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Stereoselective Synthesis of Tetrasubstituted 2,3-Dihydrofurans by One-Step Cyclization of β-Ketosulfides of Benzothiazole and Aldehydes in Ionic Liquids

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A stereoselective synthesis of tetrasubstituted 2,3-dihydrofurans was carried out in *n*-butylpyridinium tetrafluoroborate ([bpy$^+$][BF_4^-]) as solvent. The reaction proceeds smoothly in one step starting from simple materials such as aldehydes and β-ketosulfides of benzothiazole. A comparison between several ionic liquids (ILs) is presented, and the role of the benzothiazolyl moiety is discussed. Workup proved to be very easy and recycling of IL possible.

Introduction

Dihydrofurans and furans are two of the most important heterocycles commonly found in a wide variety of naturally occurring substances and possessing a multiplicity of biological activities.[1] Among them, 2,3-dihydrofurans have gained importance as structural features of natural products such as aflatoxins,[2] as well as solvents, monomers for the synthesis of biodegradable polymers (e.g., naturally occurring polyethers),[3] and other useful synthetic intermediates.[4]

Their synthetic significance has prompted a search for better methods of synthesis by using simple and feasible approaches. One of the most important methodologies is based on metal-promoted processes which involve radical intermediates, generated by Mn(III),[5] Ce(IV),[6] and Co(II)[7] salts, or by Pd-,[2a,8] Sc-,[9] and Mo-[10] catalyzed cyclization. Besides them, also 1,3-dipolar cycloaddition to alkenes of the carbenoid species generated by rhodium-[11] or copper-[12] mediated decomposition of diazocarbonyl compounds has also become an additional important route in the synthesis of dihydrofurans.

The second attractive approach to dihydrofuran derivatives involves, in a one-pot process, nucleophilic cascade reactions initiated by an attack of stabilized carbanions on suitable electrophiles, followed by a cyclization step. Nevertheless, these methods require appropriate reagents, such as 2-alkenyl-1,3-dicarbonyl compounds,[13] α-halo-enones[14] and -enoates,[15] phosphonium[16] or arsonium ylides,[17] and others.[18]

In this latter context, during our development of clean

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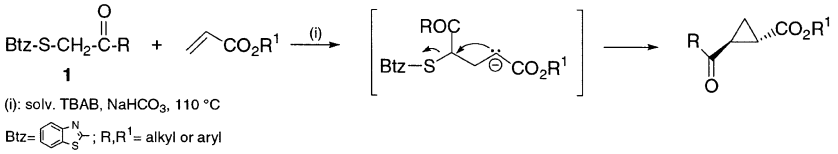
SCHEME 1



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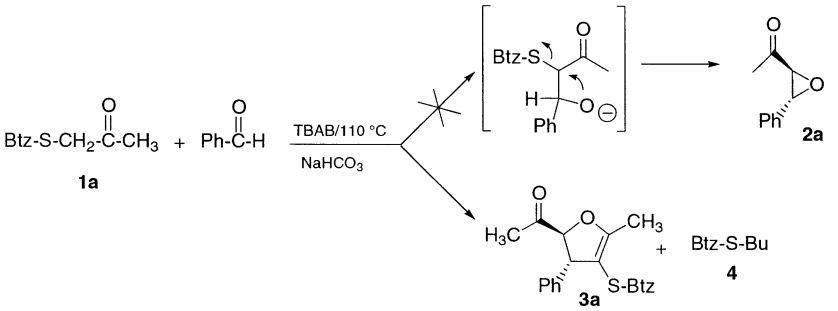
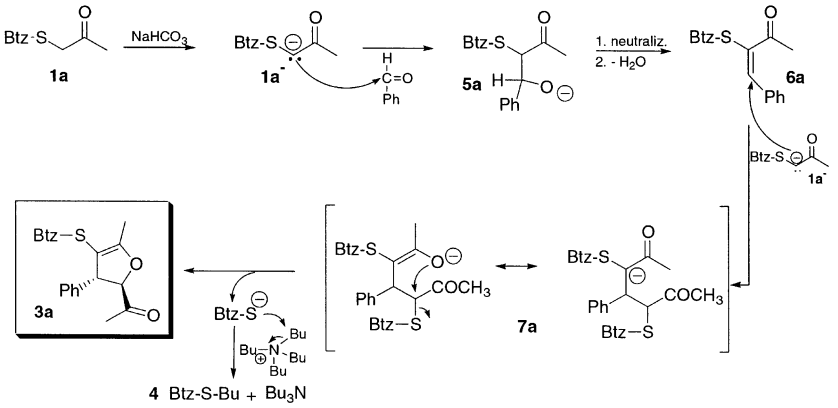


