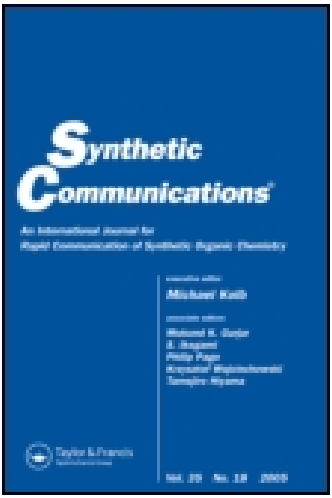

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Isomerization of Hetaryl Analogues of α-Benzoins in Basic Media

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ABSTRACT

The $\alpha \rightarrow \beta$ isomerization of hetaryl analogues of benzoins occurring in basic media on heating is a convenient preparative way to obtain hydroxymethylcarbonyl-substituted derivatives of π-excessive heterocycles. The reaction is favored by increased catalyst basicity, solvent polarity, and the electron-donor ability of a hetaryl residue. At room temperature, oxidation to hetaryl analogues of benzil becomes dominating.

Key Words: Basic catalyst; Benzoins; π-Excessive heterocycles; Isomerization; Solvent polarity.

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INTRODUCTION

Benzoin condensation represents a facile synthetic route to both symmetric and unsymmetric benzoins.[1] Using thiazolium salts as catalysts enabled not only an increase in the total yield and optical purity of benzoins but also an application of the reaction concerned in modeling the enzyme-assisted C—C bond formation in biological systems (where the catalysis is exerted by thiamine diphosphate).[2–11] The research on the benzoin condensation mechanism and the establishment of the fact that the acyl carbanion intermediate is involved in the reaction made it possible to obtain, as a result of a two-step process,[12–17] α-benzoins (less stable than β-isomers), which could not be produced by the classical procedure of the benzoin condensation.[1] However, the yields of the α-benzoins thus prepared are not high, and their hetaryl analogues obtained in this manner include only furan and pyridine derivatives.[17] Aldehydes derived from π-excessive heterocycles are inert under the conditions of the benzoin condensation;[18] that is why the synthesis of pharmacologically active hydroxymethylcarbonyl-substitutedindoles required electrophilic acylation, which subsequently resulted in several auxiliary steps requisite to obtain benzoins.[19,20] 4′-Dimethylaminobenzoin (α-isomer) can be isomerized in conforming β-isomer in the basic media.[1] It was interesting to use $\alpha \rightarrow \beta$-isomerization for obtaining more stable β-benzoins.

RESULT AND DISCUSSION

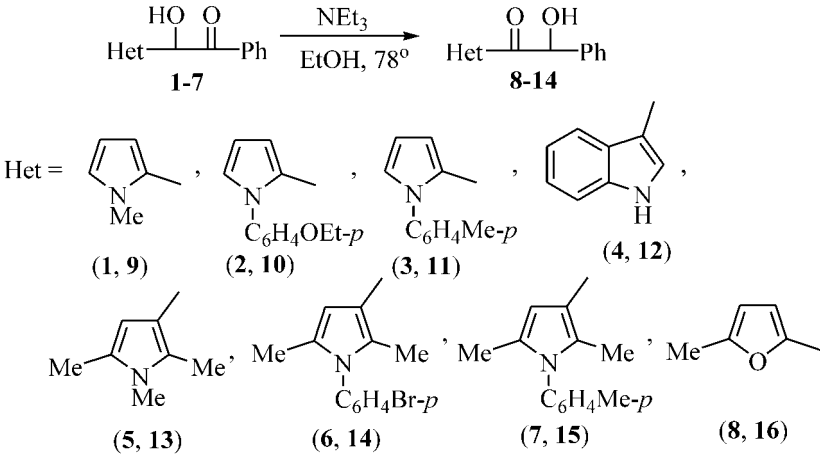
Starting compounds served hetaryl analogues of α-benzoins, which can easily be obtained by hydroxymethylation with arylglyoxals of conforming π-excessive heterocycles.[21]

Isomerization of α-benzoins **1–8** has been found to proceed at the presence of triethylamine as the base in boiling ethanol and to result in conforming hetaryl analogues of benzoins **9–16** with high yields (Sch. 1, Table 1). $\alpha \rightarrow \beta$ Isomerization is also possible in the presence of potassium hydroxide.

