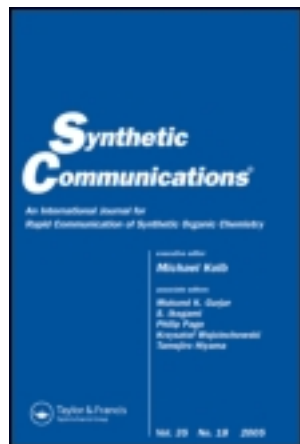




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Highly Efficient Synthesis of 1,3-Dioxanes via Prins Reaction in Brønsted-Acidic Imidazolium Ionic Liquid

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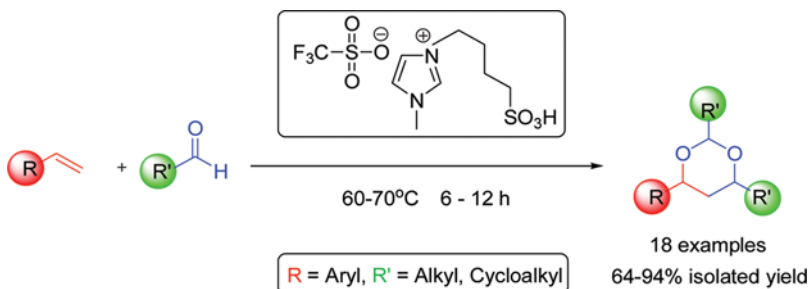
HIGHLY EFFICIENT SYNTHESIS OF 1,3-DIOXANES VIA PRINS REACTION IN BRØNSTED-ACIDIC IMIDAZOLIUM IONIC LIQUID

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GRAPHICAL ABSTRACT



Abstract The high-yielding synthesis of a wide variety of 1,3-dioxanes via the Prins reaction under mild conditions has been demonstrated using Brønsted-acidic imidazolium ionic liquid [bmim(SO₃H)][OTf] or bmimOTf. The use of ionic liquid makes this synthesis simple, convenient, cost-effective, and environmentally friendly. Furthermore, bmimOTf was conveniently separated from the products and can be easily recycled for the Prins reaction with excellent yields. This method works well with a variety of aliphatic aldehydes including formaldehyde, acetaldehyde, propionaldehyde, and cyclohexanecarboxaldehyde.

[Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications[®] for the following free supplemental resource(s): Full experimental and spectral details.]

Keywords Aldehydes; dioxanes; ionic liquids; Prins reaction; styrenes

INTRODUCTION

Dioxanes are a common structural motif present in several bioactive molecules such as (+)-dactylolide, derivatives of 2-substituted-1,3-dioxanes, and

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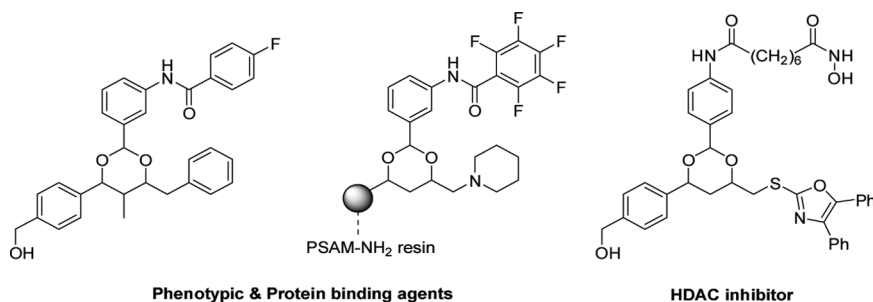


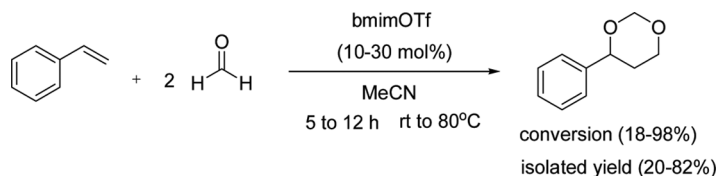
Figure 1. Structures of some biologically active 1,3-dioxanes.

novel activators of the lipoprotein receptor (+)-SCH-351448.^[1–3] Recently 1,3-dioxanes have been evaluated as effective modulators for multidrug resistance,^[4] phenotypic and protein binding agents,^[5,6] and histone deacetylase (HDAC) inhibitors^[7] (Fig. 1).

