Synthesis of bishydrazones (aldazines)

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Bishydrazones have been prepared by thermolysis of aldehyde hydrazone under reduced pressure in a sealed tube at 120-30°C. The possible mass spectral fragmentation mode of bishydrazones have also been discussed.

Among the various conjugated systems, 2,3-diazabuta-1,3-dienes (commonly known as azines) are well defined and have been thoroughly studied in recent years mainly as potential substrates for cycloaddition. Azines, like simple azomethine, react with both electrophilic and nucleophilic reagents. Oxidation of aldehydes with lead tetraacetate leads to the formation of 1,3,4-oxadiazole, via imidoyl acetate intermediates. Azines are also oxidized with NaOCl-DMSO in aqueous DMSO with luminescence.

Some heterocyclic azines inhibit murine tumor growth and act as fluorescent brightening agents and are photosensitizers and azines were developed for use as an ion-selective optical sensors. Mixed azines between opioid antagonists and steroidal ketones have shown various biological effects including ultralong opioid antagonist activity and specificity for the opioid δ receptor.

The usual synthesis of azines involves the reaction of aldehydes/ketones or the derived aldimines/ketimines in aqueous solution with an excess hydrazine salts. Recently, Quillon et al. synthesized azine by illumination of aqueous or organic solution of nitrofurazone with fluorescent or tungsten light. In all these the yields of reaction products are low as the side reaction predominates. Hence, a new procedure for the synthesis of azines remains of interest. This prompted us to synthesize azines by a simple method.

In a typical reaction for the synthesis of azines solution of semicarbazone 1 in tetrahydrofuran was heated in a sealed tube for 12 to 14 hr. In general, bishydrazones 2 were obtained in 70-90% yield and rest being the starting material (Equation 1). This transformation of semicarbazone 1 into bishydrazones 2 presumably occurs via the elimination of bisurea from two semicarbazone molecules (Scheme 1).

Note

The structures of bishydrazones 2 were characterized by spectral analysis. IR spectrum of 2a showed the absence of amide carbonyl frequency in the region 1750-1650 cm⁻¹ and the NH frequency in the region 3400-3200 cm⁻¹ and showed a new peak at 1645 cm⁻¹ due to C=N frequency. All azines showed ¹HNMR peaks due to aromatic protons and its substituents in the expected region. ¹³C NMR spectra showed a doublet at δ 160.00-162.00 ppm attributable to CH=N. The remaining aromatic ring carbons appeared in the expected region. The bishydrazones gave significantly stable molecular ion peak with relative abundance ranging from 50 to 65%. The possible common fragmentation pattern involves formation of ions involving some rearrangement with removal of nitrogen molecule or the loss of CH=N (Scheme II). The base peak is ion of mass 199, which arises due to the loss of CH-N₂ and a hydrogen radical. For instance bishydrazone 2a showed a molecular ion of mass 208 with relative abundance of 30%. The base peak is at m/z 165 and the next abundant ion is at m/z 180 (74%), which may be formed due to the loss of nitrogen.

The ion peak at m/z 131 with relative abundance 72% may be due to the loss of phenyl radical.
Experimental Section

Melting points were taken in an open capillary and are uncorrected. IR spectra were recorded on a Perkin Elmer 99 spectrophotometer, $^1$H NMR spectra on a Jeol 60 MHz NMR spectrometer using CDCl$_3$ as a solvent and TMS as an internal reference. The chemical shifts are expressed in $\delta$ ppm. Mass spectra of compounds were recorded on Hitachi RMU-6I spectrophotometer and important fragments are given with the relative abundances in the bracket. TLC was done on a Merck silica gel G coated on glass plates.

Preparation of bis-hydrazones 2. A typical procedure for the preparation of phenyl-bishydrazone 2a. Benzaldehyde semicarbazone 1a (1 g, 6 mmoles) dissolved in 5 mL of tetrahydrofuran was taken in a sealed tube and kept in an oil-bath for 15-24 hr at 120-50°C. It was then extracted into dichloromethane followed by thorough washing with water, brine solution and finally dried over anhydrous sodium sulphate. The TLC of this solution showed single spot different from the starting material. It was then purified by column chromatography. The eluant was then evaporated under reduced pressure to yield 2a as yellow crystalline solid in 85% (0.54 g) yield. mp, 88-89°C; $^1$HNMR (CDCl$_3$): $\delta$ 7.45 (m, 6H, 3,4,5-H), 7.84 (m, 4H, 2,6-H), 8.67 (s, 2H, CH$\equiv$CN); $^1$C NMR (CDCl$_3$): $\delta$ 128.53 (d, C-2,6), 128.74 (d, C-3,5), 131.13 (d, C-4), 134.14 (s, C-1), 161.90 (d, CH=). MS: m/z (relative abundance) 208(M$^+$, 31), 180(M$^+$-N$_2$, 58), 166(M$^+$-CH$_2$N$_2$, 8), 165(100), 131(M$^+$-Ar; 35), 104(12); Anal Calcd C$_{14}$H$_7$N$_2$: C, 80.77; H, 5.77; N, 13.46. Found: C, 80.60; H, 5.06; N, 13.24%.
4-Methoxyphenyl-bis-hydrazone 2b. Obtained from 1b (0.9 g, 4.7 mmoles) as pale blue green crystalline solid in 83% (0.52 g) yield, mp 166-69°C.

