

Highly Diastereoselective Friedel–Crafts Reaction of Furans with 8-Phenylmenthyl Glyoxylate

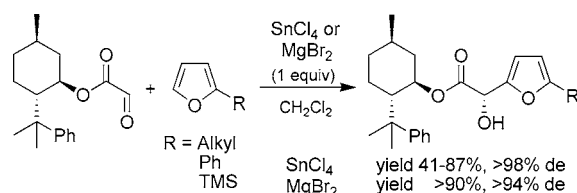
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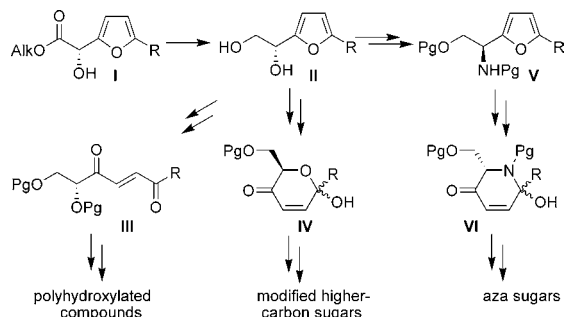
ABSTRACT



The Friedel–Crafts reaction of (1*R*)-8-phenylmenthyl glyoxylate with variously substituted furans was found to be efficiently promoted by SnCl₄ or magnesium salts with high diastereoselectivities. MgBr₂ performs especially well under simple, undemanding conditions, giving both high yields and high diastereoselectivities (>90%). The reaction afforded chiral substituted furan-2-yl-hydroxyacetic acid esters, compounds of potentially high synthetic interest.

The optically active furanyl α -hydroxyacetic acid esters (**I**) and products of their reductions, i.e., 1,2-diols of type **II**, are of great synthetic importance (Scheme 1).¹ The latter

Scheme 1. Application of Furanyl α -Hydroxyacetic Derivatives or Corresponding Diols in the Synthesis



alcohols, as a result of the presence of the furanyl moiety in their structure, can be easily converted under oxidizing conditions to very interesting linear (**III**)² as well as cyclic products (**IV**)^{3,4} (Scheme 1). Such an approach was utilized, e.g., for the synthesis of multifunctional chain compounds² or higher-carbon sugars.³ Diols bearing aryl substituents in position 5 were applied in the synthesis of spiroketal moiety of papulacandin D.^{4a} They can be transformed also to amino alcohol derivatives of type **V**,⁵ leading under oxidizing conditions to dihydropyridones **VI** useful in the synthesis of aza sugars.^{5,6}

The literature reports only a few methods for the synthesis of optically pure 2-furylcarbinols of type **I**. The most efficient methods rely on the enzymatic resolution of racemic mixtures using a lipase⁷ or on kinetic resolution using the Sharpless

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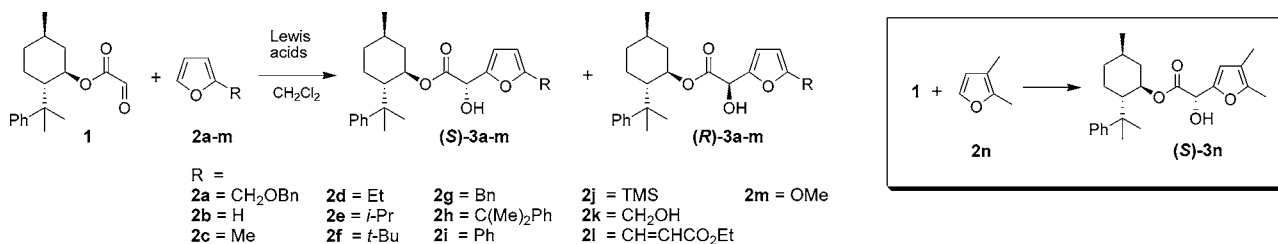
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Scheme 2. Friedel–Crafts Reaction of Variously Substituted Furans with the Glyoxylate **1**



reagent.⁸ The appropriate 1,2-diols of type **II** can be obtained via Sharpless asymmetric dihydroxylation of 5-substituted vinylfurans,⁴ and the simplest one of them, the unsubstituted diol (R = H) can be obtained from the sugar derivatives (e.g., D-glucal).⁹

The most attractive methods appear to be direct ones employing a synthesis from the corresponding furans and aldehydes. Such an approach can be performed in two ways: by addition of lithiated furans to the carbonyl group or by the Lewis acid catalyzed Friedel–Crafts reaction. Until now, there was no effective diastereoselective¹⁰ or enantioselective^{11,12} synthetic method for furan derivatives of type **I** based on the latter approach. However, there are known examples of efficient diastereoselective¹³ and enantioselective^{11,14,15} Friedel–Crafts reactions of carbonyl compounds with other aromatic derivatives.

