Indian Journal of Chemistry
Vol. 46B, March 2007, pp. 540-543

Note

Reaction of 2-acetylbenzofuranhydrazone with aromatic aldehydes: Formation of aldzaines and regeneration of 2-acetylbenzofuran

Ravi K Ujjinamatada*[a] & Yankanagouda S Agasimundin

Department of Chemistry, Gulbarga University
Gulbarga 585 106, India

E-mail: ravikum@umbc.edu

Received 11 November 2005; accepted (revised) 14 September 2006

Hydrolytic cleavage of 2-acetylbenzofuranhydrazone under acidic condition with aromatic aldehyde is described. This method of cleavage of C=N bond is shown to serve as a convenient method for the regeneration of ketone from ketohydrazone besides synthesis of aldazines.

Keywords: Hydrolytic cleavage, aromatic aldehydes, regeneration, ketone, aldazines

IPC: Int.Cl.[8] C07D

Regeneration of carbonyl compounds from oximes, hydrazones, N-substituted hydrazones and semicarbazones has been a significant aspect of organic chemical transformation for various reasons. These nitrogen derivatives of carbonyl compounds are not only important synthetic intermediates, but they are also extensively used for purification, characterrization of carbonyl compounds, semi-microcolorimetric estimations and to protect the ketone and aldehyde functions[1]. Most of the methods reported in the literature for regeneration of aldehydes and ketones involve hydrolytic cleavage by exchange under acidic conditions[2-9]. Herein is now reported an interesting hydrolytic cleavage of 2-acetylbenzofuranhydrazone using aromatic aldehyde-hydrochloric acid wherein the exchange products, aldazines are of much interest in addition to regeneration of 2-acetylbenzofuran.

In connection with the ongoing investigation on benzofuran derivatives[10,11] of pharmacological importance, the current focus is on the reaction of 2-acetylbenzofuran hydrazone with aromatic aldehydes. The starting compound 2-acetylbenzofuran hydrazone **2** was prepared by the reaction of 2-acetylbenzofuran[12] **1** with hydrazine hydrate in presence of catalytic amount of hydrochloric acid in refluxing ethanol. The reaction of hydrazone **2** with salicylaldehyde (using 1:1 molar proportion) in presence of catalytic amount of hydrochloric acid at reflux temperature in ethanol was monitored by TLC. The product, which was a mixture of three compounds, was separated and the individual components identified as salicylaldazine[13] **3a**, regenerated 2-acetylbenzofuran **1** and unreacted hydrazone **2** on the basis of spectroscopic data and comparison with authentic samples. IR spectrum (KBr) of **3a** indicated the presence of OH (3460 cm^{-1}) and C=N (1630 cm^{-1}). The ^1H NMR (300 MHz, $CDCl_3$) of **3a** showed a broad singlet at δ 11.45 and a singlet at δ 8.71 corresponding to OH and azomethine protons and a multiplet at δ 6.90-7.40 due to aromatic protons. The mass spectrum exhibited the molecular ion peak M^+ at *m/z* 240 (100%). When the same reaction was carried out under identical reaction conditions using 1:2 molar proportion of hydrazone **2** and salicylaldehyde, salicylaldazine **3a**, and 2-acetylbenzofuran **1** were obtained.

The condensation of hydrazone **2** with salicylaldehyde in the absence of hydrochloric acid in ethanol at RT/reflux temperature gave a single product, mixed azine **4a**. IR spectrum (KBr) confirmed the presence of OH (3445 cm^{-1}) and C=N (1625 cm^{-1}). The three singlets at δ 2.54, 8.84 and 11.81 in the ^1H NMR spectrum ($CDCl_3$) were assigned to CH_3, azomethine CH and OH protons, respectively and the multiplet at δ 6.94-7.67 due to aromatic protons. The mass spectrum exhibited the molecular ion peak M^+ at *m/z* 278 (100%).

The regeneration of ketone **1** due to cleavage of ketohydrazone by salicylaldehyde under acidic condition prompted the testing of the general course of the reaction on anisaldehyde, *p*-chlorobenzaldehyde, *p*-N,N-dimethylaminobenzaldehyde, *p*-nitrobenzaldehyde and benzaldehyde. All these aldehydes reacted with hydrazone **2** in the same way as salicylaldehyde. The reaction using 1:2 molar quantities of hydrazone and aldehyde in presence of catalytic amount of hydrochloric acid gave **3b-f** and

[a] Address for correspondence: Department of Chemistry and Biochemistry, University of Maryland Baltimore County, 1000 Hilltop Circle, Baltimore, MD-21250, USA.