Traditionally, dioxanes could be obtained via the Prins reaction, which is an important carbon–carbon bond-forming reaction in organic synthesis. In general, dioxanes are also common products, which are widely used as solvents or intermediates.^[8] Generally, strong protonic acid catalysts such as sulfuric acid and hydrochloric acid are required to synthesize dioxanes by the Prins reaction.^[8] However, the applications of these mineral acid catalysts is limited by their toxicity, corrosiveness, and tedious workup procedure.^[9] The use of heterogeneous catalysts for the Prins reaction, such as Lewis acids,^[10] Brønsted acids,^[11] and solid acids,^[12] showed little success. With increasing public concern over environmental degradation and future resources, it is of great importance for chemists to come up with new approaches that are less hazardous to human health and the environment.^[13] In recent years, ionic liquids (ILs) have attracted increasing interest and have been successfully used in variety of catalytic reactions as environmentally benign solvents and catalysts because of their relatively low viscosities, low vapor pressure, and high thermal and chemical stability.^[14]

Now many organic reactions with ILs (as catalysts or solvents) have been performed with good results.^[15] Owing to the useful characteristics of solid acids and mineral acids, various types of Brønsted acidic ionic liquids are designed and used as catalysts for the Prins reaction with a limited number of examples.^[16] Furthermore, these ILs were also designed to replace traditional mineral acids, such as sulfuric acid and hydrochloric acid in the chemical processes.^[17]

In view of these merits of ILs, and in continuation of our work in studying acid-catalyzed reactions in ionic liquids,^[18] we describe here a direct and efficient protocol of bmimOTf ionic liquid-mediated synthesis of dioxanes via the Prins reaction from diversely substituted styrenes and aldehydes. In comparison with the reported methods in the literature, we have demonstrated the advantages of the use of bmimOTf make this synthesis simple, convenient, cost-effective, and environmentally friendly. Furthermore, bmimOTf was conveniently separated from the products and can be easily recycled for the Prins reaction of different substrate with excellent yields.



Scheme 1. Synthesis of 4-phenyl-1,3-dioxane using bmimOTf.

RESULTS AND DISCUSSION

The desired Brønsted acidic ionic liquid was prepared by the reaction of 1-methylimidazole and 1,4-butanediol at room temperature and the resulting zwitterionic imidazolium salt was treated with trifluoromethanesulfonic acid at 40 °C to afford the IL in quantitative yield.^[19] To establish its catalytic importance for the Prins reaction, a preliminary experiment was carried out to synthesize 4-phenyl-1,3-dioxane from styrene and formaldehyde in anhydrous MeCN (Scheme 1).

Unfortunately at 10 mol% of the catalyst (Table 1) the reaction did not go well either at rt or at 50–80 °C. A periodical increase in the molar ratio of catalyst increases the conversion rate steadily. This gave a clue that the amount of catalyst has more significant impact than the temperature and the nature of the solvent (MeCN, tetrahydrofuran [THF], and H₂O). To our delight, an almost complete conversion (98% by gas chromatography–mass spectrometry GC-MS) was noticed in 6 h at 60 °C when IL was used in excess (to serve as both catalyst and solvent).

After optimization of bmimOTf, we carried out the series of reactions for the synthesis of dioxanes via Prins reaction from diversely substituted styrenes and aldehydes (Scheme 2).

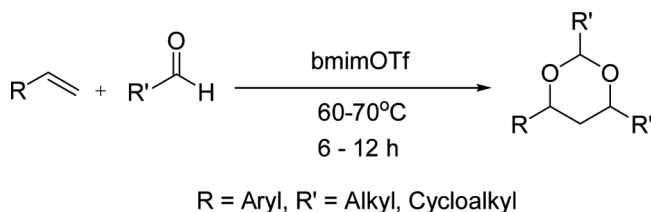
Table 1. Optimization of catalytic activity of bmimOTf on model reaction (Scheme 1)

Entry	bmimOTf (mol%)	Solvent	Temperature (°C)	Time (h)	Conversion ^a (%)	Yield ^b (%)
1	10	MeCN	Rt	≤12	10	NI
2	10	MeCN	50	≤12	18	NI
3	10	MeCN	80	≤12	21	NI
4	15	MeCN	Rt	≤12	14	NI
5	15	MeCN	50	≤12	26	NI
6	20	MeCN	Rt	≤12	22	NI
7	20	MeCN	50	≤12	35	20
8	20	MeCN	80	≤12	41	27
9	30	MeCN	80	≤12	52	43
10	30	THF	80	≤12	30	NI
11	30	H ₂ O	80	≤12	00	NI
10	bmimOTf		60	6	98	82 ^c

^aConversion based on GC-MS analysis.

