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Ionic liquid promoted interrupted Feist–Benary reaction with high diastereoselectivity

Brindaban C. Ranu *, Laksmikanta Adak, Subhash Banerjee

Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Kolkata 700 032, India

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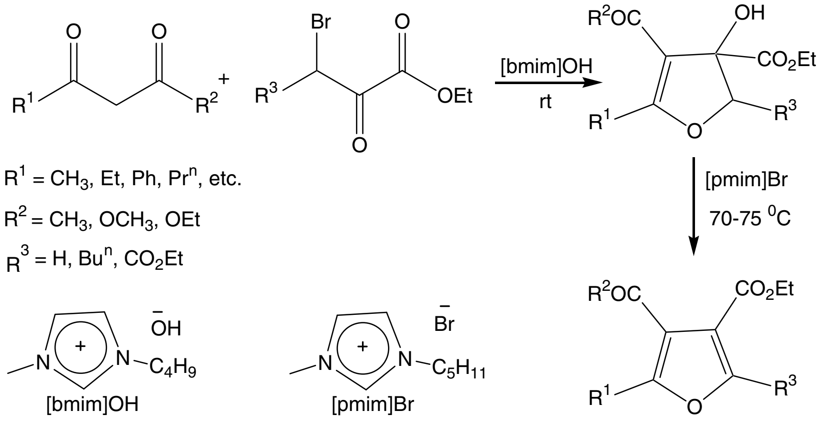
ABSTRACT

A basic ionic liquid, 1-butyl-3-methylimidazolium hydroxide promotes the interrupted Feist–Benary reaction at room temperature under organic solvent-free conditions to produce a variety of substituted hydroxydihydrofurans. The hydroxydihydrofurans are converted to furans (Feist–Benary products) using the ionic liquid, 1-methyl-3-pentylimidazolium bromide at 70–75 °C. The reactions are very clean, high yielding and highly stereoselective.

The Feist–Benary (FB) reaction, discovered over a century ago,[1] is a very useful reaction for the construction of highly substituted furan derivatives via condensation of β-dicarbonyl compounds with α-haloketones in the presence of a base. If this reaction is stopped at the hydroxydihydrofuran stage using a milder base, it is called the 'Interrupted Feist–Benary' (IFB) reaction. The IFB reaction is important for an easy access to substituted dihydrofurans which are constituents of many natural products arising from plants and marine organisms with promising biological activities.[2] However, only a limited number of methods are available for FB and IFB reactions.[3]

Ionic liquids have been the subject of considerable interest because of their roles as 'green' reaction media[4] and efficient catalysts.[5] As a part of our continuing programme to explore ionic liquid promoted novel reactions,[6] we discovered that a basic ionic liquid, 1-butyl-3-methylimidazolium hydroxide, [bmim]OH



Scheme 1.

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* Corresponding author. Tel.: +91 33 24734971; fax: +91 3324732805.
E-mail address: ocbcr@iacs.res.in (B. C. Ranu).

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Table 1
Synthesis of hydroxydihydrofurans catalyzed by the basic ionic liquid [bmim]OH