A higher thermodynamic stability of the β-isomer resulting from the electron-donor nature of a π-excessive hetaryl residue is a driving force of the isomerization. Thus, the reaction time increases with the decreasing electron-donor ability of a hetaryl group in the series (Sch. 2).

As a consequence of the much lower electron-donor ability of furan compared to pyrrole, α-benzoin **8** is considerably less reactive than **1** and **4**.

By varying substituents at the pyrrole ring and its binding position, we have shown that the isomerization time increases as the electron-donor ability of hetaryl residues reduces in the order shown in Sch. 3.



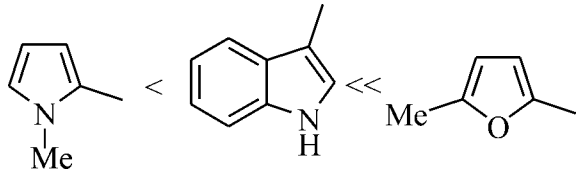
Scheme 1. Izomerization of hetaryl analogues of α-benzoins in basic media.

The highest reactivity is exhibited by α-benzoin **4** in which the reaction center is bound to the most active electron-donor residue. Substituting an alkyl group at the nitrogen atom by a less active electron-donor aryl group results in an increased isomerization time. Because the reaction center is sensitive to the electronic effects of substituents in the aryl ring, the pyrrole derivative **2** is somewhat more reactive than **3**. For α-benzoins **5–7**, the α-hydroxyketone moiety is bound to the less active electron-donor 3-pyrrolyl

Table 1. Times and yields of isomerization of α-benzoins **1–8**.

Starting compound	Product	Time (h)[a]	Yield (%)
1	**9**	1.5	50
2	**10**	3.5	80
3	**11**	4	70
4	**12**	3	85
5	**13**	11.5	64
6	**14**	12	92
7	**15**	12	85
8	**16**	6.5	90

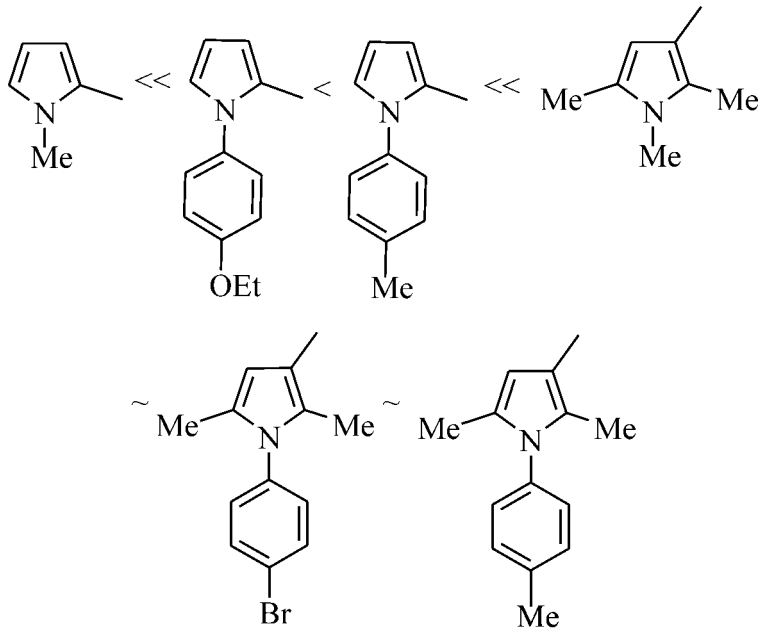
[a]The reaction time was determined by monitoring the vanishing spot of a starting compound on the thin-layer chromatography (TLC) (each 30 min).



Scheme 2.

residue. Therefore, the isomerization proceeds slower, because a substituent at the nitrogen atom has a secondary and, hence, veiled effect.

For the β-benzoins obtained, ^{1}H-NMR doublet signals arising from the *o*-protons of the unsubstituted phenyl ring are shifted 0.5–0.6 ppm upfield from those for initial α-benzoins. Moreover, α- and β-benzoins differ from each other by the characteristic shape of the doublet concerned.[21] These regularities were employed in structural determination of isomeric benzoins.[22] A behavior of α-benzoin **17** in the presence of triethylamine proved to be interesting. Boiling **17** with triethylamine in ethanol finally resulted in product **18**



Scheme 3.