^bIsolated yields of pure products; NI: no isolation.

^cReaction was carried out in bmimOTf (in absence of MeCN).



Scheme 2. Synthesis of various substituted 1,3-dioxanes using bmimOTf.

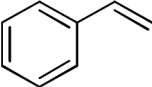
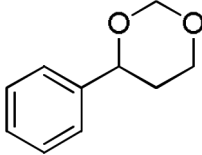
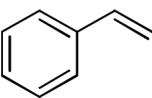
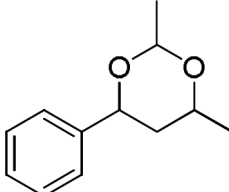
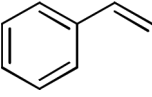
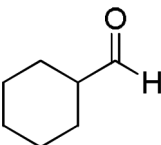
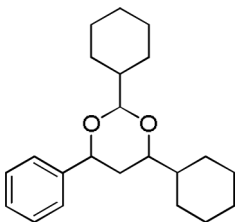
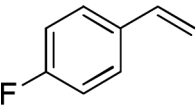
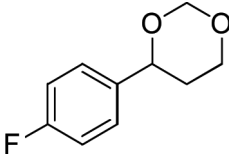
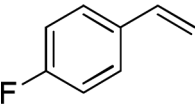
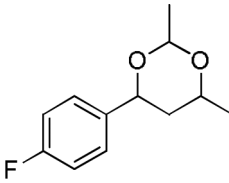
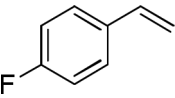
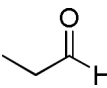
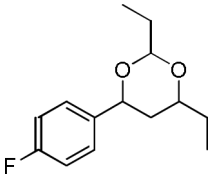
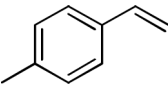
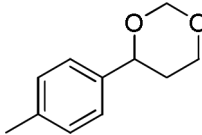
All the reactions listed in Table 2 were carried out at 60–70 °C and were monitored by thin-layer chromatography (TLC) and GC-MS from 6–12 h. The results revealed that both substituents in styrene (either F or Me) provided uniformly good results (Table 2, entries 4–10). Encouraged by these results, we then extended our protocol to various styrenes and aldehydes to check general applicability. It is obvious from Table 2 that all the reactions went smoothly at 60–70 °C in a time interval of 6–12 h. These results suggest that the nature of the substitution on the phenyl ring has no influence on the product yield (Table 2, entries 11–14). Cyclic systems like 1,2-dihydronaphthalene and indene also worked well as noticed from the isolated yield (Table 2, entries 15–18).

Further, to extend the scope of bmimOTf in the Prins reaction, bmimOTf was recycled up to three times (Table 2, entries 2, 3, 5, 6, 8, 9, etc.) where the recovered bmimOTf of a different reaction was used. The products obtained by using recycled bmimOTf were clean and isolated without any significant loss in the product yield (77–90%). (Table 2, entries 3, 6, 8, 9, 13, etc.).

Because there have been very few reports on the use of aliphatic aldehydes, except formaldehyde, we have also attempted the study of reactivity of other aliphatic aldehydes such as acetaldehyde, propionaldehyde, and cyclohexanecarboxaldehyde besides formaldehyde. Interestingly, these substrates reacted well with alkenes to produce the corresponding 2,4,6-trisubstituted 1,3-dioxane derivatives under similar reaction conditions. Though the reaction was successful with aliphatic aldehydes, no coupling of aromatic aldehydes and heteroaromatic aldehydes with styrene was observed even by increasing the reaction temperature (80–90 °C) (Table 2, entries 19–21). In general, in the present methodology the IL can be recycled for up to three attempts without any significant loss in the product yield. The reactions were clean, the products containing stereo centers were isolated as racemic mixture, and no other side products were detected under these conditions as determined from the NMR spectra of the crude products. The structures of the products were established from their spectral data and also by comparison with authentic samples. A plausible reaction mechanism is depicted in Scheme 3.