Following our attempts to use chiral metallosalen complexes,¹² we decided on more detailed investigation of the possibility of using chiral derivatives of glyoxylic acid. Until now, menthyl glyoxylate has been tried for this reaction,^{10,12b} but as one could expect, it gave low asymmetric inductions. Because of that, we used its 8-phenylmenthyl derivative **1**¹⁶

(Scheme 2). Glyoxylate **1** had been originally applied to the nucleophilic additions of organometallic species (e.g., Grignard reagents) and ene reaction by Whitesell.^{17,18} In the literature, there are also examples of application of the glyoxylate **1**, e.g., in Diels–Alder,¹⁹ Morita–Baylis–Hillman,²⁰ nitroaldol,²¹ allyl,²² and vinyl substitution reactions.²³ Besides, it was also used by Bigi et al. in the Friedel–Crafts reaction, but only with phenols^{13a,b} and O-protected phenols^{13c} in the presence of TiCl₄ or SnCl₄, leading to 2- and 4-hydroxymandelic esters, respectively with high stereoselectivities. According to the literature, these Lewis acids are also the most efficient in other types of reactions with glyoxylate **1** (usually, 1 equiv is needed).^{18–23}

In this paper, we describe a highly diastereoselective Friedel–Crafts reaction of (1*R*)-8-phenylmenthyl glyoxylate (**1**) with variously substituted furans **2a–n** (Scheme 2, 14 examples). In our study, SnCl₄ gave higher diastereoselectivities (>98% de) compared to those of TiCl₄. We have studied extensively the reaction of **1** with benzyl furfuryl ether (**2a**), which was originally used by Achmatowicz in the total synthesis of racemic uloses.³ This reaction, in the presence of a stoichiometric amount of SnCl₄, proceeds to give good yield and very high diastereoselectivity (Table 1, entry 1). We have tested also several other furan systems in this reaction, e.g., furan itself, and 2-methyl-, benzyl-, and phenyl-substituted furans, and each time we have observed also a very high diastereoselectivity (>99% de, Table 1, entries 2–6). This procedure can be successfully applied even to 2-trimethylsilylfuran (**2j**), unprotected furfuryl alcohol (**2k**), and furans bearing an electron-withdrawing group (**2l**)

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Table 1. Friedel–Crafts Reaction of Furans with **1** Promoted by SnCl₄^a

entry	furan	time (h)	product		
			no.	yield (%) ^b	de (%) ^c
1	2a	5	3a	87	>99
2	2b	2	3b	56	>99 (<i>S</i>)
3	2c	2	3c	41	>99 (<i>S</i>)
4	2g	2	3g	79	>99
5	2h	2	3h	50	>99
6	2i	4	3i	87	>99
7	2j	2	3j	45	>99
8	2k	2	3k	60	>99
9	2l	5	3l	63	98

^a The reactions were carried out using 0.5 mmol of the glyoxylate **1** in 3.0 mL of CH₂Cl₂, 1 equiv of SnCl₄, and 1.5 equiv of furan at –78 °C.

^b Isolated yield. ^c Diastereomeric excess determined by HPLC and ¹H NMR.

(entries 7–9). However, the yields were substantially lower (about 50%) in many cases, probably because of partial decomposition of the furan derivatives.

Therefore, we decided to search for milder Lewis acids that would allow these reactions to be conducted efficiently and highly stereoselectively, catalysts that would be less toxic than SnCl₄, require less demanding conditions, and avoid the necessity of using dry solvents. We focused our attention, inter alia, on zinc and magnesium salts. Zinc bromide was used by our research group in the reactions with chiral derivatives of glyoxylic acids, often giving high stereoselectivities, e.g., in the allylation reaction.^{22b} As a model furan substrate, benzyl furfuryl ether (**2a**) was used, but the reaction using zinc bromide gave a moderate diastereomeric excess (~65% de, Table 2, entry 1). Replacing **2a** with silvan (**2c**)

Table 2. Screening of Lewis Acids in the Reaction of **1** with **2a**^a

entry	Lewis acid	time (h)	yield (%) ^b	de (%) ^c
1	ZnBr ₂	4	60	65
2	MgCl ₂	24	61	85
3	MgBr ₂ , anhydrous	2	96	89
4	MgBr ₂ ·Et ₂ O	5	93	86
5	MgBr ₂ ·0.5H ₂ O	5	97	90
6	MgBr ₂ ·1.5H ₂ O	24	58	91
7	MgBr ₂ (20 mol %)	72	39	65

^a The reactions were carried out using 0.5 mmol of **1** in 2.5 mL of CH₂Cl₂, 1 equiv of Lewis acid (entries 1–6), and 1.5 equiv of **2a** at 20 °C.