(Sch. 4). A switch from ethanol to aprotic THF or pyridine exerted no effect on the course of the reaction.

Interestingly, the β-benzoin **19** is stable in boiling pyridine.

In conclusion, we have shown that the reaction studied represents a convenient preparative way to obtain hydroxymethylcarbonyl-substituted derivatives of π-excessive heterocycles.

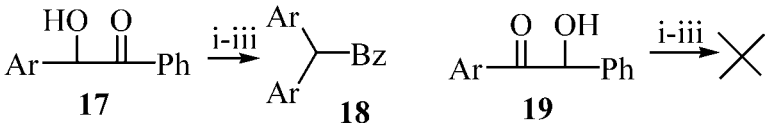
EXPERIMENTAL

Hydrogen nuclear magnetic resonance (^{1}H-NMR) spectra were recorded in DMSO-D_6 on a Varian VXR-300 instrument with tetramethylsilane (TMS) as the internal standard. 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 and iodine vapor for visualization. α-Benzoins **1–8**, **17** were prepared by the procedure in the literature.[21] The physical and spectroscopic data of compounds **18** are in agreement with published data.[21]

General Procedure of Isomerization of Benzoins 1–8 (Table 1)

A solution of benzoin (1.50 mmoles) and base (1.80 mmoles) in ethanol (6 ml) was boiled. The solution obtained was evaporated under vacuum, and the residue was recrystallized. The following β-benzoins were thus obtained:

2-Hydroxy-1-(1-methyl-1H-pyrrol-2-yl)-2-phenyl-ethanone (**9**). Colorless prisms (hexane). M.p. 107–108°C. ^{1}H-NMR: $\delta = 3.84$ (s, 3H), 5.58 (d, $J = 5.7$, 1H), 5.70 (d, $J = 5.7$, 1H), 6.05 (dd, $J = 3.9$, $J = 2.4$, 1H), 7.05 (d, $J = 2.4$, 1H), 7.20 (d, $J = 6.9$, 1H), 7.21 (d, $J = 3.9$, 1H), 7.27 (t, $J = 6.9$, 2H), 7.42 (d, $J = 6.9$, 2H). Anal. Calcd. for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09. Found: C, 72.53; H, 6.10.



i, NEt_3, EtOH, 78°; ii NEt_3, THF, 67°; iii, Py, 115°
Ar = 4-$Me_2NC_6H_4$

Scheme 4.

1-[1-(4-Ethoxy-phenyl)-1H-pyrrol-2-yl]-2-hydroxy-2-phenyl-ethanone (**10**). Straw-colored powder (80% ethanol). M.p. 78–79°C. ^{1}H-NMR: $\delta = 1.40$ (t, $J = 7.0$, 3H), 4.10 (q, $J = 7.0$, 2H), 5.60 (d, $J = 5.6$, 1H), 5.64 (d, $J = 5.6$, 1H), 5.88 (dd, $J = 3.9$, $J = 2.4$, 1H), 6.04 (d, $J = 2.4$, 1H), 6.87 (d, $J = 3.9$, 1H), 7.04 (d, $J = 8.7$, 2H), 7.36 (d, $J = 7.8$, 1H), 7.45 (d, $J = 8.7$, 2H), 7.47 (t, $J = 7.8$, 2H), 7.58 (d, $J = 7.8$, 2H). Anal. Calcd. for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96. Found: C, 74.79; H, 5.99.

2-Hydroxy-2-phenyl-1-(1-*p*-tolyl-1H-pyrrol-2-yl)-ethanone (**11**). Colorless oil (hexane). ^{1}H-NMR: $\delta = 2.38$ (s, 3H), 5.71 (d, $J = 6.3$, 1H), 5.82 (d, $J = 6.3$, 1H), 6.30 (dd, $J = 3.9$, $J = 3.9$, 1H), 6.93 (d, $J = 9.0$, 2H), 7.17 (d, $J = 9.0$, 2H), 7.25 (d, $J = 3.9$, 1H), 7.29 (d, $J = 3.9$, 1H), 7.31 (d, $J = 8.1$, 1H), 7.34 (t, $J = 8.1$, 2H), 7.44 (d, $J = 8.1$, 2H). Anal. Calcd. for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88. Found: C, 78.27; H, 5.59.

