Conversions of unsymmetrical benzoins in basic media

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Abstract
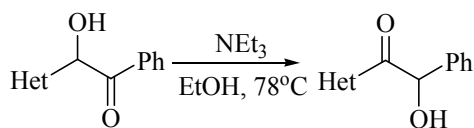
Some factors (temperature, nature of base and solvent) influential in isomerization of unsymmetrical benzoins (*p*-dimethylaminobenzoins and its indole analogues) in basic media are reported and a mechanism of isomerization proposed.

Keywords: Basic catalysis, benzoins, indoles, isomerization, reaction mechanisms

Introduction

Benzoins have found a wide application as synthons in organic synthesis.[1] A particular recent interest in benzoin chemistry has been aroused by using them as model biochemical substrates.[2] One of the most interesting chemical properties of unsymmetrical benzoins is their propensity for isomerizations to give a mixture of isomeric products.[3] The isomerizations of less stable to more stable benzoins were studied in the 1930s.[4] However, the structures of the compounds obtained in these early investigations were established merely by comparing the melting points of the isomeric benzoins. The isomerization mechanism and the factors governing this conversion have also been unclear.

Earlier we used an isomerization of hetaryl analogues of α-benzoins[5] in the preparation of hydroxymethylcarbonyl-substituted derivatives of π-excessive heterocycles (Scheme 1) and found that reaction time increases with decreasing electron-donor ability of a heterocyclic group.[6] The reaction proceeded in the presence of triethylamine in boiling ethanol and did not proceed at r.t.

Het = Pyrrol-2-yl, Pyrrol-3-yl, Indol-3-yl, Furan-2-yl
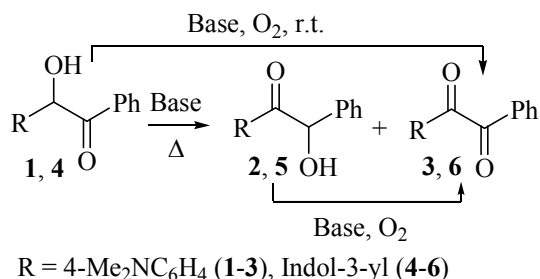
Scheme 1

Results and Discussion

The present study is focused on the effect caused by the nature of base, temperature and solvent on the conversions in basic media of model *p*-dimethylaminobenzoins and indole analogues (Scheme 2, Table 1).

Temperature has been found to be the most significant factor dictating the behavior of α-benzoin **1** in ethanol in the presence of potassium hydroxide. Indeed, the isomerization to β-benzoin **2** proceeds on boiling, in accordance with literature data.[4b] In parallel, **1** and / or **2** oxidizes under the action of potassium hydroxide an air to form benzil **3**. An attempted "isomerization" at r.t. provided the oxidation product **3** and the unreacted starting compound **1** rather than isomer **2**, in contrast to a previous report.[4b] A decrease in the benzoin:KOH ratio gives rise to α-benzoin **1** being completely oxidized to **3** at r.t., the reaction mixture containing no traces of β-isomer **2**. The isomerization **1→2** also does not proceed if the reaction is carried out under argon.

The temperature effect on the reactions of α-benzoin **4** in basic media has been found to be much the same as with α-benzoin **1**.

R = 4-Me$_2$NC$_6$H$_4$ (**1-3**), Indol-3-yl (**4-6**)

Scheme 2

Another factor affecting the α→β isomerization is the nature of the base. The isomerization time is in the inverse to the basicity of a catalyst:

$$AcO^- > Py > CN^- > NEt_3 > HO^- > F^- > t\text{-}BuO^-.$$

α-Benzoin **1** in the presence of triethylamine and pyridine disproportionates leading to bis(*p*-dimethylaminophenyl)benzoylmethane as shown by us.[6b]

The time required for isomerization decreases, with increase in solvent polarity:

$$PhMe > ClCH_2CH_2Cl > MeCN,$$

Table 1. Reaction conditions and product yields for the conversion of unsymmetrical benzoins **1, 2, 4, 5** in basic media
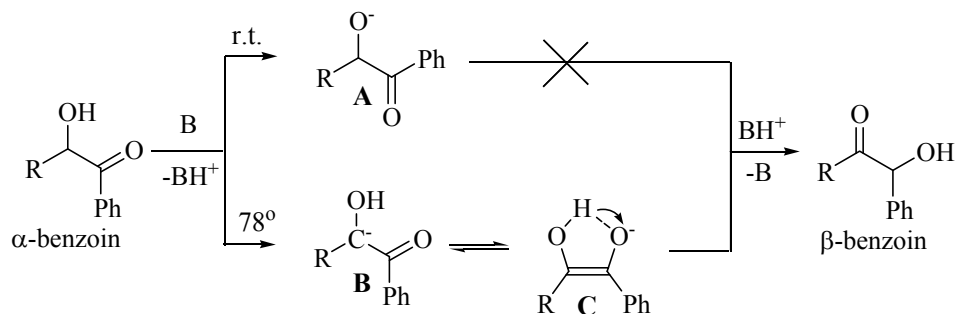
Entry	Starting α-benzoin	Base	Benzoin/ Base	Solvent	t, °C	τ, h[a]	Yields, % benzoin	benzil
1	**1**	KOH	1:1	EtOH	78	2	**2** (70)	**3** (21)
2[4b]	**1**	KOH	1:3	EtOH	78	2	**2**+**3** (75)	
3	**4**	KOH	1:1	EtOH	78	2	**5** (82)	**6** (12)
4	**2**	KOH	1:1	EtOH	78	24	0	**3** (70)
5	**5**	KOH	1:1	EtOH	78	24	0	**6** (60)
6	**1**	KOH	50:1	EtOH	20	48	**1** (80)	**3** (20)
7[4b]	**1**	KOH	50:1	EtOH	20	48	**1** or **2** (40)?	**3** (20)
8	**1**	KOH	1:1	EtOH	20	72	0	**3** (87)
9	**4**	KOH	1:1	EtOH	20	72	0	**6** (73)
10	**2**	KOH	1:1	EtOH	20	72	**2** (20)	**3** (60)
11	**5**	KOH	1:1	EtOH	20	72	**5** (20)	**6** (60)
16	**1**	t-BuOK	1:1	THF	20	0.5	**2** (100)	0
17	**4**	t-BuOK	1:1	THF	20	0.5	**5** (63)	**6** (20)
20	**1**	KF, 18-crown-6	1:1	MeCN	82	1	**2** (75)	**3** (10)
21	**4**	KF, 18-crown-6	1:1	MeCN	82	1	**5** (85)	**6** (5)
24	**1**	NaCN	1:1	EtOH	78	3	**2** (60)	**3** (10)
25	**4**	NaCN	1:1	EtOH	78	4	**5** (78)	**6** (5)
26	**1**	NaOAc	1:1	EtOH	78	3	**2** (82)	**3** (5)
27	**4**	NaOAc	1:1	EtOH	78	6	**5** (70)	**6** (10)
36	**4**	NEt₃	1:1	EtOH	78	3	**5** (85)	**6** (5)
37	**4**		Py		115	5	**5** (70)	**6** (15)
38	**4**	NEt₃	1:1	MeCN	82	2	**5** (93)	0
39	**4**	NEt₃	1:1	ClCH₂CH₂Cl	83	5	**5** (75)	**6** (10)
40	**4**	NEt₃	1:1	PhMe	111	8	**5** (88)	**6** (5)

[a] The reaction time was determined by monitoring the vanishing spot of a starting compound on the TLC (each 30 minutes).

And this we attribute to the increased stability of the charged intermediate in polar media.
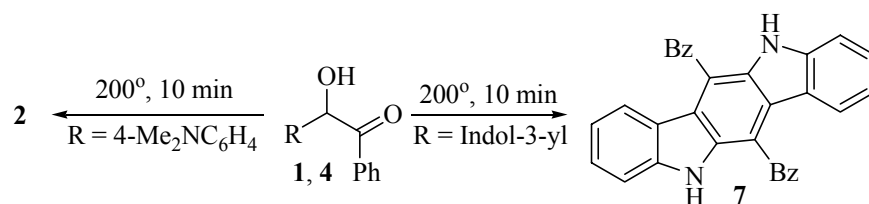
The evidence suggests kinetic and thermodynamic control of the manifold conversions undergone by the isomeric benzoins in basic media (Scheme 3). The hydroxyl proton of benzoins is known[7] to be chelated in solution, which favours its lability. This proton is abstracted first from benzoin by a base at low temperatures. A hydride shift is improbable in the resulting anion

A. At elevated temperatures or with a stronger base, abstraction of the more tightly bound proton from α-benzoin becomes possible, leading to anion **C** that is stabilized by a intramolecular hydrogen bond. It is the thermodynamic preference for the prototropically generated β-isomer that represents the driving force of the α→β isomerization. The reverse proton shift is disadvantageous; therefore α-benzoin does not form on boiling β-benzoin in ethanol with a base.