SCHEME 3



organic syntheses by using environmentally friendly reaction media such as ionic liquids, we were attracted by the enhanced reactivity exhibited by charged nucleophiles in these alternative solvents, certainly due to the low solvation toward the anions. Concerning this argument, we recently reported the stereoselective synthesis of trans-disubstituted cyclopropanes by reaction of benzothiazolic β-ketosulfides **1** as pronucleophiles with acrylates as Michael acceptor, in the presence of sodium hydrogencarbonate as base. In this process, the tetrabutylammonium bromide (TBAB), used as solvent, was essential to efficiently promote the reaction, preventing some drawbacks such as the use of strong bases, lack of stereoselectivity, and ring cleavage (Scheme 1).[19]

The choice of the 2-thiobenzothiazolyl moiety was reasonable considering its double nature of electron-withdrawing group, which increased the acidity of α-methylene protons, and its good leaving group properties. As an extension of this study, we now describe herein further synthetic utility of this method as a novel simple stereoselective synthesis of substituted dihydrofurans by using aldehydes as electrophiles.

Results

Initial investigations aimed at the synthesis of oxiranes were performed by using the synthetic procedure depicted in Scheme 1, choosing the model reaction between β-ketosulfide **1a** and benzaldehyde. However, instead of the expected oxirane **2a**, *trans*-2,3-dihydrofuran **3a** (yield 45%), 2-(butylsulfanyl)benzothiazole **4**, and 0.5 equiv of starting aldehyde were isolated after extraction from the ionic liquid (Scheme 2).

Reaction monitoring did not exhibit any intermediate, but when the reaction temperature was decreased to 50 °C, a GC-MS analysis revealed the formation of an intermediate species with m/z = 311, subsequently isolated and identified as 3-(benzothiazol-2-ylsulfanyl)-4-phenylbut-3-en-2-one **6a**. On the basis of these findings, a plausible reaction mechanism (Scheme 3) envisages the initial nucleophilic attack by the stabilized carbanion **1a**$^-$ on aldehyde followed by neutralization and dehydration steps. Once formed, the vinyl sulfide **6a** undergoes a Michael addition by the anion **1a**$^-$, affording the enolate

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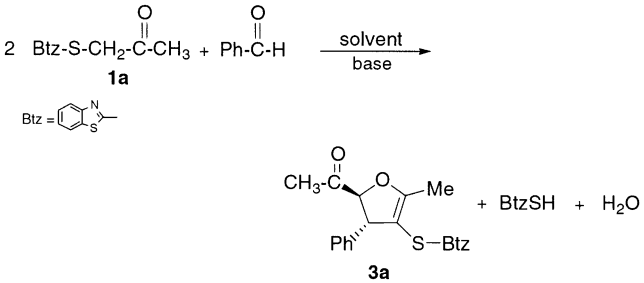
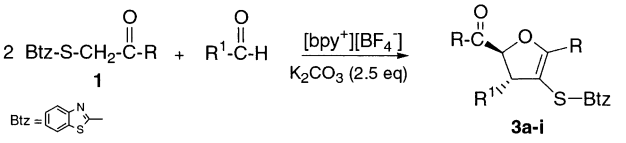
TABLE 1. Optimization of Reaction Conditions in the Synthesis of Dihydrofuran 3a[a]