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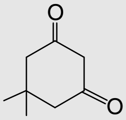
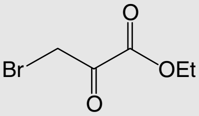
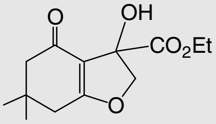
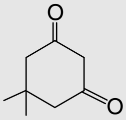
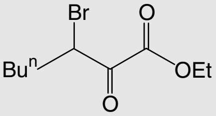
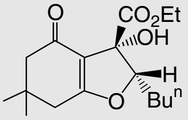
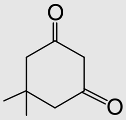
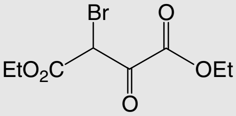
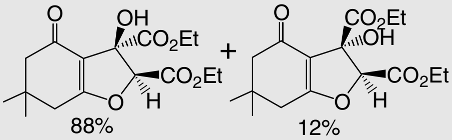
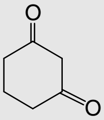
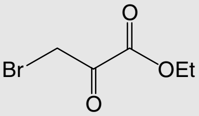
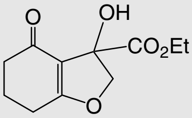
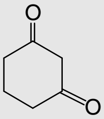
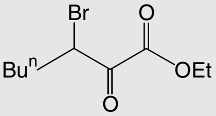
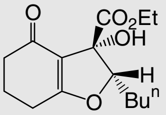
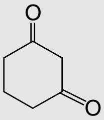
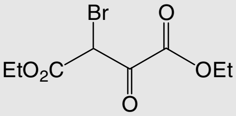
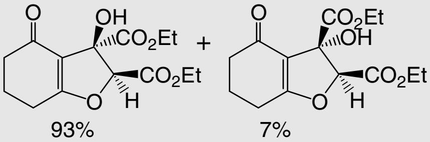
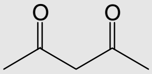
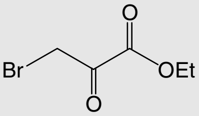
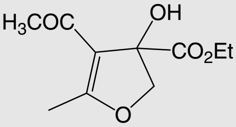
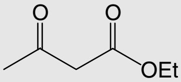
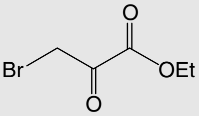
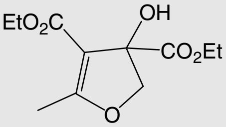
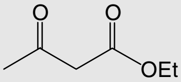
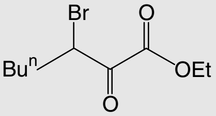
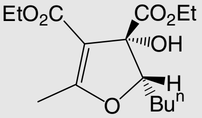
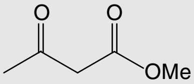
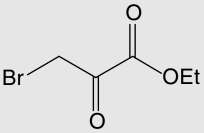
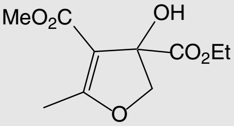
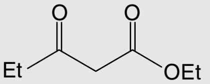
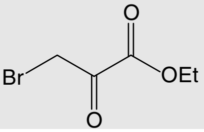
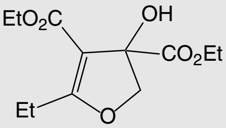
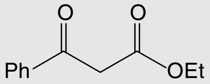
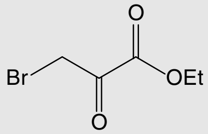
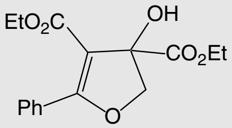
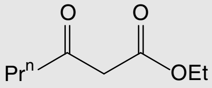
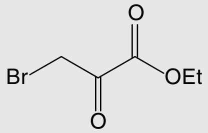
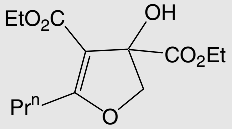
1			0.5		90	
2			2.0		82	
3			4.0		70	
4			0.5		88	3f
5			1.5		78	
6			4.0		68	
7			0.5		85	3e
8			1.5		80	
9			3.0		72	
10			1.5		78	
11			2.0		75	

Table 1 (*continued*)

Entry	1,3-Dicarbonyl compound	α-Bromoketone	Time (h)	Product	Yield[a] (%)	Ref.
12			4.0		60	
13			3.5		70	

[a] Yield refers to that of pure isolated product characterized by spectroscopic data (IR, ^{1}H and ^{13}C NMR and HRMS).

