

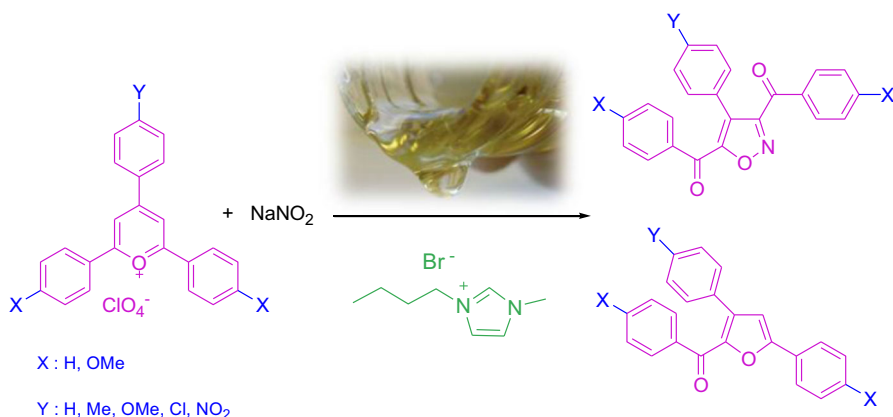
Synthesis of 2-arylfuran and novel 3,5-diaroyl-4-arylisoxazole derivatives by ring contraction of pyrylium salts

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Abstract Ring contraction of 2,4,6-triarylpyrylium perchlorates by use of sodium nitrite mediated by ionic liquid has been used as a new, direct, and environmentally benign method for synthesis of bioactive 2-arylfuran and novel 3,5-diaroyl-4-arylisoxazole derivatives in excellent yields. The versatility of the approach enables rapid and simple access to these pharmaceutically important compounds. The products were readily isolated from the reaction mixture by simple filtration.

Graphical Abstract



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Introduction

Heterocyclic compounds have always attracted much attention because of their numerous uses in the design of biologically active molecules with pharmaceutical applications [1, 2]. Hence, practical methods for preparation of such compounds is of great interest in synthetic organic chemistry.

Isoxazole derivatives are important heterocycles which are widely used in pharmaceuticals and therapeutics, for example as potent and selective antagonists of the NMDA receptor and because of their anti-HIV activity [3, 4]. They have antihyperglycemic [5], antitumor [6], inflammatory [7], antifungal [8], antibacterial [9, 10] and immunosuppressive activity [11]. They have also been used as versatile building blocks in organic synthesis [12]. Several methods have been developed for synthesis of substituted isoxazoles. Commonly used methods include addition of nitrile oxides to supported alkynes [13], condensation [14], anchoring of a nitrile oxide precursor to a solid phase [15], intermolecular cycloadditions [16], intramolecular cyclization of amino acids [17], and condensation of 1,3-dicarbonyl compounds with hydroxylamine [18]. However, many of these procedures are not environmentally benign and have been associated with other disadvantages including use of toxic, expensive, and unrecyclable catalysts, multi step reactions, low product yields, difficult work-up procedures, and use of organic solvents. It is, therefore, still a major challenge to find simple ways to synthesize novel isoxazole derivatives from inexpensive and readily available starting materials by use of mild reaction conditions.

Substituted furans, because of their unique chemical and structural properties, have received much attention over the past decade and found wide application in medicinal chemistry [19–25]. In this context, organic and medicinal chemists continually seek new approaches for synthesis of furan derivatives.

Because readily available pyrylium salts can function as intermediates in a very wide variety of syntheses, because of their high reactivity toward nucleophiles, their use as simple and available precursors has attracted much interest [26–28].

Ionic liquids are widely used as green reaction media to replace conventional harmful organic solvents in both academic and industrial research [29–35]. The possibility of recycling and their low vapor pressure ensure their utility in environmentally friendly technology. They have been used as solvents for many organic transformations [36].

Because of the importance of both the isoxazole and furan structures, and in continuation of our efforts to develop new synthetic methods for promising molecules [26–28, 37–42], we report, for the first time, a new, highly practical, and eco-friendly approach for synthesis of novel 3,5-diaroyl-4-arylisoxazole **2** and 2-aroylfuran **3** derivatives by novel ring contraction of readily available triarylpyrylium salts **1** with sodium nitrite in the presence of 1-*n*-butyl-3-

methylimidazolium bromide, [bmim]Br, as promoter and efficient reaction medium (Scheme 1).