run	solvent	base (equiv)	*T* [°C]	time (h)	yields (%)[b]
1	TBAB	$NaHCO_3$ (2.5)	110	1.5	91[c]
2	DMA	$NaHCO_3$ (2.5)	110	4	85
3	DMA	$NaHCO_3$ (2.5)	r.t.	24	<5
4	DMA	K_2CO_3 (2.5)	r.t.	22	87
5	[bmim$^+$]Br$^-$	$NaHCO_3$ (2.5)	r.t.	24	28
6	[bmim$^+$]Br$^-$	K_2CO_3 (2.5)	r.t.	16	85
7	[bmim$^+$]I$^-$	K_2CO_3 (2.5)	r.t.	24	87
8	[bpy$^+$][BF_4^-]	K_2CO_3 (2.5)	r.t.	1.5	93
9	[bpy$^+$][BF_4^-]	K_2CO_3 (1)	r.t.	36	85
10	[bpy$^+$][BF_4^-]	K_2CO_3 (0.1)	r.t.	44	80

[a] Typical procedure: to the solvent (3 g of IL or 5 mL of DMA), stirred and heated at the reaction temperature, were added ketosulfide **1a** (4,5 mmol), aldehyde (2,2 mmol), and base. [b] Isolated products. [c] In this case a further purification step by column chromatography was necessary to eliminate the byproduct **4**.

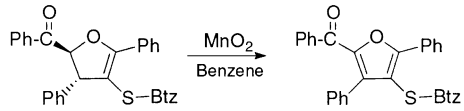
TABLE 2. Synthesis of 2,3-Dihydrofurans in Ionic Liquids[a]



	ketosulfide	aldehyde			2,3-dihydrofuran	
run	(**1**) R	R^1	T/°C		yields%[b] [t/h]	*E*:*Z*[c]
1	(**1a**) CH_3	Ph	r.t.	**3a**	93 [1.5]	97:3
2	(**1a**) CH_3	$CH_3(CH_2)_6$	r.t.	**3b**	85 [4]	95:5
3	(**1a**) CH_3	$CH_3(CH_2)_{12}$	50	**3c**	72 [29]	98:2
4	(**1a**) CH_3	4-$NO_2C_6H_4$	r.t.	**3d**	84 [3.3]	>99:1
5	(**1a**) CH_3	4-ClC_6H_4	r.t.	**3e**	80 [4]	92:8
6	(**1a**) CH_3	3-$CH_3OC_6H_4$	r.t.	**3f**	80 [5.5]	95:5
7	(**1b**) Ph	Ph	50	**3g**	85 [9]	98:2[d]
8	(**1b**) Ph	$CH_3(CH_2)_6$	50	**3h**	82 [12]	>99:1[d]
9	(**1b**) Ph	$CH_3(CH_2)_{12}$	50	**3i**	82 [38]	>99:1[d]

[a] Same procedure as reported in Table 1. [b] Isolated products. [c] Evaluated by GLC. [d] Evaluated by ^{1}H NMR.

SCHEME 4



anion **7a**, which gives rise to the cyclization product *trans*-2,3-dihydrofuran **3a**. When tetrabutylammonium bromide (TBAB) was used as reaction medium, the leaving group Btz-S$^-$ led to a side-reaction with the solvent consisting of a nucleophilic displacement on the ammonium cation, which affords the byproduct **4** and tributylamine (Table 1, run 1).

Thus, to obtain complete conversion of aldehyde, 2 equiv of ketosulfides **1a** and sodium hydrogencarbonate were necessary. A similar reaction pathway has been recently reported in the synthesis of dihydrofurans by using α-haloenones as substrates under PTC conditions.[14] To obtain milder reaction conditions, we tested the use of a stronger base such as K_2CO_3 and a number of low-melting ionic liquids. Optimization experiments were performed on the model reaction affording dihydrofuran **3a**, and results are summarized in Table 1.

When the reaction temperatures were decreased, low yields were obtained both in DMA and in 1-butyl-3-methylimidazolium bromide ([bmim$^+$]Br$^-$) as solvents (runs 3, 5). However, replacement of $NaHCO_3$ with K_2CO_3 as base led to a great increase of yields, while among the various low-melting ionic liquids investigated, 1-butylpyridinium tetrafluoroborate ([bpy$^+$][BF_4^-]) furnished highest reaction rates (runs 6−8). Reaction at room temperature occurred also in DMA although with decreased reaction rate (run 4). It is noteworthy that the base may be used even in catalytic amounts (runs 9−10). These latter findings are not surprising since some reaction intermediates, such as anion **5a** or the leaving group Btz-S$^-$, can behave as a base to deprotonate the ketosulfide **1a** (see Scheme 3).