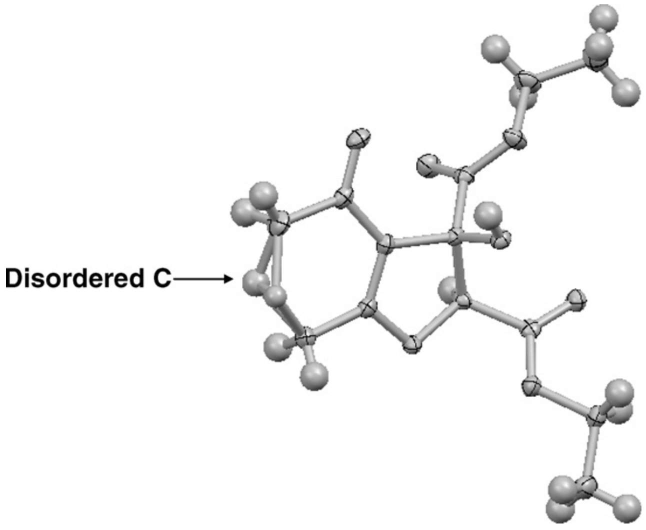


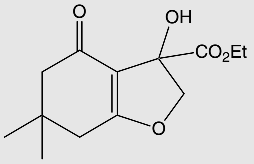
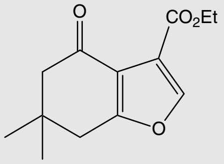
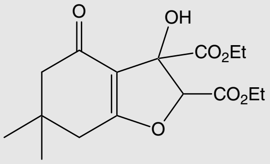
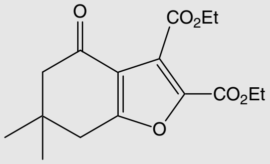
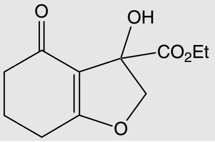
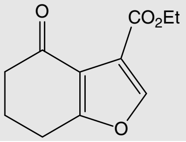
Figure 1. ORTEP diagram of the hydroxydihydrofuran in entry 6, Table 1.

promotes the condensation of β-dicarbonyl compounds with α-haloketones to furnish hydroxydihydrofurans at room temperature. The hydroxydihydrofurans are converted to the corresponding furan derivatives (FB products) using [pmim]Br, 1-methyl-3-pentylimidazolium bromide at 70–75 °C (Scheme 1).

The experimental procedure is very simple.[7] A mixture of β-dicarbonyl compound and α-bromopyruvate was stirred at room temperature for the required period of time (TLC) in the presence of [bmim]OH; work-up provided the hydroxydihydrofuran. In a separate experiment, heating the hydroxydihydrofurans at 70–75 °C in the presence of another ionic liquid, [pmim]Br, gave the corresponding furans after work-up.

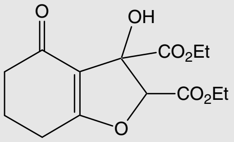
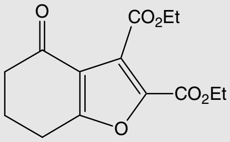
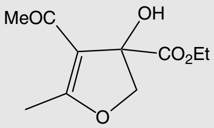
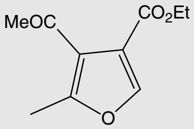
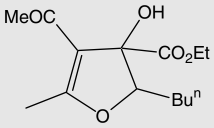
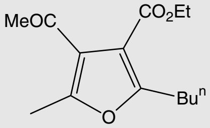
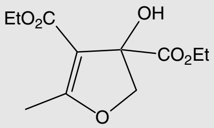
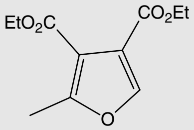
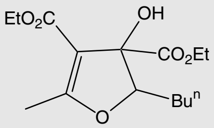
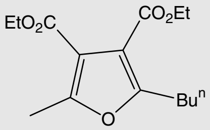
Several cyclic and acyclic β-diketones and β-keto-carboxylic esters underwent the condensation reaction with unsubstituted or substituted α-bromoethyl pyruvates via this procedure to produce the corresponding substituted hydroxydihydrofurans. The results are summarized in Table 1. As is evident from the results in Table 1, excellent stereoselectivity was achieved in reactions with substituted α-bromocarbonyl compounds (entries 2, 3, 5, 6 and 9, Table 1). The X-ray crystallographic analysis of the major (93%) isomer of the hydroxydihydrofuran, obtained from the reaction in entry 6