2-acetylbenzofuran and that in the absence of hydrochloric acid gave only **4b-f**. The mixed azines **4b-f** when subjected to react with respective aldehydes: anisaldehyde, *p*-chlorobenzaldehyde, *p*-N, N-dimethylaminobenzaldehyde, *p*-nitrobenzaldehyde and benzaldehyde in presence of catalytic amount of hydrochloric acid gave symmetrical aldazine **3a-f**, along with regeneration of 2-acetylbenzofuran **1** (**Scheme I**). The identity of the aldazines **3a-f** obtained directly from 2-acetylbenzofuran hydrazone and through mixed azines **4a-f** were established by mixed m.p., superimposible IR, ^{1}H NMR spectra and comparison with authentic samples[13-18] (**Table I**).

The selective deblocking of ketone in bis-semicarbazones of ketoaldehydes using Dowex-50 has been reported[19]. The present investigation also reveals similar selectivity for regeneration of ketone functionality over that of aldehyde group. In this context, the reactions using simple ketohydrazones with aldehydes are under investigation for extending the generality of this reaction and preparation of mixed aldazines using this method.

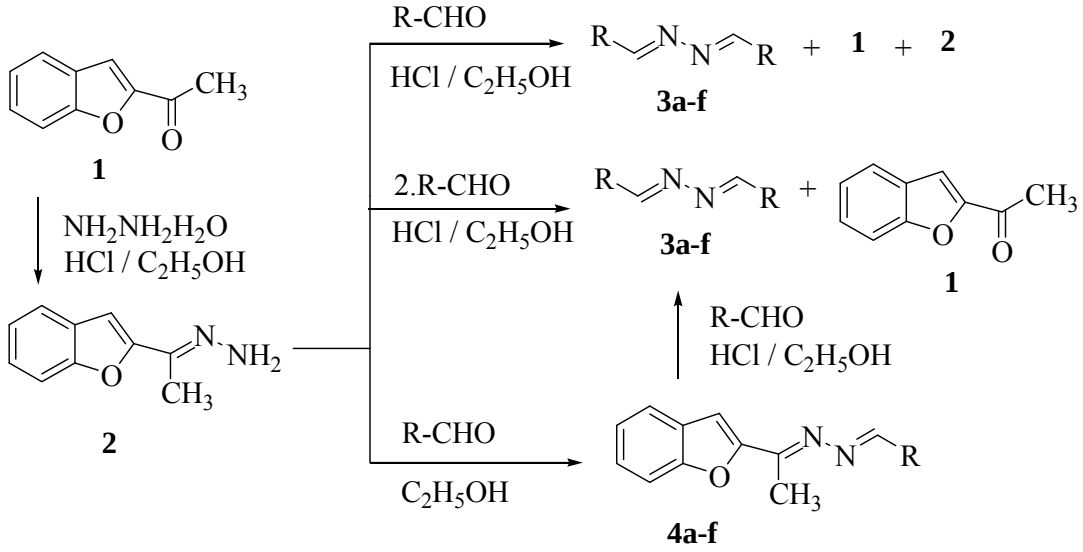
Experimental Section

Melting points were determined in open capillary tubes and are uncorrected. IR spectra (KBr) were recorded on Perkin-Elmer FTIR 1615 double beam spectrophotometer (ν_{max} in cm^{-1}), ^{1}H NMR spectra were recorded at 60 MHz (on CW, EM360, Varian) and 300 MHz (on a Bruker AM-200) machines using $CDCl_3$ as a solvent (chemical shifts in δ, ppm downfield from TMS as internal reference), and mass spectra on a Varian MAT CH-5 and CH-7 instruments at 70 eV. The elemental analyses were determined on a Perkin-Elmer apparatus. Homogeneity of the compounds was checked by TLC.