The reaction did not occur on replacing ketosulfides **1** by α-halogenated ketones,[20] thus showing the importance of benzothiazole as activating group for this process. In addition, the reaction carried out on simple ketones as electrophiles afforded very low conversions. On the basis of these results, by choosing [bpy$^+$][BF_4^-] as solvent and K_2CO_3 (2.5 equiv) as base, we applied this method to other substrates as listed in Table 2.

The method proved to be of general applicability on aldehydes, although a slightly higher reaction temperature (50 °C) was required for aliphatic ones (runs 3, 8, 9). In addition, a great benefit of this protocol arises from the simplicity of the separation procedure, which can be performed by diethyl ether extraction of the reaction products, thus leaving the ionic liquid which can be recycled. This latter operation can be smoothly accomplished since the reaction byproduct Btz-SH (or its potassium salt), being insoluble in Et_2O, remains dissolved into the ionic liquid.

It is noteworthy that 2,3-dihydrofurans **3a**−**i** can be further converted into other synthetic intermediates. A first example is the oxidation to the corresponding furans by treatment with chemical manganese dioxide (CMD).[21] For this purpose, a benzene solution of dihydrofuran **3g** was refluxed for 36 h in the presence of an excess (12 equiv) of activated MnO_2, affording the tetrasubstituted furan **8g** (Scheme 4).

Alternatively, an interesting transformation is the removal of benzothiazolic group, leaving a thiolic functionality on dihydrofuran ring. This can be done by

(20) Either α-chloroacetophenone or α-chloroacetone treated with benzaldehyde in the same reaction conditions did not afford any products.

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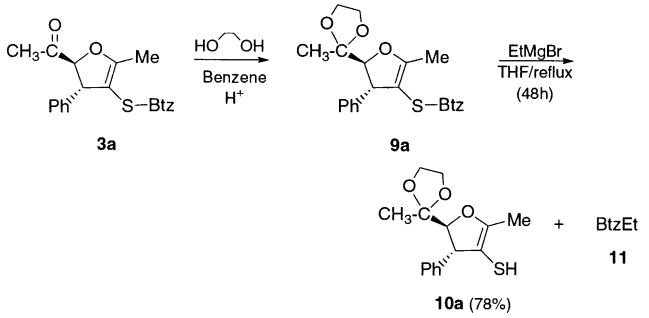
SCHEME 5



treating dihydrofuran **9a**, bearing the protected carbonyl moiety, with an excess of ethylmagnesium bromide, providing *trans*-2-methyl-5-(2-methyl-[1,3]dioxolan-2-yl)-4-phenyl-4,5-dihydrofuran-3-thiol (**10a**) and 2-ethylbenzothiazole (**11**). These compounds derived from a nucleophilic displacement carried out by the Grignard reagent onto the C-2 position of benzothiazolic ring (Scheme 5). Further attempts are in progress to find reaction conditions for deblocking the entire S-Btz group.

A further question concerns the stereoselectivity of the cyclizations. These occurred in most cases with a high degree of trans stereoselectivity (trans/cis ratio > 98:2) probably due to the major thermodynamic stability of trans isomer. The trans configurational assignment of the predominant isomer of compounds **3a**−**i** has been unequivocally established by NMR, mainly by analysis of chemical shifts, coupling constants, and NOESY experiments, subsequently confirmed by X-ray diffraction (see Supporting Information).

In conclusion, a convergent stereoselective synthesis of highly substituted dihydrofurans has been described. By using a ionic liquid as solvent, the following advantages have been achieved: (i) very mild reaction conditions, such as room temperature and catalytic amounts of base, (ii) enhanced yields and shorter reaction times compared with analogous processes in molecular solvents, (iii) easy workup and recycling of reaction medium possible. In addition, most of the starting reagents, such as aldehydes and ketosulfides **1**, are commercially available compounds or can be easily prepared via costless synthesis. For these reasons, we believe that this method could provide a new viable access to dihydrofurans.

