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Improved synthesis of pyrylium salts leading to 2,4-disubstituted diarylfurans via novel mechanism[☆]

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Abstract—Improved synthesis of pyrylium salts from either substituted benzoic acids or their methyl esters, and substituted acetophenone is reported en route to the synthesis of 2,4-diarylfurans. The mechanism involved in the formation of the pyrylium salt using these starting materials is proposed.

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Substituted furans, frequently found in Nature, exhibit interesting biological and pharmacological properties. Alkyl and aryl furans have shown antibacterial,¹ fungicidal,² muscle relaxant,³ insecticidal⁴ and enzymatic inhibition⁵ activities as well as nucleic acid binding properties.⁶ Routes to synthesize substituted diaryl-furans, however, are limited.^{7,8} Usually, they are synthesized from either 1,4-diketones⁹ or the condensation of acetophenone and various benzaldehydes,^{2a,10} α , β -unsaturated ketones¹¹ or pyrylium salts.^{12,13}

Pyrylium salts have played an important role as intermediates for the synthesis of various aryl furan derivatives. As part of our strategic drug discovery program, we were interested in exploring different pathways to efficiently synthesize substituted furan derivatives during the synthesis of some biologically interesting molecules. In this report, we disclose an improved and facile synthesis of pyrylium salts en route to 2-aroyl-3,5-diarylfurans and 2,4-diarylfurans. We discovered that the substituted pyrylium salts can be synthesized



Scheme 1.

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starting from either substituted benzoic acids or substituted benzoyl esters (Scheme 1). We propose a possible mechanism involved in the formation of pyrylium salts when either a carboxylic acid or an ester is used as a starting material, instead of an aryl aldehyde.

Typically, condensation of 4-substituted benzaldehyde with 4-substituted acetophenone mediated by the Lewis acid catalyst, boron trifluoride etherate in benzene, was reported many years ago for the synthesis of a large number of 2,4,6-triarylpyrylium salts.¹⁴ This procedure follows a mechanism of condensation-dehydrogenation to provide pyrylium salts.

We used substituted benzoic acids/esters instead of substituted aldehydes as the starting material because of the availability of diverse analogs, the ease to handle and store these starting materials. Furthermore, it seemed possible to synthesize the pyrylium salts through these alternate starting materials, considering the mechanistic details involved in the formation of pyrylium salts (vide infra).

Thus, $BF_3 \cdot OEt_2$ (2 equiv.) was added to a solution of benzaldehyde, benzoic acid, or methyl benzoate (1 equiv.) and 4-bromoacetophenone (2 equiv.) in anhydrous toluene. The clear solution was refluxed for 2 h. After cooling to room temperature, acetone was added and the dark red solution was poured into excess ether. A yellow precipitate was formed which was then filtered, washed with ether and dried under vacuum. Analyses confirmed that the yellow precipitate was the pyrylium salt, which was spectroscopically identical whether the starting material was benzaldehyde, benzoic acid, or methyl benzoate. Methyl benzoate produced higher yields of pyrylium salts than benzoic acid and benzaldehyde (Table 1). Similar procedures were used with substituted benzaldehydes, benzoic acids, or methyl benzoates. The best yields were obtained with *p*-nitro and *p*-methoxy substituted derivatives. Yields reported in the literature using benzaldehydes to obtain the respective pyrilium salts are in general lower than those obtained using benzoic acids or their respective esters in this study (Table 1).12,14-16

 Table 1. Pyrylium salts obtained from substituted benzaldehyde, benzoic acid and methyl benzoate

R ₁	R ₂ (% yield)			Published yields
	-H	-OH	-OMe	(70)
-H	42	37	55	38 (Ref. 14)
-Br	22	28	31	22 (Ref. 15)
-OMe	42	51	61	^a (Ref. 12)
-NO ₂	45	53	65	13 (Ref. 16)

^a Yield for the pyrylium salt was not reported.

