocyanate, as shown in Scheme 1 [13].



Scheme 1.

A systematic investigation of this reaction was undertaken as a continuation of our previous work [13], in order to investigate the generality of this reaction and to confirm the formation of N-substituted isocyanates as reactive intermediates. This systematic study provided strong evidence to support the proposed molecular transformation through a reactive N-substituted isocyanate intermediate. This transformation also provides a novel route to a N-substituted isocyanates, highly reactive dipolarophiles, which opens up new avenues for the synthesis of molecules having different structural features such as β -lactams [14], N-substituted ureas and carbamates.

The aryl semicarbazones (**A**), when heated at 260°C in an oil bath formed benzalazines (**B**) [13]. The identity of the benzalazine was established through comparison with previously reported work [13] and by independent synthesis [15,18].



A literature survey revealed that there are no previous records of pyrolytic transformations of aryl semicarbazones to benzalazines. However, the formation of azines was postulated in the mass spectral fragmentation of alicyclic semicarbazones [16].

The proposed mechanism (Scheme 1) involves the initial generation of a N-substituted isocyanate

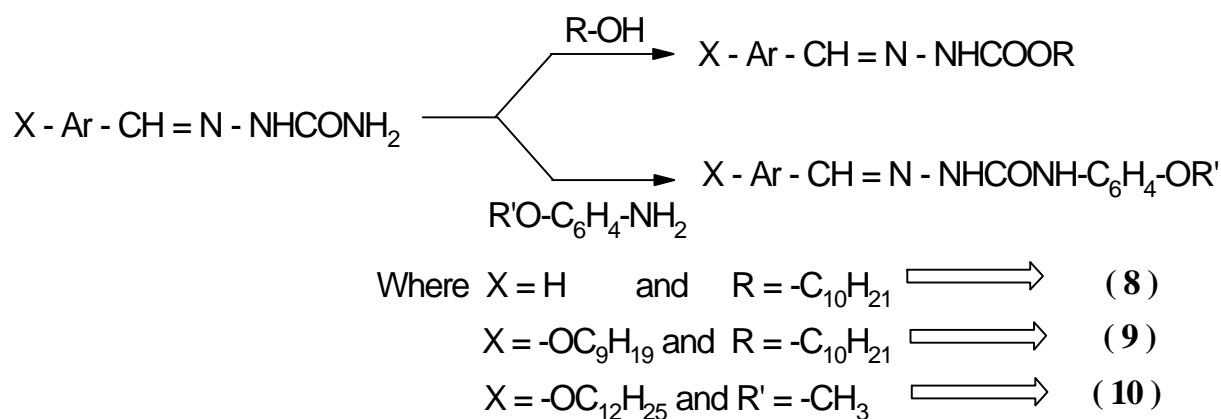
(Ia) which forms a diazine through the following two steps:

(Ia) undergoes $\pi^{2s} + \pi^{2a}$ cycloaddition [17] giving the relatively unstable isocyanate dimer (Ib).

(Ib) undergoes a threefold extrusion (2CO , N_2) to give benzalazine (II).

The proposed mechanism is supported by detection of the decomposition products NH_3 , CO and N_2 and by trapping the reactive isocyanate intermediates (Ia) with nucleophiles. Evolution of NH_3 was detected by the normal method (litmus paper test) and was also observed in the mass spectra of the reaction mixtures. CO and N_2 were also observed in the mass spectra and detected by gas chromatography.

The formation of N-substituted isocyanates seems to be a general process, since a number of semicarbazones **1A-7A** were pyrolyzed to benzalazines **1B-7B** (Table 1). In order to confirm the generation of isocyanate, we conducted the thermolysis of some semicarbazones in the presence of nucleophiles and isolated the corresponding 1,2 adducts along with benzalazines as shown in Scheme 2. The intermediate isocyanates were trapped to give compounds **8-10** (Scheme 2) whose structures were determined through elemental analysis and spectral data.



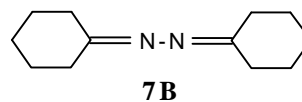
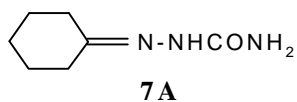
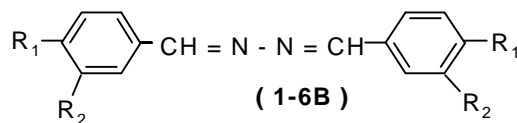
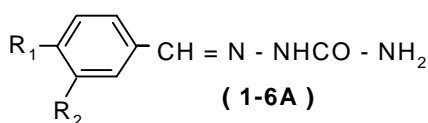
Scheme 2.

Reactive intermediate N-substituted isocyanates offer tremendous scope for further study. It has opened up a new and convenient route for the synthesis of a number of bioactive molecules. Further studies are underway, to evaluate the scope, limitations and utility of this process.

Conclusion

We have presented a facile route for the generation of highly reactive intermediate N-substituted isocyanates through thermolysis of semicarbazones.

Table 1.



R ₁	R ₂	Semicarbazones A	Azines B	Literature References for Azines B
H	H	1A	1B	[18]
Cl	H	2A	2B	[20]
CH ₃	H	3A	3B	[21]
NO ₂	H	4A	4B	[18]
N(C ₂ H ₅) ₂	H	5A	5B	[19]
OCH ₃	OCH ₃	6A	6B	[22]
-	-	7A	7B	[23]

Experimental

General

¹H NMR spectra were obtained using a Perkin Elmer R-32 NMR and were recorded at 90 MHz. IR spectra were recorded on a Shimadzu IR 408 instrument.