^b Isolated yield. ^c Determined by HPLC and ¹H NMR.

gave somewhat better results (80% de). These results were utterly unsatisfactory because most of the products of these reactions were oils.

We found magnesium chloride to be a stereochemically more effective (85% de) Lewis acid catalyst for the reaction of **2a** with **1** (Table 2, entry 2). However, the yield was rather moderate, and the reaction required prolonged time. Because

of that, we decided to try other easily available magnesium salts. The best results were obtained for magnesium bromide, which appeared to be much more active than MgCl₂, requiring only 2 h at room temperature to complete the reaction (entry 3) with a slight increase of the asymmetric induction. Magnesium bromide etherate can be also used successfully (entry 4).

We have also investigated the effect of the presence of water and the possibility of using catalytical amounts of MgBr₂. In the case of using anhydrous MgBr₂, trace amounts of byproducts are observed. Addition of water in an amount of ca. 0.5–0.7 equiv with respect to the magnesium salt had practically no influence on the asymmetric induction nor the yield (entry 5), but it did help to eliminate byproducts.²⁴ In order to obtain such hydrated magnesium bromide, it is enough to keep anhydrous MgBr₂ or its etherate in an open flask for ca. 12 h.²⁵ The presence of water in an amount slightly exceeding 1 equiv slows down the reaction rate substantially, but the selectivity is still high (entry 6). In the case of using MgBr₂·6H₂O, the reaction practically does not occur.

In conclusion, MgBr₂ containing less than 1 equiv of water is an efficient promoter of this reaction. The reaction in the presence of MgBr₂ is not reversible,²⁶ and the diastereomeric ratio is practically constant during the reaction.²⁷ Unfortunately, in order to obtain high diastereomeric excess, one has to use stoichiometric amounts of the magnesium salts, probably because of the strong affinity of magnesium to the product. In the case of using catalytical amounts of MgBr₂, a substantial drop in the selectivity as well as low reaction yield are observed (entry 7)

The results of the model reaction using a stoichiometric amount of MgBr₂, although inferior to the diastereoselectivities using SnCl₄, demonstrate that this reaction can be easily conducted at room temperature without a need for using dry solvents and reagents with very high yield. Prompted by very good results in the reaction of 8-phenylmenthyl glyoxylate (**1**) with benzyl furfuryl ether (**2a**) in the presence of the magnesium salts, we decided to investigate the possibility of using other furans for the reaction in the presence of conditioned MgBr₂, containing ca. 0.5 equiv of water (Table 3). Because of the very attractive properties of MgCl₂,²⁸ we also studied systematically the possibility of using it in the reactions in question.

Alkyl derivatives of furan are more reactive than benzyl furfuryl ether (**2a**). Because of that, MgCl₂ catalyzes these reactions, giving very good yields (usually >90% after 24 h). However, in many instances, the obtained inductions do not exceed 90%, usually being about 85%, as in the case of the furans **2a** (Table 2, entry 2) as well as **2c** (Table 3, entry 3). The rare exceptions are the furans substituted with benzyl

(24) The TLC chromatogram of the reaction mixture is very neat.



















(25) The weight of anhydrous MgBr₂ was steadily rising.

(26) MgBr₂ (1 equiv) added to a mixture of product **3a** (65% de) causes no change in diastereomeric ratio after 24 h.

(27) Diastereomeric excess of **3a** in the reaction promoted by 1 equiv of MgBr₂ was practically constant after 5, 10, 15, 30 min, 1 h and 3 h.

(28) Despite low activity, from the application viewpoint MgCl₂ seems to be an ideal promoter-Lewis acid, because of minimum toxicity, low cost, and ease of handling.

