ARYLBENZOINS

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Unsymmetrical arylbenzoins and aryl(heteryl)benzoins exist in two isomeric forms, α -benzoins and β -benzoins for example aryl(furyl)benzoins **1a** and **1b** (Scheme 1, Ar = 4-ClC₆H₄), possess different stability.



The development of efficient and general methodology for the synthesis of α -functionalized α -(indol-3-yl) ketones is highly desirable now. These compounds become relevant precursors for the preparation of biologically active molecules. It was firstly shown by Zhungietu that phenylglyoxal hydrate and 2-thienylglyoxal hydrate react with indole in boiling PhH giving as products stable α -ary(indol-3-yl)benzoins **2a,b** (Scheme 2, i). Also Zhungietu had reported that indole non reacted with 4-methoxyphenylglyoxal in boiling PhH, and with 4-chlorophenylglyoxal yields the adduct 2:1, none α -benzoin **2d**. Recently China's chemists has reported that indole reacted with arylglyoxals in 1,4-dioxane solution at the CuCl₂ presence at room temperature forming α -ary(indol-3-yl)benzoins **2a–h** with good yields Scheme 2 (i – PhH, 80°C; ii – PhH, 20°C; iii – 1,4-dioxane, CuCl₂, 25 °C; iv – AcOH, 18°C).



Ar = Ph(2a), 2-thienyl(2b),4-MeC6H4 (2c), 4-ClC6H4 (2d), 4-BrC6H4(2e), 4-FC6H4(2f), 4-O2NC6H4(2g), 4-MeOC6H4 (2h)

We had synthesized known α -benzoins **2a** and **2b** with moderate yields by reaction of indole with proper arylglyoxals in PhH at rt (Scheme 2, ii) or in AcOH at rt (Scheme 2, iv). α -Aryl(indolyl)benzoin **2c** has been synthesized in boiling PhH accordingly Zhungietu (Scheme 2, i). α -Aryl(indolyl)benzoins **2d**, **e** had been synthesized as by known method (Scheme 2, i), as in AcOH at rt during 1 h (Scheme 2, iv). α -(4-Fluorophenyl)(indolyl)benzoin **2f** was obtained by 4-fluorophenylglyoxal

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itnteraction with indole in PhH at rt (Scheme 2, ii). α -(4-Nitrophenyl)(indolyl)benzoin **2g** was obtained by interaction of 4-nitrophenylglyoxal hydrate with indole in acetic acid at 19°C during no more than 1 h. α -(4-Methoxyhenyl)(indolyl)benzoin **2h** was synthesized with moderate yield by 4-methoxyphenylglyoxal hydrate interaction with indole in boiling PhMe. In al cases CuCl₂ presence was not necessary. We have found that α -benzoins, **2** readily isomerise into β -benzoins **3** in presence of bases (Et₃N (i), EtONa in EtOH (ii)) (Scheme 3, Ar = Ph (**a**), 2-thienyl (**b**), 4-ClC₆H₄(**d**), 4-Br-C₆H₄(**e**)).



Structure of isomeric α -aryl(indolyl)benzoins **2** and β -aryl(indolyl)benzoins **3** was confirmed by data of ¹H and ¹³C NMR spectra and mass spectra. In ¹H NMR spectra of compounds **3** the chemical shifts of C(2)H indolyl proton and NH proton lie in more low field then chemical shifts of proper protons of α -benzoins **2**. Probably, this phenomenon is caused by conjugation of indol-3-yl moiety with carbonyl group in β -benzoins **3** (Table 1).

Table 1. The characteristic ¹H NMR chemical shifts (ppm) of α -aryl(indolyl)benzoins **2** and β -aryl(indolyl)benzoins **3** in (CD₃)₂SO

α-benzoins			β-benzoins		
Ar	C(2) _{ind} H	NH	Ar	C(2) _{ind} H	NH
Ph (2a)	7.355	11.075	Ph (3a)	8.544	11.984
2-C ₄ H ₃ S (2b)	7.411	11.085	2-C ₄ H ₃ S (3b)	8.563	12.042
$4-ClC_{6}H_{4}(2d)$	7.334	11.077	$4-ClC_{6}H_{4}(3d)$	8.58	12.04
$4-BrC_{6}H_{4}(2e)$	7.3285	11.073	$4-BrC_{6}H_{4}(3e)$	8.564	12.025

In ¹³C MR spectra of α -aryl(indolyl)benzoins **2** and β -aryl(indolyl)benzoins **3** the characteristic carbon shifts are shifts of CHOH carbon and C=O carbon atoms (Table 2). In compounds **3** shift of C=O carbon lies in some upper field than of C=O carbon of α -benzoins **2** due to more conjugation of C=O group with 3-indolyl moiety. Shift of CHOH carbon for β -aryl(indolyl)benzoins **3** is observed in some lower field than that of α -aryl(indolyl)benzoins **2**. MS spectra of α - and β -aryl(indol-3-yl)benzoins also have some substantial distinctions.

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Table 2. The characteristic ¹³C NMR chemical shifts (ppm) of α -aryl(indolyl)benzoins 2 and β -aryl(indolyl)benzoins 3 in (CD₃)₂SO

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α-benzoins			β-benzoins			
Ar	CHOH	C=O	Ar	CHOH	C=O	
Ph (2a)	69.5	199.0	Ph (3a)	76.2	194.3	
2-C ₄ H ₃ S (2b)	70.8	192.3	2-C ₄ H ₃ S (3b)	72.4	193.1	
$4-ClC_{6}H_{4}(2d)$	69.7	197.8				
$4-BrC_{6}H_{4}(2e)$	69.7	198.2	$4-BrC_{6}H_{4}(3e)$	75.5	194.0	
$4-O_2NC_6H_4(2g)$	70.3	198.2				

Thus the synthetic route to β -aryl(indol-3-yl)benzoins **3** had been proposed.