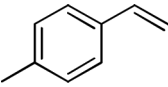
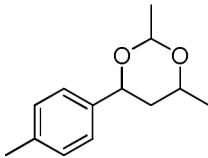
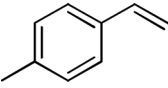
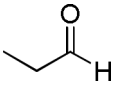
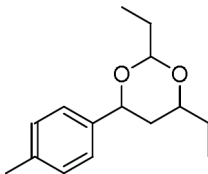
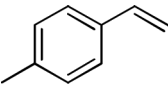
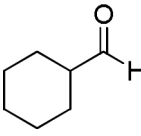
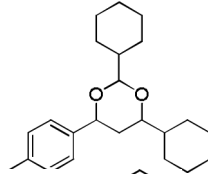
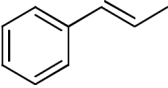
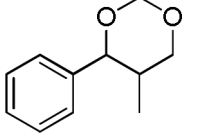
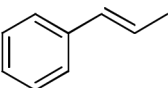
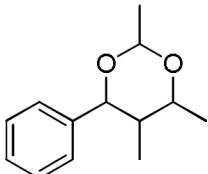
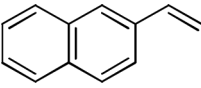
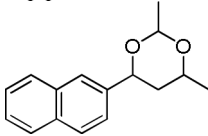
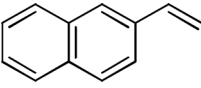
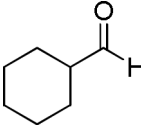
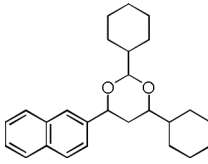
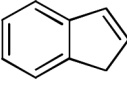
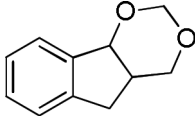
It should be noted that the reactions were faster with paraformaldehyde compared to other aliphatic aldehydes. In addition, styrene derivatives gave greater yields of products with paraformaldehyde when compared with other olefins (Table 2, entries 1, 4, 7, and 11) as reported by Yadav et al. in iodine.^[20] The scope and generality of this process is illustrated with respect to various aldehydes and alkenes.

Table 2. List of 1,3-dioxanes synthesized using bmimOTf

Entry	Olefin	Aldehyde	Product	Time (h)	Yield ^a
1		$(\text{CH}_2\text{O})^n$		6	82
2				10	68 ^b
3				8	77 ^c
4		$(\text{CH}_2\text{O})_n$		8	89
5				12	64 ^d
6				12	90 ^b
7		$(\text{CH}_2\text{O})_n$		6	92

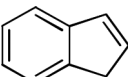
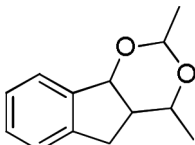
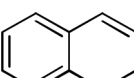
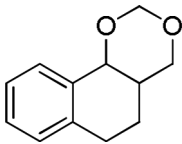
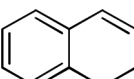
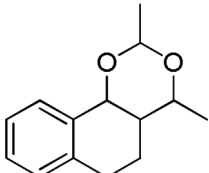
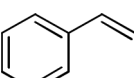
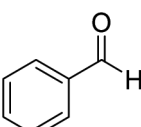
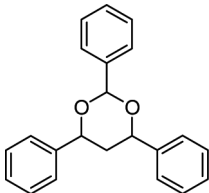
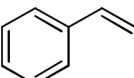
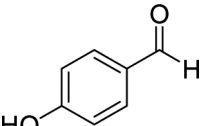
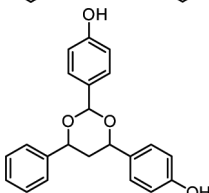
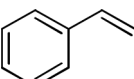
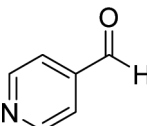
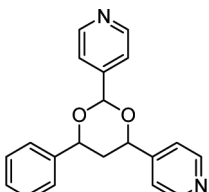
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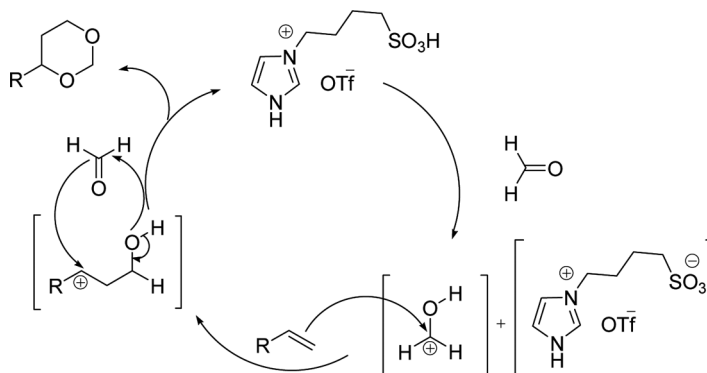
Entry	Olefin	Aldehyde	Product	Time (h)	Yield ^a
8				6	85 ^b
9				8	72 ^c
10				12	70 ^b
11		$(\text{CH}_2\text{O})_n$		12	80
12				12	67 ^b
13				8	80 ^c
14				6	80
15		$(\text{CH}_2\text{O})_n$		6	78 ^b