Experimental

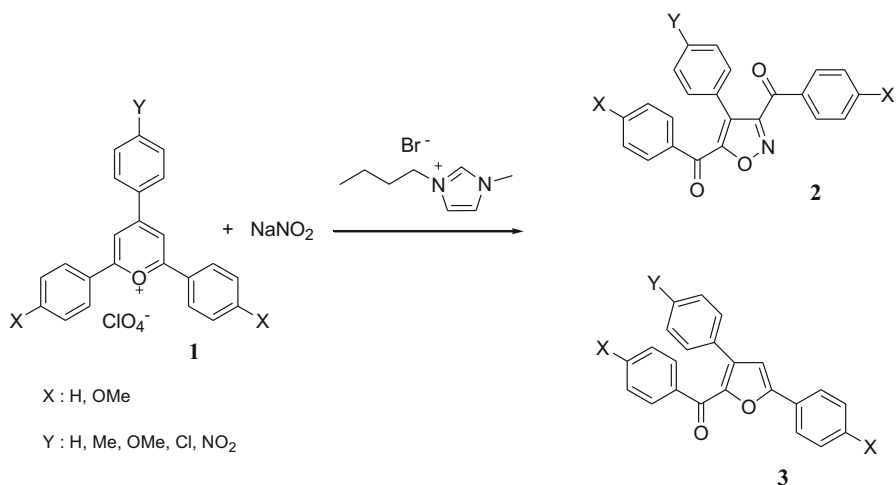
Chemicals were purchased from Fluka, Merck, and Aldrich. Reactions were monitored by TLC. IR spectra were acquired with a Bomem MB:102 FTIR spectrophotometer. ^1H NMR and ^{13}C NMR spectra were acquired with a Bruker spectrometer at 400 and 100 MHz, respectively, in CDCl_3 as solvent with tetramethylsilane as internal standard. Mass spectra were acquired with a Finnigan MAT TSQ 70 mass spectrophotometer.

General procedure for synthesis of triarylpyrylium perchlorates

All triarylpyrylium perchlorates were synthesized from the corresponding aldehydes and ketones by the method described elsewhere [43, 44]. Briefly, the corresponding benzaldehyde (0.1 mol) and acetophenone (0.2 mol) were stirred at room temperature, and sulfuric acid (6 mL) was added dropwise during 30 min. The mixture was stirred at 100 °C for 60 min, then ethanol (200 mL) and perchloric acid 70 % (10 mL) were added. The mixture was left 24 h and the precipitate formed was recrystallized from acetic acid.

General procedure for synthesis of [bmim]Br

A mixture of 1-methylimidazole (4.1 g, 0.05 mol) and 1-bromobutane (6.85 g, 0.05 mol) in the absence of solvent was heated with stirring at 80 °C for 12 h. The product was washed with diethyl ether and dried in vacuum to afford [bmim]Br.



Scheme 1 Synthesis of novel 3,5-diaroyl-4-arylisoazole **2** and 2-arylfuran **3** derivatives by reaction of triarylpyrylium perchlorates **1** with NaNO_2 in the presence of [bmim]Br

General procedure for synthesis of 3,5-diaroyl-4-arylisoazole (2) and 2-aroylfuran (3) derivatives

Reactions were typically performed by addition of triarylpyrylium perchlorates (0.1 mmol) to sodium nitrite (0.3 mmol) in [bmim]Br (1 g) as solvent (this ratio was optimized under our experimental conditions) and heated to 110 °C. After completion of the reaction, as indicated by TLC (*n*-hexane–ether, 4:1), the reaction mixtures were quenched with H₂O and the insoluble products were isolated by filtration. The products were adsorbed on silica, transferred to a silica column, and eluted with a 4:1 mixture of *n*-hexane–ether. The first and second fractions contained the 3,5-diaroyl-4-arylisoazole and 2-aroylfuran derivatives, respectively.

Results and discussion

In continuation of our systematic research on the reactions of pyrylium and thiopyrylium salts [26–28, 37–42], reactions between triarylpyrylium perchlorates and sodium nitrite were investigated.

Nucleophilic reaction of triarylpyrylium salts with sodium nitrite in the presence of a variety of organic solvents, for example ethanol, acetonitrile, dichloromethane, and toluene, among others, resulted in mixtures of compounds in poor yields, in agreement with previously reported research [45].