Scheme 3

Earlier we confirmed this course of intramolecular prototropy at α→β isomerization of *O*-deuterated α-benzoin **4**. The content of deuterium in the isomeric benzoins does not change.[6a] The α→β isomerization *via* keto-enol tautomerism in the absence of a catalyst only occurs at high temperatures, e.g., on heating the melt of **1** at 200˚C. Indol **4** undergoes thermolysis to give a product of electrophilic dimerization indolo[3,2-b]carbazole **7**. β-Benzoins **2**, **5** are stable to these thermolysis conditions.

Scheme 4

Conclusions

The α→β isomerization of unsymmetrical benzoins in basic media has been shown to proceed only on heating and to be favoured by an increase in catalyst basicity, solvent polarity and electron-donor ability of a hetaryl residue.

Experimental Section

General Methods. ^{1}H NMR spectra were recorded in DMSO-d_6 on a Varian VXR-300 instrument with TMS as internal standard. IR spectra were measured with a UR-20 spectrometer in KBr tablets. UV spectra were scanned using a Specord M-40 apparatus with 1-cm path length cuvettes. MS spectra were run at electronic ionization at 70 eV on a MX-1321 spectrometer. To monitor the course of the reactions and to control the product purities, TLC on Silufol-UV-254 plates was performed, using benzene:acetone (5:1) for elution. Composition and structure of products were confirmed by an elemental analysis and spectral data in each experiment. α-Benzoins **1** and **4** were prepared by literature procedures.[5] The physical and spectroscopic data of compounds **2**, **3**,[8] **5**[6] are in agreement with published data.

General procedure of conversions of benzoins (Scheme 2, 4. Table 1) Benzoin (250 mg, 1.00 mmol), with or without base (1.20 mmol), in solvent (4 ml) or melt was kept at indicated temperature or boiled. The solvent was evaporated under vacuum. The residue was recrystallized from ethanol (**1**, **2**) or toluene (**4**, **5**). The filtrate was evaporated under vacuum; the residue of benzil was recrystallized from hexane (**3**) or toluene (**6**). The compound **7** was purified boiling it many times in benzene.

1-(1*H*-Indol-3-yl)-2-phenylethane-1,2-dione (6). Mp 194-195˚C. IR: ν = 3240, 3070, 2950, 1660, 1600, 1577, 1514, 1490, 1456, 1427, 1390, 1310, 1269, 1238, 1150 cm^{-1}. UV (EtOH): λ (lg ε) = 250 (4.15), 319 (3.87) nm. ^{1}H NMR: δ = 7.27 (t, 1H, J = 8.1, H^{6}Ind), 7.32 (t, 1H, J = 8.1, H^{5}Ind), 7.58 (d, 1H, J = 8.1, H^{7}Ind), 7.58 (t, 2H, J = 7.4, H^{3,5}Ph), 7.72 (d, 1H, J = 7.4, H^{4}Ph), 7.97 (d, 2H, J = 7.4, H^{2,6}Ph), 8.13 (d, 1H, J = 3.0, H^{2}Ind), 8.22 (d, 1H, J = 8.1, H^{4}Ind), 12.25 (d, 1H, J = 3.0, H^{1}Ind). MS: *m/z* (%) = 249 M$^+$ (7), 144 (100), 116 (11), 89 (8). Anal. Calcd. for C$_{16}$H$_{11}$NO$_2$: C, 77.10; H, 4.45. Found C, 77.10; H, 4.44.

(11-Benzoyl-6,12-dihydro-6,12-diaza-indeno[1,2-*b*]fluoren-5-yl)phenylmethanone (7). Mp 299-301°C. IR: ν = 3420, 3080, 1695, 1610, 1470, 1333, 1239, 1012 cm^{-1}. UV: λ (lg ε) = 284.8 (4.40) nm. ^{1}H NMR: δ = 6.90 (t, 2H, J = 7.8, H^{3,9}Het), 7.30 (t, 2H, J = 7.8, H^{4,10}Het), 7.31 (d, 2H, J = 7.8, H^{2,8}Het), 7.45 (d, 2H, J = 7.8, H^{5,11}Het), 7.57 (d, 4H, J = 7.8, H^{3,5}Ph), 7.73 (t, 2H, J = 7.8, H^{4}Ph), 7.99 (d, 4H, J = 7.8, H^{2,6}Ph), 11.32 (s, 2H, NH). MS: *m/z* (%) = 464 M$^+$ (100), 359 (5), 245 (19), 179 (10), 105 (46), 77 (24). Anal. Calcd. for C$_{32}$H$_{20}$N$_2$O$_2$: C, 82.74; H, 4.34. Found: C, 82.70; H, 4.25.

Acknowledgements

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