Table 2
Synthesis of substituted furans from hydroxydihydrofurans catalyzed by [pmim]Br

Entry	Substrate	Time (h)	Product	Yield[a] (%)	Ref.
1		4.0		85	9
2		6.0		60	
3		4.0		84	9

(*continued on next page*)

Table 2 (*continued*)

Entry	Substrate	Time (h)	Product	Yield[a] (%)	Ref.
4		6.0		75	
5		3.0		95	
6		4.5		88	10
7		4.0		90	11
8		5.0		80	10

[a] Isolated yields of pure products characterized by IR, ^{1}H and ^{13}C NMR and HRMS spectroscopic data.

showed the two carboxylic ester groups at C2 and C3 in *anti* orientation (Fig. 1)[8] resulting in cis stereochemistry. The ratio of isomers (93:7) was determined by GC and ^{1}H NMR. By analogy and through comparison of ^{1}H NMR spectra[3d–f] the products in entries 2, 3, 5 and 9 were also assigned cis stereochemistry. In all these reactions the cis-isomer was formed selectively. Significantly, the cis product obtained by condensation of 1,3-cyclohexadione and bromooxaloacetate (Table 1, entry 6) via our procedure is in contrast to the trans isomer (major) reported earlier from the same reaction using Et_3N and CH_2Cl_2.[3d]

The hydroxydihydrofurans (IFB products, Table 1), when heated at 70–75 °C in the presence of [pmim]Br for the appropriate period of time (TLC) furnished the corresponding furans by dehydration. The results are presented in Table 2. Interestingly, the use of [bmim]OH in place of [pmim]Br failed to produce any dehydrated furan product. On the other hand, the use of [pmim]Br in place of [bmim]OH in the initial condensation of the β-dicarbonyl compound and α-bromopyruvates did not stop at the IFB stage and instead afforded the FB products. In this case, the reactions were not clean and were not successful for substituted α-bromopyruvates.

In general, the reactions (Tables 1 and 2) are very clean, reasonably fast and high yielding compared to those of other procedures.[3] The interrupted Feist–Benary reaction is believed to proceed through the usual pathway as with other bases.[3] The ionic liquid, [bmim]OH works here as a base, reaction medium and HBr quencher. The dehydration of the IFB product upon heating in the presence of [pmim]Br leading to aromatization is straightforward.

In conclusion, the present procedure using the ionic liquid, [bmim]OH provides an efficient route to highly substituted Interrupted Feist–Benary hydroxydihydrofuran derivatives. The hydroxydihydrofurans are converted to furans (Feist–Benary products) using another ionic liquid, 1-methyl-3-pentylimidazolium bromide at 70–75 °C. The significant advantages offered by this procedure are room temperature operation, considerably fast reaction, high yields and excellent cis stereoselectivity for the IFB products. To the best of our knowledge, this is the first report of an interrupted Feist–Benary reaction using an ionic liquid and avoiding hazardous bromine as a reagent.[3d]

Acknowledgements

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Supplementary data

The characterization data (IR, ^{1}H NMR, ^{13}C NMR, HRMS) of new compounds (Table 1, entries 2, 3, 5, 6, 8–13 and Table 2, entries 2, 4, 5). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.05.083.