1HNMR (CDCl3): δ 3.80 (s, 6H, OCH3), 6.95 (d, 4H, 3-5-H), 7.78 (d, 4H, 2-6-H) 8.61 (s, 2H, CH=); 13C NMR (CDCl3): δ 55.38 (q, OCH3), 128.53 (d, C-2, 6), 128.74 (d, C-3, 5), 131.11 (d, C-4), 134.14 (s, C-1), 161.90 (d, CH=); MS: m/z (relative abundance) 288(M+, 31), 260(M+-N2, 31), 246(M+-CH2N2, 18), 245(100), 231(M+-Ar, 10), 144(6); Anal Calcd: C, 61.76; H, 6.01; N, 7.02%.  

3,4′-Dimethoxyphenyl-bis-hydrazone 2c: Obtained from 1c (1.1 g, 4.3 mmoles) as pale blue green crystalline solid in 68% (0.55 g) yield, mp 187-88°C.

1HNMR (CDCl3): δ 3.94 (s, 12H, OCH3), 6.91 (d, 2H, 5-H), 7.25 (d, 2H, 6-H), 7.54 (s, 2H, 2-H), 8.60 (s, 2H, CH=); 13C NMR (CDCl3): δ 56.38 (q, OCH3), 108.94 (d, C-2), 110.74 (d, C-5), 123.81 (d, C-6H), 127.30 (s, C-1), 149.40 (s, C-3), 151.81 (s, C-4), 161.90 (d, CH=); MS: m/z (relative abundance) 328(M+, 31), 300(M+-N2, 60), 286(M+-CH2N2, 10), 285(100), 131(M+-Ar): 164(4); Anal Calcd: C, 65.85; H, 6.09; N, 8.54%. Found: C, 65.65; H, 6.00; N, 8.40%.  

3,4,5-Trimethoxyphenyl-bis-hydrazone 2d: Obtained from 1d (1.25 g, 6.16 mmoles) as pale yellow crystalline solid in 87% (0.77 g) yield, mp 190-92°C.

1HNMR (CDCl3): δ 3.92 (s, 12H, OCH3), 3.94 (s, 6H, OCH3), 7.09 (s, 4H, 2,6-H), 8.60 (s, 1H, CH=); 13C NMR (CDCl3): δ 56.30 (q, OCH3), 105.75 (d, C-2, 6), 129.50 (d, C-1), 141.09 (s, C-4), 153.55 (s, C-3, 5), 161.36 (d, CH=); MS: m/z (relative abundance) 288(M+, 31), 260(M+-N2, 54), 246(M+-CH2N2, 18), 245(100), 131(M+-Ar, 10), 144(6); Anal Calcd: C, 61.85; H, 6.19; N, 7.22. Found: C, 61.76; H, 6.01; N, 7.02%.  

3,4-Methylenedioxy-bis-hydrazone 2e: Obtained from 1e (1.35 g, 6.25 mmoles) as pale yellow crystalline solid in 84% (0.78 g) yield, mp 194-96°C.

1HNMR (CDCl3): δ 6.03 (s, 4H, OCH2O), 6.86 (s, 2H, 5-1), 7.20 (s, 2H, 6-H), 7.45 (s, 2H, 2-H), 8.54 (s, 1H, CH=); 13C NMR (CDCl3): δ 101.54 (t, OCH2O), 106.70 (d, C-2), 108.36 (d, C-5), 125.14 (d, C-6), 128.86 (s, C-1), 148.35 (s, C-3), 150.29 (s, C-4), 161.07 (d, CH=); MS: m/z (relative abundance) 296(M+, 31), 284(M+-N2, 58), 254(M+-CH2N2, 14), 255(100), 131(M+-Ar, 8), 148(4); Anal Calcd: C, 61.85; H, 6.19; N, 7.22. Found: C, 61.76; H, 6.01; N, 7.02%.  

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References