To enhance the selectivity of the reaction, and because of the importance of ionic liquids (IL) in green synthesis of heterocyclic compounds, in our next attempt we investigated this reaction in the presence of [bmim]Br as a green and efficient medium.

Initially, [bmim]Br was prepared in accordance with a literature procedure, from 1-bromobutane and 1-methylimidazole. Preliminary tests were then conducted to determine the best conditions for reaction of triarylpyrylium perchlorates and sodium nitrite. Triphenylpyrylium perchlorate (**1a**) was chosen as model compound. In a typical reaction, when **1a** was treated with sodium nitrite in [bmim]Br we obtained **2a** and **3a** in excellent yield and short reaction time. No byproducts were formed. In classical organic solvents the same reaction gave poor yields (15–5 % for **2a** and **3a** respectively) even under reflux conditions for long reaction times (approx. 20–24 h).

This green method is of substantial interest because it was an atom-efficient and straightforward route for synthesis of valuable 2-aroylfurans and novel 3,5-diaroyl-4-arylisoazole derivatives, which are present in many biologically active molecules.

We believe the high polarity of IL and their ability to dissolve both inorganic and organic compounds can result in enhanced rates of chemical reactions and higher selectivity compared with conventional solvents.

After completion of the reaction and quenching with water, the insoluble products **2a** and **3a** were isolated by filtration of the reaction mixture, without laborious aqueous workup.

Further experiments were designed to survey other optimization conditions. The model reaction was investigated in the presence of different amounts of sodium nitrite. As is apparent from Table 1, the reaction is favored by increasing nucleophile-to-substrate ratio, as shown by the substantial decrease in the reaction time. Bearing in mind that the reaction proceeds via addition then ring contraction, an increase in the concentration of the nucleophile favors the first reaction step and, on the whole, product formation. The best results were obtained when 3 mmol nucleophile and 1 mmol substrate were used (Table 1).

To evaluate the effect of reaction temperature, the reaction was performed at different temperatures under similar experimental conditions and monitored by TLC. The reaction occurred at r.t., but only slowly. After 2 h, the reaction was still incomplete. To improve the reaction time and yield, higher temperatures were used (Table 2). Higher temperatures resulted not only in better yields but also in much shorter reaction times. As shown in Table 2, when the reaction was conducted at 110 °C it was complete in 30 min and the total yield was as high as 97 %. It should be noted that temperatures >110 °C did not result in significant improvements.

To further examine the efficacy of the reaction it was repeated with a variety of triarylpyrylium perchlorates containing electron-donating and withdrawing groups in the *para* position of substituted phenyl rings, again with sodium nitrite in the presence of [bmim]Br (Table 3).

The results in Table 3 clearly show that aromatic aldehydes and acetophenones bearing either electron-donating or electron-withdrawing functional groups participate in the reaction smoothly and produce **2** and **3** in good yields. The results also show that electron-donating groups cause the reactions to become slow (e.g., entries B–D). This may be rationalized by considering that these groups reduce the positive charge on the α -position of the heterocyclic ring. In contrast electron-withdrawing groups (e.g., entries E and F) accelerate the reaction.

Table 1 Trend of the model reaction with different amounts of NaNO₂ in [bmim]Br solution

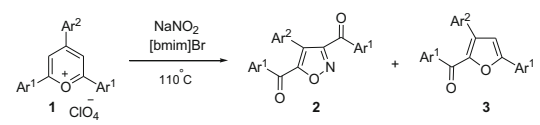
Entry	[Nu]/[Sub]	Time (min)	Yield % (2/3)
1	2/1	45	93 (73/20)
2	3/1	30	97 (75/22)
3	4/1	30	97 (75/22)

Nu, nucleophile, Sub, substrate

Table 2 Trend of the model reaction with different temperature

Entry	<i>T</i> (°C)	Time (min)	Yield % (2/3)
1	r.t.	120	Reaction not completed
2	80	95	90 (70/20)
3	100	65	90 (70/20)
4	105	50	90 (70/20)
5	110	30	97 (75/22)
6	120	30	97 (75/22)

Table 3 Conversion of different triarylpyrylium salts **1** into the corresponding 3,5-diaroyl-4-arylisoazole **2** and 2-arylfuran **3** derivatives in [bmim]Br under the optimized conditions