2-Acetylbenzofuran hydrazone, 2

To a solution of 2-acetylbenzofuran (3.2 g, 0.02 mole) in absolute ethanol (30 mL), hydrazine hydrate (1.5 g, 0.03 mole) and few drops of hydrochloric acid were added. The reaction mixture was heated under reflux for 6 hr. The product which separated on cooling was collected and purified by recrystallization from aqueous ethanol as colorless needles (3.1 g, 89%), m.p. 148-50°C (lit m.p. 148°C)[20], ^{1}H NMR ($CDCl_3$): δ 2.18 (s, 3H, CH_3), 5.95 (s, 2H, NH_2), 6.81 (s, 1H, CH of ArH), 7.17-7.59 (m, 4H, ArH); MS: *m/z* 174 (100%). Anal. $C_{10}H_{10}N_2O$: Calcd. C, 68.95; H, 5.79; N, 16.08. Found: C, 68.73; H, 5.82; N, 16.17%.

General method for the synthesis of mixed azine from 2-acetylbenzofuranhydrazone and aldehydes, 4a-f



a **b** **c** **d** **e** **f**

R = 2-OH.C_6H_4, 4-OCH_3.C_6H_4, 4-Cl.C_6H_4, 4-$N(CH_3)_2$.C_6H_4, 4-NO_2.C_6H_4, C_6H_5

Scheme I

Table I — Comparative physical data of aldazines and ketone **1**

Compd	R	m.p. [lit. m.p.] in °C	Yield (Y) of **1** and aldazine in %			
			Method A		Method B	
			Y of **1**	Y of aldazine	Y of **1**	Y of aldazine
3a	2-OH.C_6H_4	222-24 [222](Ref.13)	85	89	77	81
3b	4-OCH_3.C_6H_4	169-71 [170](Ref.14)	79	86	80	83
3c	4-Cl.C_6H_4	210-12 [211](Ref.15)	81	68	72	74
3d	4-$N(CH_3)_2$.C_6H_4	255-57 [253](Ref.16)	72	80	85	80
3e	4-NO_2.C_6H_4	308-10 [308](Ref.17)	74	53	78	61
3f	C_6H_5	92-94 [93](Ref.18)	67	59	72	65

A solution of 2-acetylbenzofuranhydrazone (0.02 mole) and aromatic aldehyde (0.02 mole) in ethanol (30 mL) was heated under reflux for 30 min. The product which separated as a crystalline solid was collected by filtration after cooling and purified by recrystallization from suitable solvent.

4a: Pale yellow (ethanol); m.p.165-67°C. Yield, 92%; ^{1}H NMR($CDCl_3$): δ 2.54 (s, 3H, CH_3), 6.94-7.67 (m, 9H, ArH), 8.84 (s, 1H, CH), 11.81 (s, 1H, OH); MS: *m/z* 278 (100%). Anal. $C_{17}H_{17}N_2O_2$: Calcd. C, 77.37, H, 5.07, N, 10.07. Found C, 77.55, H, 5.17, N, 10.20%.

4b: Pale yellow (ethanol); m.p.133-35°C. Yield, 87%; ^{1}H NMR ($CDCl_3$): δ 2.60 (s, 3H, CH_3), 3.70 (s, 3H, CH_3), 6.90-7.70 (m, 9H, ArH), 8.50 (s, 1H, CH); MS: *m/z* 292 (100%). Anal.$C_{18}H_{16}N_2O_2$: Calcd. C, 73.95, H, 5.52, N, 9.58. Found C, 73.82, H, 5.49, N, 9.87%.

4c: Pale yellow (ethanol); m.p. 214-16°C. Yield, 82%; ^{1}H NMR ($CDCl_3$): δ 2.50 (s, 3H, CH_3), 7.10-7.50 (m, 8H, ArH), 8.60 (s, 1H, CH); MS: *m/z* 296 (100%). Anal. $C_{17}H_{13}N_2ClO$: Calcd. C, 68.81, H, 4.42, N, 9.44. Found C, 68.66, H, 4.58, N, 9.27%.

4d: Pale yellow (ethanol); m.p. 241-43°C. Yield, 86%; ^{1}H NMR ($CDCl_3$): δ 2.60 (s, 3H, CH_3), 2.80 (s, 6H, $(CH_3)_2$), 6.80-7.40 (m, 8H, ArH), 8.40 (s, 1H, CH); MS: *m/z* 305 (100%). Anal. $C_{19}H_{19}N_3O$: Calcd. C, 74.73, H, 6.27, N, 13.76. Found C, 74.94, H, 6.45, N, 13.55%.

