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Microwave-promoted synthesis of polyhydroxydeoxybenzoins in ionic liquids

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Abstract—A microwave-promoted synthesis of polyhydroxydeoxybenzoins and -phenylpropanones has been developed, using bis{(trifluoromethyl)sulfonyl}amine ($HNTf_2$) or $BF_3{\cdot}OEt_2$ in an ionic liquid solvent.
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Microwave irradiation as an energy source provides a powerful tool for synthetic work. Under microwave heating of dipolar or ionic solvent mixtures, the energy can be transferred to the reaction media via two mechanisms—dipole rotation and ionic conduction. The use of ionic liquids as solvents therefore makes them highly suitable media for energy transfer as both mechanisms for energy absorption can operate.[1]

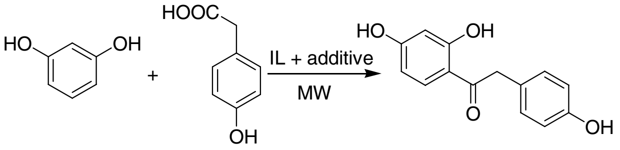
Recently, certain polyhydroxydeoxybenzoins (1,2-diarylethanones) were reported to possess considerable selectivity and transcriptional bias towards the estrogen receptor β, and were considered to constitute a promising new class of ERβ-biased phytoestrogens.[2] Deoxybenzoins are traditionally produced by the laborious and time-consuming Hoesch reaction, where HCl gas is bubbled into the reaction mixture for several hours.[3] Although other methods exist for the synthesis of deoxybenzoins, they are not generally applicable to the polyhydroxy derivatives unless protection/deprotection sequences are used.[4]

Friedel–Crafts (FC) acylation in ionic liquid (IL) solvents has been extensively studied,[5] using catalysts such as chloroaluminate-,[6] chloroferrate-[7] and chloroindate-ILs,[8] zeolites,[9] triflate salts,[10] bismuth derivatives,[11] $HNTf_2$ or metal sulfonamides.[12] The product ketones were simple representative acetophenones or benzophenones, and no deoxybenzoins, hydroxy substituted or otherwise, appear to have been studied.

We report here the synthesis of polyhydroxydeoxybenzoins using various ionic liquid reaction media under microwave irradiation.

The activity of various ionic liquid/acidic additive systems was assessed in the synthesis of 2,4,4′-trihydroxydeoxybenzoin **1** (Scheme 1, Table 1). In addition to the additive, 1-butyl-3-methylimidazolium chloride–indium(III) chloride ([bmim]Cl–$InCl_3$) and $HNTf_2$, $BF_3{\cdot}OEt_2$ was also included, even though the reagent cannot be recycled after isolation of the product. However, $BF_3{\cdot}OEt_2$ in [bmim][BF_4] (entry 5) showed the highest conversion and isolated yield although in order to achieve complete reaction it was necessary to use it in a stoichiometric amount. Comparable yields were also obtained using a substoichiometric amount of the Brønsted acid $HNTf_2$ in [bmim][NTf_2] (entry 2). $Co(NTf_2)_2$, in either solvent, gave only marginally higher yields than the reactions with no catalyst at all (10–20%).

The use of 0.5 molar equiv of [bmim][NTf_2] gave optimal yields of compound **1** as higher ratios interfered with



Scheme 1. Synthesis of 2,4,4′-trihydroxydeoxybenzoin **1**.

Keywords: Microwave; Friedel–Crafts reaction; Ionic liquids; Polyhydroxydeoxybenzoins.

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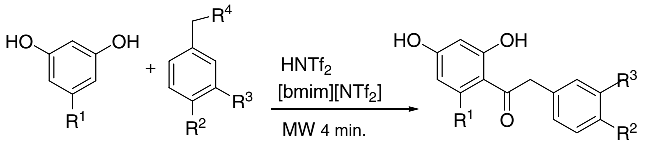
Table 1. Comparison of different reaction media in the synthesis of 2,4,4′-trihydroxydeoxybenzoin (Scheme 1)[13]

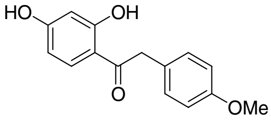
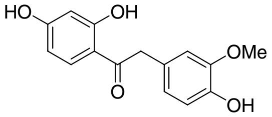
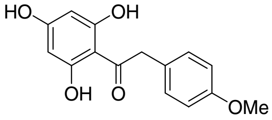
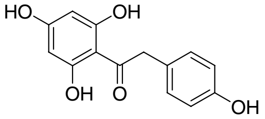
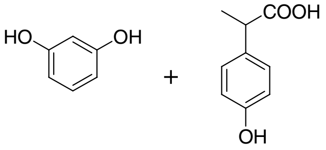
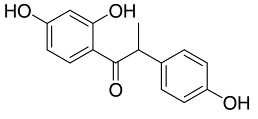
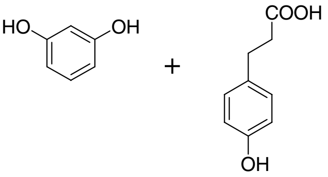
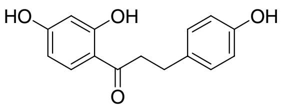
Entry	Solvent/additive, ratio[a]	T (°C)	t (min)	Yield (%) (conversion by ^{1}H NMR)
1	$[bmim]Cl–InCl_3$, 0.6:2.0	100	6	60 (67)
2	$[bmim][NTf_2]/HNTf_2$, 0.5:0.3	90	4	73 (85)
3	$[bmim][NTf_2]/HNTf_2$, 0.5:0.3	100	120[b]	70 (85)
4	$[bmim][BF_4]/HNTf_2$, 1:0.3	120	4	30 (40)
5	$[bmim][BF_4]/BF_3{\cdot}OEt_2$, 2:1	100	4	88 (93)

[a] Relative to 1 equiv of substrate.