These pyrylium salts were converted into 2,4-diarylfurans using a procedure previously described¹² (Scheme 2). Briefly, 2,4,6-triarylpyrylium salts in acetone were treated with an aqueous solution of Na_2CO_3 , and the mixture was stirred for 1 h at room temperature. Iodine was added, and the stirring was continued for an additional 12 h. The resulting dark mixture was poured into aqueous $Na_2S_2O_3$ solution, and the aqueous phase was extracted with CHCl₃. The organic layer was subjected to work-up followed by purification to obtain 2-aroyl-3,5-diarylfurans (6a-c). In this reaction, compounds 6a-c were purified by chromatography if the starting material was benzaldehyde. However, if the pyrylium salt was obtained from benzoic acid or its ester, the purification was easier and a precipitation in CHCl₃-hexanes generated pure product. In order to obtain the desired diarylfurans such as 7a-c from the 2-aroyl-3,5-diarylfurans 6a-c, we employed the Hallar–Bauer reaction.^{17,18}

A mechanism for the formation of pyrylium salts from esters or carboxylic acids is proposed herein (Scheme 3). We propose the formation of keto-enol equilibrium of acetophenone 4, induced by the Lewis acid, boron trifluoride etherate as the first step (Scheme 3, species 4A-B). The enol form of the acetophenone 4B initiates a nucleophilic attack onto the activated carboxylic functionality (2 or 3) followed by the elimination of -OR moiety (either hydroxyl or alkoxy group) (8) generating the β -diketone 9. The latter species is then proposed to undergo condensation with another enol





Scheme 3.

form of acetophenone (4B), forming the β -hydroxy- δ -diketone 10. This underscores the requirement for 2 equiv. of acetophenone 4 for the reaction to progress and to obtain respectable yields. The elimination of the hydroxyl group in the form of (OBF₃)⁻ will result in an unsaturated δ -diketone 11.

If the starting material was benzaldehyde instead of a benzoic acid or its ester, the leaving group in species similar to **10** is a hydride (in the form of hydrogen molecule).¹⁴ This important difference of the elimination of $(OBF_3)^-$ instead of a hydrogen molecule, in the proposed scheme, makes the reported procedure using aryl carboxylates or esters a facile reaction for the formation of pyrylium salts. The δ -diketone **11** is then enolized to form the specie **12**. Species **12** upon internal cyclization through the elimination of a BF₃ molecule generates the six-membered ring **13**, which is followed by the elimination of $(OBF_3)^-$ and is assisted by the lone-pair electrons on oxygen atom, producing the pyrylium salt **5** (Scheme 3).

In our experiments, we observed that the isolated pyrylium salts obtained from either benzoic acid or methyl benzoate is cleaner than those obtained from benzaldehyde (according to the TLC and NMR analyses). The only by-product obtained from the reaction using the benzoic acids or their methyl esters as starting material is compound 14, which is a result of condensation of three molecules of acetophenone.¹⁹ Unlike during the synthesis of pyrylium salts from benzaldehyde, the procedure using benzoic acid or its methyl ester does not involve any dehydrogenation in the last step of salt formation (vide supra), which in turn avoids formation of reduced by-products. Furthermore, using the *p*-nitro substituent required lower temperatures (approximately at 80°C) than p-methoxy (approximately 140°C) to form the pyrylium salt. In agreement

with the proposed mechanism, an electron-withdrawing moiety such as nitro in the *para* position to the carboxyl group makes the latter to be more susceptible to an electrophilic attack. The possibility to use various substituted aryl carboxylic acids or esters opens the door to a wide variety of diaryl furans, which perhaps earlier had to be synthesized through a corresponding aldehyde or some other means.

In summary, we have presented the synthesis of pyrylium salts from aromatic substituted carboxylic acids and esters. A possible mechanism involved in the formation of pyrylium salts starting from acetophenones and either carboxylic acid or a methyl ester mediated through a Lewis acid catalyst is proposed. These findings are very useful for the synthesis of biologically relevant diaryl furans from readily available and easily manageable aryl carboxylates and/or their corresponding esters.

Supplementary data

Syntheses of compound **5a–d**, **6a–c** and **7a–b**, and X-ray crystal structure of compound **14** and the corresponding crystallographic data are provided. The supplementary data is available online with the paper in ScienceDirect.

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- 19. Compound 14 was isolated and characterized fully, including X-ray crystallography (see supplementary material for more information).