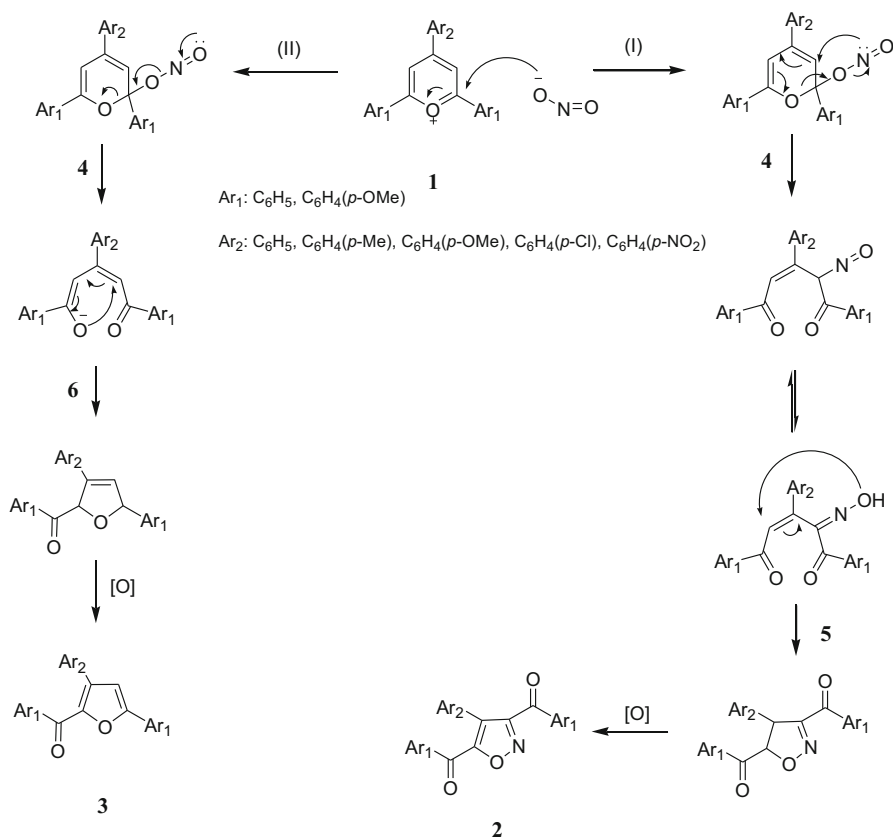
					
Entry	Substrate (1)	Product (2)	Product (3)	Yield % (2/3)	Time (h)
A				97 (75/22)	0.5
B				69 (50/19)	1.3
C				67 (52/15)	6
D				96 (63/33)	16
E				95 (80/15)	0.5
F				32 (20/12)	0.4

The structures of the products were determined from their physical and IR, ^1H NMR, ^{13}C NMR and mass spectrometric data.

A conceivable mechanism for the synthesis of 3,5-diaroyl-4-arylisoazole **2** and 2-arylfuran **3** derivatives via nucleophilic attack of nitrite is outlined in Scheme 2.

The isoxazole **2** is assumed to be formed by initial attack of nitrite on **1** to give intermediate **4** which in turn rearranges to oxime **5**. Subsequently, nucleophilic attack by the hydroxyl group of **5** gives product **2** by nucleophilic ring closure and oxidative aromatization (path I). 2-Arylfuran **3** was formed by thermal elimination of NO^+ from compound **4** followed by nucleophilic ring closure of pseudobase **6** and oxidative aromatization (path II).

This procedure results in a substantial decrease in reaction time and improved yield compared with conventional conditions. Furthermore, the procedure gives the



Scheme 2 Plausible mechanism for the formation of 3,5-diaroyl-4-arylisoazole **2** and 2-arylfuran **3** derivatives

desired 2-arylfuran and novel 3,5-diaroyl-4-arylisoazole derivatives exclusively with no byproducts. In addition, [bmim]Br is much less hazardous to use than organic solvents. This is, therefore, an atom-efficient process that produces less waste than would otherwise have arisen from use of excess reagents.

Conclusion

In summary, we have described a clean and atom-efficient process for synthesis of valuable 2-arylfuran and novel 3,5-dibenzoyl-4-arylisoazole derivatives by novel ring-contraction of pyrylium salts. Readily available and easily varied tri-arylpyrylium salts react with sodium nitrite mediated by the ionic liquid. The approach is environmentally benign, and more straightforward than established methods. We believe this method is a useful alternative to existing methods for synthesis of these pharmaceutically important compounds.

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