References and notes

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7. *Representative procedure for the interrupted Feist–Benary reaction using [bmim]OH (Table 1, entry 1).* A mixture of dimedone (140 mg, 1 mmol), ethyl 3-bromopyruvate (234 mg, 1.2 mmol) and 1-butyl-3-methylimidazolium hydroxide[6b] (235 mg, 1.5 mmol) was stirred at room temperature (25–30 °C) for 0.5 h (TLC). The reaction mixture was extracted with ethyl acetate (3×10 mL) and the extract was washed with brine (2×5 mL) and dried (Na_2SO_4). Evaporation of the solvent left a crude product which was purified by column chromatography over silica gel (ethyl acetate–hexane 2:3) to afford the pure product, 3-hydroxy-6,6-dimethyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-3-carboxylic acid ethyl ester (228 mg, 90%) as a low melting solid; IR (neat) 3445, 2960, 2874, 1737, 1699, 1456, 1080 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (s, 3H), 1.08 (s, 3H), 1.19 (t, J = 7.11 Hz, 3H), 2.09-2.4 (m, 4H), 3.63 (br s, 1H), 4.12–4.28 (m, 2H), 4.45 (d, J = 10.6 Hz, 1H), 4.68 (d, J = 10.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 28.3, 29.2, 34.9, 38.2, 51.2, 63.2, 80.1, 83.8, 116.1, 172.9, 180.2, 193.8; HRMS *m/z* calcd for $C_{13}H_{18}O_5$ $[M+Na]^+$: 277.1154; found: 277.1149.

   This procedure was followed for all the reactions (for the entries 3 and 6, Table 1, bromocarbonyl compound was added after 5 min). Although this procedure was based on mmol scale, the reaction was also carried out on multigram quantities without any difficulty. Some of these products (Table 1, entries 4 and 7) are known compounds and were identified by comparison of their spectroscopic data (IR, ^1H and ^{13}C NMR) with those reported (see references in Table 1). The unknown compounds (Table 1, entries 1–3, 5, 6, 8, 9–13) were characterized from spectroscopic data (IR, ^1H and ^{13}C NMR, HRMS) (see Supplementary data).

   Representative procedure for the synthesis of furan derivatives from IFB products (Table 1) using 1-methyl-3-pentylmidazolium bromide, [pmim]Br (Table 2, entry 1). A well-stirred mixture of 3-hydroxy-6,6-dimethyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-3-carboxylic acid ethyl ester (254 mg, 1 mmol) and [pmim]Br (117 mg, 0.5 mmol) was heated at 70–75 °C for 4 h(TLC). The reaction mixture was extracted with ethyl acetate (3×10 mL) and the extract was washed with brine (2×5 mL) and dried (Na_2SO_4). Evaporation of the solvent left a crude product which was purified by column chromatography over silica gel (ethyl acetate–hexane 2:3) to afford the pure product, 6,6-dimethyl-4-oxo-4,5,6,7-tetrahydrobenzofuran-3-carboxylic acid ethyl ester (200 mg, 85%) as a colorless liquid which was identified by comparison of its spectroscopic data with those reported.[9]

   All the other reactions were carried out following this procedure. The known compounds were identified by comparison of their spectroscopic data with those reported (see references in Table 2) and unknown products were characterized from spectroscopic data (IR, ^1H and ^{13}C NMR, HRMS) (see Supplementary data).
8. Single crystal X-ray diffraction (ccdc No. CCDC 684381): Crystal data for: $C_{14}H_{16}O_7$, FW = 296.27. monoclinic, $P2_1/c$, a = 12.0874(11), b = 8.3643(8), c = 14.1378(13), β = 95.2730(10), V = 1423.3(2) Å^3, D_c = 1.383 g cm^{-3}, $F(000)$ = 624, T = 100(2) K, final residuals (for 254 parameters) were R_1 = 0.0407 for 2270 reflections with $I > 2\sigma(I)$ and R_1 = 0.0443, wR_2 = 0.1206, GOF = 1.069 for all 5189 reflections. X-ray single crystal data were collected using Mo Kα (λ = 0.7107 Å) radiation on a SMART APEX diffractometer equipped with a CCD area detector. The structure was solved by direct methods and refined in a routine manner. C(7) was found to be disordered between two positions and was refined using the second variable (FVAR) facility of SHELXTL software.
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