2-Hydroxy-1-(1H-indol-3-yl)-2-phenyl-ethanone (**12**). Colorless prisms (toluene). M.p. 194–196°C. ^{1}H-NMR: $\delta = 5.70$ (d, $J = 4.2$, 1H), 5.77 (d, $J = 4.2$, 1H), 7.12 (t, $J = 8.1$, 1H), 7.15 (t, $J = 8.1$, 1H), 7.20 (d, $J = 7.3$, 1H), 7.28 (t, $J = 7.3$, 2H), 7.40 (d, $J = 8.1$, 1H), 7.51 (d, $J = 7.3$, 2H), 8.18 (d, $J = 8.1$, 1H), 8.43 (d, $J = 3.0$, 1H), 11.88 (d, $J = 3.0$, 1H). Anal. Calcd. for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21. Found: C, 76.47; H, 5.21.

2-Hydroxy-2-phenyl-1-(1,2,5-trimethyl-1H-pyrrol-3-yl)-ethanone (**13**). Colorless plates (benzene). M.p. 135–136°C. ^{1}H-NMR: $\delta = 2.08$ (s, 3H), 2.45 (s, 3H), 3.31 (s, 3H), 5.26 (d, $J = 5.7$, 1H), 5.53 (d, $J = 5.7$, 1H), 6.29 (s, 1H), 7.18 (d, $J = 6.9$, 1H), 7.27 (t, $J = 6.9$, 2H), 7.36 (d, $J = 6.9$, 2H). Anal. Calcd. for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04. Found: C, 74.01; H, 7.04.

1-[1-(4-Bromo-phenyl)-2,5-dimethyl-1H-pyrrol-3-yl]-2-hydroxy-2-phenyl-ethanone (**14**). Straw-colored powder (80% ethanol). M.p. 160–161°C. ^{1}H-NMR: $\delta = 1.91$ (s, 3H), 2.25 (s, 3H), 5.39 (d, $J = 5.7$, 1H), 5.55 (d, $J = 5.7$, 1H), 6.44 (s, 1H), 7.22 (d, $J = 7.5$, 1H), 7.23 (d, $J = 8.4$, 2H), 7.31 (t, $J = 7.5$, 2H), 7.42 (d, $J = 7.5$, 2H), 7.68 (d, $J = 8.4$, 2H). Anal. Calcd. for $C_{20}H_{18}BrNO_2$: C, 62.51; H, 4.72. Found: C, 62.53; H, 4.71.

1-(2,5-Dimethyl-1-*p*-tolyl-1H-pyrrol-3-yl)-2-hydroxy-2-phenyl-ethanone (**15**). Straw-colored powder (80% ethanol). M.p. 126–127°C. ^{1}H-NMR: $\delta = 1.89$ (s, 3H), 2.24 (s, 3H), 2.40 (s, 3H), 5.29 (d, $J = 6.3$, 1H), 5.52 (d, $J = 6.3$, 1H), 6.37 (s, 1H), 7.09 (d, $J = 8.1$,

2H), 7.21 (d, $J = 6.9$, 1H), 7.28 (d, $J = 8.1$, 2H), 7.30 (t, $J = 6.9$, 2H), 7.41 (d, $J = 6.9$, 2H). Anal Calcd. for $C_{21}H_{21}NO_2$: C, 78.97; H, 6.63. Found: C, 78.98; H, 6.65.

2-Hydroxy-1-(5-methyl-furan-2-yl)-2-phenyl-ethanone (**16**). Colorless needless (ethanol). M.p. 150–151°C. ^{1}H-NMR: $\delta = 2.33$ (s, 3 H), 5.63 (d, $J = 3.9$, 1H), 5.94 (d, $J = 3.9$, 1H), 6.24 (d, $J = 3.0$, 1H), 7.21 (d, $J = 7.5$, 1H), 7.29 (t, $J = 7.5$, 2H), 7.43 (d, $J = 7.5$, 2H), 7.46 (d, $J = 3.0$, 1H). Anal. Calcd. for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 72.19; H, 5.62.

2,2-*Bis*-(4-dimethylamino-phenyl)-1-phenyl-ethanone (**18**). A solution of α-benzoin 1 (250 mg, 1.00 mmol) with or without triethylamine (0.17 mL, 1.20 mmol) in corresponding (Scheme 4) solvent (4 mL) was boiled for 2 h. The precipitating product **18** on cooling was recrystallized from ethanol. Yield 96%. Yellow needless. M.p. 167–168°C.

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