General Procedure for the Preparation of Azines (B) from Semicarbazones (A)

The semicarbazones were heated at 260°C in an oil bath for 5-10 mins. The crude product was dissolved in chloroform and filtered. Filtrate was loaded onto silica gel and subjected to column chromatography. A mixture of ethyl acetate - petroleum ether (5:95) was used as eluent solvent. The physical properties of the azines are summarized as follows:

Spectral and Melting Point Data

Benzalazine 1B

Mp 95°C, Reported[18] mp 92-93°C.

¹H NMR (CDCl₃) δ 8.6 (s, 2H, H-C=N), 7.8 (s, 4H, aromatic H), 7.4 (s, 6H, aromatic H).

IR (KBr) 1620, 1580, 1450, 1300, 1210, 1070, 1020, 950, 850 cm⁻¹.

Elemental analysis: C₁₄H₁₂N₂ requires: C, 80.76; H, 5.76; N, 13.46. Found: C, 80.33; H, 6.13; N, 13.05.

p-Chlorobenzalazine 2B

Mp 207°C. Reported [20] mp 211°C.

Elemental analysis: C₁₄H₁₀N₂Cl₂ requires: C, 60.86; H, 3.62; N, 10.14. Found: C, 61.70; H, 4.01; N, 10.15

p-Tolualdazine 3B

Mp 155-157°C. Reported [21] mp 153°C.

Elemental analysis: C₁₆H₁₆N₂ requires: C, 81.35; H, 6.79; N, 11.86. Found: C, 81.22; H, 6.68; N, 11.39

p-Nitrobenzalazine 4B

Mp 309°C. Reported [20] mp 307°C.

Elemental analysis: C₁₄H₁₀N₄O₄ requires: C, 56.37; H, 3.35; N, 18.79. Found: C, 56.47; H, 3.25; N, 18.57.

Bis(diethylamino)benzalazine 5B

Mp 201°C. Reported [19] mp 188-191°C.

Elemental analysis: C₂₂H₃₀N₄ requires: C, 75.42; H, 8.57; N, 16.00. Found: C, 75.38; H, 8.21; N, 15.99.

3,4-Dimethoxybenzalazine 6B

Mp 190°C. Reported [22] mp 193-193°C.

Elemental analysis: C₁₈H₂₀N₂O₄ requires: C, 65.85; H, 6.09; N, 8.53. Found: C, 66.24; H, 6.13; N, 8.38.

Cyclohexanoneketazine 7B

Mp 36°C. Reported [23] mp 33-34.5°C.

Elemental analysis: C₁₂H₂₀N₂ requires: C, 75.00; H, 10.42; N, 14.58. Found: C, 74.96; H, 10.84; N, 14.76.

Synthesis of 1-2 adducts (trapped products) 8, 9 and 10

Equimolar proportions of aryl semicarbazone and alcohol or amine was heated for 5-10 mins. in an oil bath at 260°C. The crude product obtained was cooled and washed with ethanol in case of the alcohols and washed with petroleum ether in the case of the amines and subjected to column chromatography. The NMR and IR spectra of compound No. **8**, **9** and **10** are summarized as follows:

Spectral and Melting Point Data

Benzylidene-N-decyl carbamate 8

Mp 90°C; ¹H NMR (CDCl₃) δ 8.5 (s, 1H, NH), 7.9 (s, 1H, H-C=N), 7.7 (s, 2H, aromatic H), 7.3 (m, 3H, aromatic H), 4.2 (t, J=8Hz, 2H, -OCH₂), 1.8 (en, 2H, CH₂), 1.4 (broad s, 19H, CH₂'S), 0.9 (broad t, 3H, CH₃).

IR (KBr) 3250, 1707, 1540, 1475, 1360, 1250, 1095, 1050 cm⁻¹.

Elemental analysis: C₁₈H₂₈N₂O₂ requires: C, 71.05; H, 9.21; N, 9.21. Found: C, 70.68; H, 8.78; N, 8.88.

4-n-Nonyloxy-benzylidene-N-decyl carbamate 9

Mp 97-102°C, ¹H NMR (CDCl₃) δ 8.0 (broad s, 1H, NH), 7.8 (br s, 1H, H-C=N), 7.6 (d, J=9Hz, 2H, aromatic H), 6.9 (d, J=9Hz, 2H, aromatic H), 4.2 (t, J=8Hz, 2H, -OCH₂), 1.8 (broad en, 4H, CH₂), 1.5-1.2 (broad s, 30H, CH₂'S), 0.9 (b t, 6H, CH₃'S).

IR (KBr) 3250, 2900, 2850, 1707, 1600, 1545, 1510, 1475, 1250 cm⁻¹.

Elemental analysis: C₂₇H₄₆N₂O₃ requires: C, 72.64; H, 10.31; N, 6.27. Found: C, 72.21; H, 10.01; N, 6.05.

[(4'-n-Dodecyloxy-benzaldehyde)- N-phenyl-(4-n-methoxy)] semicarbazone 10

Mp 222-224°C, ¹H NMR (CDCl₃) δ 8.6 (s, 1H, H-C=N), 7.9 (s, 2H, NH x 2), 7.5 (m, 4H, aromatic H), 6.85 (m, 4H, aromatic H), 4.0 (t, 4H, -OCH₂ x 2), 3.8 (s, 1H, CH₃'S), 1.3 (broad s, 20H, CH₂'S), 0.9 (broad s, 20H, CH₂'S).

IR (KBr) 3300, 1630, 1600, 1519, 1440, 1420, 1300, 1245, 1160, 1105, 1055, 1033, 825 cm⁻¹.

Elemental analysis: $C_{27}H_{39}N_3O_3$ requires: C, 71.52; H, 8.60; N, 9.27. Found: C, 71.33; H, 8.90; N, 9.47.

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Samples Availability: Available from the authors.