Experimental Section

Butylmethylimidazolium iodide and butylpyridinium tetrafluoroborate were prepared according to the literature.[22] Ketosulfides **1a**,**b** were prepared according to our procedure.[23] The stereochemistry of dihydrofurans was secured by NMR signals and by NOESY experiment, subsequently confirmed by X-ray diffraction (see Supporting Information).

General Procedures for the Synthesis of 2,3-Dihydrofurans. A Pyrex reaction flask was charged with ionic liquid (3 g) and heated at the reaction temperature. To the stirred molten salt were added ketosulfide **1** (4.48 mmol), aldehyde (2.24 mmol), and potassium carbonate (5.60 mmol). The reaction was monitored by GLC until consumption of the reagents. After completion of the reaction, the mixture was extracted four times with 20 mL of ethyl ether. The collected organic fractions were concentrated under vacuum and filtered to separate the insoluble residual 2-mercaptobenzothiazole. Then, after drying on Na_2SO_4 and complete solvent evaporation, dihydrofurans products were obtain as oils or yellow solids in almost 95% purity.

When tetrabutylammonium bromide (TBAB) was used as solvent, the reaction mixture was extracted with 80 mL of hexane for 1 h in a Soxhlet apparatus. After solvent evaporation, the oily residue was chromatographed on silica gel (eluent petroleum ether/ethyl acetate) to separate the byproducts **4** and tributylamine. Instead, when the reaction was carried out in dimethylacetamide (DMA), the reaction mixture was treated with aqueous HCl (30 mL) and extracted with 3 × 30 mL portions of diethyl ether. The organic layers were dried on Na_2SO_4, and the solvent evaporated under vacuum. The oily residue was chromatographed on silica gel (eluent petroleum ether/ethyl acetate) to give purified dihydrofurans **3a**−**i**.

Typical Procedure for Oxidation to Tetrasubstituted Furans. To a 20 mL benzene solution of dihydrofuran **3g** (1.0 g, 2.0 mmol) was added 2.09 g (24 mmol) of activated manganese dioxide, and the suspension was refluxed for 36 h. After the completion of reaction, the solvent was removed in vacuo and the mixture chromatographed on silica gel (eluent hexane/ethyl acetate 5/1) to give 0.92 (92%) of tetrasubstituted furan **8g**.

Typical Procedure for Deblocking Benzothiazolic Group. A 20 mL benzene solution containing 2.0 g (5.4 mmol) of dihydrofuran **3a**, 0.51 g (8.2 mmol) of ethylene glycol, and 90 mg (0.54 mmol) of *p*-toluensulfonic acid was refluxed overnight in a round-bottomed flask equipped with a Dean−Stark apparatus. Then, the mixture was washed with 20 mL of aqueous $NaHCO_3$. After drying and solvent removal, *trans*-(±)-4-(benzothiazol-2-yl)sulfanyl-2(2-methyl-[1,3]dioxolan-2-yl)-5-methyl-3-phenyl-2,3-dihydrofuran (**9a**) was isolated as pale yellow solid (yield 95%).

In a three-necked round-bottomed flask, equipped with a condenser, 1.0 g (2.4 mmol) of protected dihydrofuran **9a** was dissolved, under nitrogen atmosphere, in 20 mL of dry THF. Then, 3.5 mmol of ethylmagnesium bromide was added by syringe, and the mixture was refluxed monitoring by GLC until the disappearance of starting material (48 h ca.). Silica gel chromatography of the reaction mixture (eluent petroleum ether/ethyl acetate 6/1) gave 0.53 g (78%) of *trans*-(±)-2-methyl-5-(2-methyl-[1,3]dioxolan-2-yl)-4-phenyl-4,5-dihydro-furan-3-thiol (**10a**) together with 0.31 g of 2-ethylbenzothiazole[24] (**11**).

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Supporting Information Available: Physical and spectral data of compounds **3a**−**i**, **6a**, **8g**, **9a**, **10a**, phase-sensitive NOESY ^{1}H NMR experiment of dihydrofuran **3b**, and crystallographic data for compound **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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