Table 3. Application of Various Furans (**2a–n**) in the Magnesium-Promoted Reaction with **1**: Scope and Limitation^a

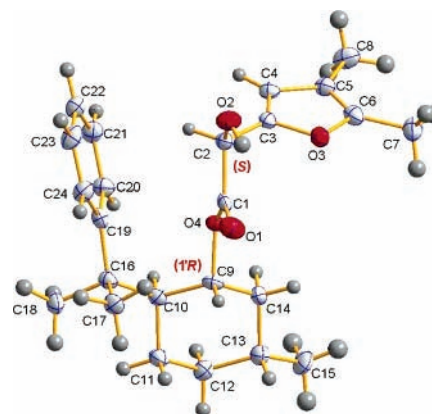
entry	furan	Lewis acid (1 equiv)	time (h)	product		
				no.	yield (%) ^b	de (%) ^c
1		MgCl ₂	18	3b	72	88 (<i>S</i>)
2		MgBr ₂	3	3b	97	90 (<i>S</i>)
3		MgCl ₂	24	3c	98	86 (<i>S</i>)
4		MgBr ₂	2	3c	94	94 (<i>S</i>)
5		MgBr ₂	3	3n	97	94 (<i>S</i>)
6		MgBr ₂	3	3d	97	95
7		MgBr ₂	3	3e	91	95
8		MgBr ₂	3	3f	97	97
9		MgCl ₂	24	3g	98	96
10		MgBr ₂	2	3g	98	96
11		MgBr ₂	2	3h	96	97
12		MgCl ₂	45	3i	97	98
13		MgBr ₂	3	3i	98	99
14		MgCl ₂	24	3j	72	92
15		MgBr ₂	3	3j	98	98
16		MgBr ₂	5	3k	85	79
17		MgBr ₂	24	3l	70	83
18 ^d		MgBr ₂	2	3m	95	84

^a The reactions were carried out using 0.5 mmol of **1** in 2.5 mL of CH₂Cl₂, 1 equiv of magnesium salt, and 1.5 equiv of furan at 20 °C. ^b Isolated yield. ^c Determined by HPLC and ¹H NMR. ^d The reaction was carried out at –5 °C.

(**2g**), phenyl (**2i**), and trimethylsilyl (**2j**), where the asymmetric inductions in the presence of MgCl₂ exceed 90% de (Table 3, entries 9, 12, and 14, respectively). In the other cases, much better results are obtained using the more active MgBr₂. Actually, all alkyl derivatives of furan **2c–h** and **2n**, and even phenylfuran (**2i**) and trimethylsilylfuran (**2j**), in the presence of MgBr₂, make it possible obtain the products having very high diastereomeric excesses (94–99%). Although the stereoselectivities obtained for MgBr₂ are slightly lower compared to those with SnCl₄, the reaction gives clearly better yields (>90% in not more than 3 h) and is much easier to carry out.

As shown in Table 3, the synthesis is highly selective (usually >90% de). The differences are very small for the furans substituted at the 2-position with alkyls of various spatial requirements (**2c–h**), aryl (**2i**), trimethylsilyl (**2j**), and even 2,3-disubstituted furans (**2n**). Lower selectivities (~80% de) are obtained only for furans **2k–m**.

Out of the 14 novel products, two compounds (**3b**, **3c**) have been subjected to determination of the absolute configuration by chemical correlations,^{9,12b} and the configuration of **3n** has been directly determined using X-ray crystal-

**Figure 1.** X-ray crystal structure of compound (*S*)-**3n**

lographic analysis (Figure 1). In all the cases, a product of (*S*)-configuration was obtained from (*1R,2S,5R*)-8-phenylmenthyl glyoxylate (**1**). Such a direction of induction is in accordance with the literature data concerning other additions and cycloadditions to **1**.^{17–23} One can assume with a high likelihood that the induction direction is identical for all of the investigated reactions of furans with aldehyde **1** in the presence of SnCl₄ or MgBr₂.

In conclusion, we have developed a general, efficient, and undemanding method for the diastereoselective synthesis of chiral variously 5-substituted furan-2-yl-hydroxyacetic acid esters, compounds of significant synthetic interest, with high optical purity (de usually over 90% up to >99%). Although SnCl₄ allows for obtaining very high diastereoselectivities, the magnesium salts seem to be more attractive since they give better yields. The reaction is clearly and reproducibly promoted by inexpensive and low-toxicity MgBr₂ and MgCl₂ at room temperature without the need of using dry solvents and inert atmosphere. According to our knowledge, this is the first example of a highly stereoselective reaction of furans with glyoxylates.

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Supporting Information Available: Experimental procedures and analytical data for all new compounds (**3a–n**) with reprints of NMR spectra and X-ray information for (*S*)-**3n** in CIF format. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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