(Continued)

Table 2. Continued

Entry	Olefin	Aldehyde	Product	Time (h)	Yield ^d
16				12	80 ^c
17		(CH ₂ O) _n		9	94
18				8	90
19				12	NR
20				12	NR
21				12	NR

^aIsolated yields of pure products; NR; no reaction.^bThe reactions were carried out with recycled bmimOTf, cycle 1.^cThe reactions were carried out with recycled bmimOTf, cycle 2.^dThe reactions were carried out with recycled bmimOTf, cycle 3.



Scheme 3. Plausible mechanism of formation of 1,3-dioxanes from bmimOTf.

EXPERIMENTAL

The reagents employed were high-purity commercial samples, which were used as received. Reactions were carried out in an oven-dried round-bottom flask. Column chromatography was performed on silica gel (200–400 mesh). TLC was performed on alumina silica gel 60F₂₅₄ (Fischer) detected by ultraviolet light (254 nm) and iodine vapors. The melting points were determined by open capillaries on a Buchi apparatus and are uncorrected. The infrared (IR) spectra were recorded on a Nicolet-impact-410 FT-IR spectrometer, using KBr pellets. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker AC-300F 300-MHz spectrometer in dimethylsulfoxide (DMSO-*d*₆) using tetramethyl silane (TMS) as an internal standard with ¹H resonance frequency of 300 MHz and ¹³C resonance frequency of 75 MHz. GC analyses were performed on a Nucon 5700 series gas chromatograph. GC-MS analyses were performed on a Shimadzu 2010 series mass selective detector instrument. Elemental analysis was carried out by using a Heraeus CHN rapid analyzer. All the compounds gave C, H, and N analysis within ±0.4% of the theoretical values.

Typical Procedure for the Synthesis of 1,3-Dioxanes

In a typical experiment, styrene (10.0 mmol) and formaldehyde (20.0 mmol) were added successively into an oven-dried Schlenk tube. Upon efficient magnetic stirring (for 10–20 min) the reaction mixture was then charged with bmimOTf (2–3 mL). The reaction mixture was stirred at 60–70 °C and the progress of the reaction was monitored by TLC and GC-MS (Table 2). After the completion of the reaction (TLC and GC-MS), the mixture was cooled to room temperature and the product was extracted in dichloromethane (DCM). The pure product was obtained by column chromatography (80:20 hexane–ethyl acetate mixture) and was fully characterized by GC-MS, ¹H NMR, ¹³C NMR, and elemental analysis. The spectral data were found to be in agreement with the reported values.^[20] The ionic liquid left after the extraction of product was dried and reused again.

Typical Method for the Reusability of bmimOTf

The crude ionic liquid left after the extraction of products was dissolved in MeCN and filtered through sintered crucible to remove the suspended particals (if present). Pure IL was obtained after the removal of MeCN under reduced pressure; it was dried under high vacuum and directly reused in subsequent reactions. The ionic liquid as catalyst and solvent were reused up to three times.

Supporting Information

Details of analysis of [bmim(SO₃H)][OTf] and full experimental details, IR, ¹H and ¹³C NMR spectra, and elemental analysis of various 1,2-benzisoxazoles derivatives can be found via the Supplementary Content section of this article's webpage.

CONCLUSIONS

In summary, bmimOTf has proved to be a useful, novel, efficient, recyclable catalyst and environmentally benign solvent for the Prins reaction to produce various substituted 1,3-dioxanes in excellent yield. The experimental procedure is simple and convenient and the reaction conditions are amenable to scale-up. This method provides easy access to a wide range of 1,3-dioxanes with diverse chemical structures. Further work, including the development of synthetic applications of bmimOTf as a reagent/catalyst and solvent in organic synthesis, is under way in our laboratory.

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