4e: Pale yellow (methanol); m.p.129-31°C. Yield, 81%; ^{1}H NMR ($CDCl_3$): δ 2.50 (s, 3H, CH_3), 6.70-7.40 (m, 8H, ArH), 8.60 (s, 1H, CH); MS: *m/z* 307 (100%). Anal. $C_{17}H_{13}N_3O_3$: Calcd. C, 66.64, H, 4.26, N, 13.67. Found C, 66.48, H, 4.07, N, 13.41%.

4f: Pale yellow (ethanol); m.p.155-57°C. Yield, 73%; ^{1}H NMR ($CDCl_3$): δ 2.40 (s, 3H, CH_3), 6.60-7.30 (m, 9H, ArH), 8.30 (s, 1H, CH); MS: *m/z* 262 (100%). Anal. $C_{17}H_{14}N_2O$: Calcd. C, 77.84, H, 5.38, N, 10.68. Found C, 77.69, H, 5.57, N, 10.34%.

General method for the isolation of regenerated ketone and aldazines, 3a-f

Method A: From 2-acetylbenzofuranhydrazone

A solution of 2-acetylbenzofuran hydrazone **2** (0.001 mole) and aromatic aldehyde (0.002 mole) in ethanol (15 mL) containing two drops of hydrochloric acid was refluxed for 30 min. The aldazine which separated as a solid was filtered, washed with ethanol, dried and purified by recrystallization from a suitable solvent. Removal of the solvent from the filtrate gave regenerated 2-acetylbenzofuran as pale yellow solid.

Method B: From mixed azines, 4a-f

Mixed azine **4** (0.001 mole) and aromatic aldehyde (0.001 mole) were refluxed in ethanol (10 mL) containing two drops of hydrochloric acid for 30 min. The aldazine which separated was collected after washing with ice cold ethanol. Removal of the solvent from the filtrate gave regenerated 2-acetylbenzofuran as pale yellow solid.

The melting points and spectral characterization data of compounds obtained by both the methods were identical and there was no depression in mixed m.p.

Acknowledgement

Authors are thankful to the Head, RSIC, Punjab University Chandigarh, and Head, RSIC, Indian Institute of Technology, Mumbai for providing spectral and microanalysis data.

References

1 Green T W & Wuts P G M, *Protective Groups in Organic Synthesis* (Wiley, New York) **1991**, pp214-215.
2 Hershberg E B, *J Org Chem*, 13, **1948,** 542.
3 Chamberlin E M & Chemerda J M, *J Am Chem Soc*, 77, **1955,** 1221.
4 Royals E E & Horne S E, *J Am Chem Soc*, 73, **1951,** 5856.

5 Herzog H L, Payne C C, Jevnik M A, Gould D, Shapiro E E & Oliveto E P, *J Am Chem Soc,* 77, **1955,** 4781.
6 DePuy C H & Pondev B W, *J Am Chem Soc,* 81, **1959,** 4629.
7 Cava M P, Little R L & Napier D R, *J Am Chem Soc,* 80, **1958,** 2257.
8 Taub D, Hoffsommer R D, Slates H L, Kuo C H & Wendler N L, *J Am Chem Soc*, 82, **1960,** 4012.
9 Pines S H, Chemerda J M & Kolowski M A, *J Org Chem,* 31, **1966,** 3446.
10 Ujjinamatada R K, Appla R S & Agasimundin Y S, *J Heterocyclic Chem,* 43, **2006,** 437.
11 Ujjinamatada R K, Harwalkar G S, Kalyane N & Agasimundin Y S, *Indian J Chem,* 39B, **2000,** 587.
12 Shriner R L & Anderson J, *J Am Chem Soc,* 61, **1939,** 2705.
13 Elderfield R C & Prasad R N, *J Org Chem,* 26, **1961,** 3863.
14 Hegarty F A, Kearney J A, Cashell P A & Scott F L, *J Chem Soc Perkin Trans 2,* **1976,** 242.
15 Smith R F, Albright J A & Waring A M, *J Org Chem,* 31, **1966,** 4100.
16 Callaghan C N, *J Chem Soc Perkin Trans 1,* **1972,** 1416.
17 Taylor E C, Barton J W & Paudler W W, *J Org Chem,* 26, **1961,** 4961.
18 Llyod N F & Thomas C G, *J Am Chem Soc,* 71, **1949,** 633.
19 Brindaban C R & Dipak C S, *J Org Chem,* 53, **1988,** 878.
20 Gatta F & Settimj G, *J Heterocylic Chem,* 21, **1984**, 937; ^{1}H NMR of compound **2** was not reported in this paper.