[b] Conventional heating.

Table 2. $HNTf_2$ Mediated synthesis of polyhydroxydeoxybenzoins, *O*-demethylangolensin **6** and polyhydroxyphenylpropanone **7**



Entry	Starting materials				Yield (%) (conversion by ^{1}H NMR)	Product
	R^1	R^2	R^3	R^4		
1[a]	H	OMe	H	COOH	74 (85)	 **2**
2[a]	H	OH	OMe	COOH	70 (74)	 **3**
3[b]	OH	OMe	H	CN	73 (88)[c]	 **4**
4[b]	OH	OH	H	CN	65 (77)[c]	 **5**
5[a]					55 (70)	 **6**
6[a]					60 (75)	 **7**

[a] $[bmim][NTf_2]/HNTf_2$ 0.5:0.5, at 90 °C.

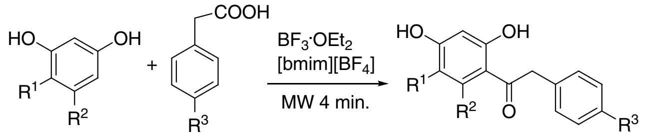
[b] $[bmim][NTf_2]/HNTf_2$ 0.5:1.0, at 90 °C.

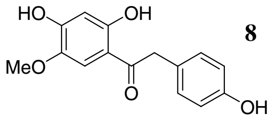
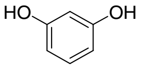
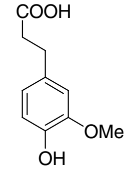
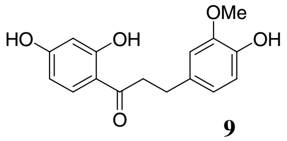
[c] Conversion by ^{1}H NMR to the intermediate imino compound.

isolation procedures. The mechanism of action of $HNTf_2$ in FC reactions probably depends on its superacidic nature, as previously stated in similar cases in the literature.[14] When the solvent was changed to $[bmim][BF_4]$ (entry 4), $HNTf_2$ probably reacted with the ionic liquid, undergoing anion exchange, which produced a less acidic solution, and thus reduced the reaction rate. The $[bmim]Cl–InCl_3$ system (entry 1) appeared to be less active possibly due to the hydrophilicity of the ionic liquid. However, isolation and purification of the compound from chloroindate(III) ionic liquid was straightforward and no additional purification was required.

Additional polyhydroxydeoxybenzoins were readily prepared from arylacetic acids and resorcinols by $HNTf_2$ or $BF_3{\cdot}OEt_2$ catalysis as shown in Tables 2 and 3. A

Table 3. $BF_3{\cdot}OEt_2$ Mediated synthesis of polyhydroxydeoxybenzoins and a polyhydroxyphenylpropanone in [bmim][BF_4]



Entry	Starting materials			Yield (%)	Product
	R^1	R^2	R^3		
1[a]	OMe	H	OH	85	 **8**
2[a]	H	OH	OH	67	**5**
3[a]	H	OH	OMe	54	**4**
4[b]				88	 **9**

[a] [bmim][BF_4]/$BF_3{\cdot}OEt_2$ 4:2, at 90 °C.
[b] [bmim][BF_4]/$BF_3{\cdot}OEt_2$ 2:1, at 90 °C.

Hoesch-type reaction using arylacetonitriles gave 2,4,6-trihydroxy-4′-methoxy- and 2,4,6,4′-tetrahydroxydeoxybenzoins (**4** and **5**, respectively) in ionic solvent. The intermediate imino compound was hydrolysed by the addition of aqueous acid to the reaction medium. The homologous 1,2- and 1,3-diarylpropanones **6**, **7** and **9** are also available by our method. Unfortunately, the isolation of compound **6** (entry 5) was not as straightforward as for other compounds in Table 2. The isolation of pure material required flash column chromatography of the crude reaction product. This also made recycling of the ionic liquid difficult. Normally the ionic liquid solvent [bmim][BF_4] can be recovered in >90% yield, and pure by ^{1}H NMR analysis.

A key starting material for the phytoestrogen glycitein, 2,4,4′-trihydroxy-5-methoxydeoxybenzoin **8**, has been previously prepared using either the Hoesch[15] or FC reaction.[16] In the latter case, the reaction of 4-methoxyresorcinol and 4-hydroxyphenyl acetic acid with $BF_3{\cdot}OEt_2$ as solvent and catalyst was reported to give **8** as a 'dark yellow oil', in 77% yield. This contrasts with the present synthesis where an 88% yield of **8** was obtained as a crystalline compound.[17]

In summary, we have developed an expedient synthesis, involving microwave irradiation in combination with an ionic liquid/acidic additive system, of several polyhydroxydeoxybenzoins and arylpropanones, circumventing any protection/deprotection sequences, the use of volatile organic compounds and with minimum purification to yield the title compounds. Other green chemistry considerations satisfied in our synthesis are very short reaction times and moderate temperatures, thus requiring much lower energy input, and the ready recyclability of the reaction solvent.

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