



A concise method for the synthesis of 2-tetralone by titanium tetrachloride-promoted cyclization of 4-aryl-2-hydroxybutanal diethyl acetal

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ABSTRACT

4-Aryl-2-hydroxybutanal diethyl acetal, prepared from the reaction of benzyl Grignard reagent and glycidaldehyde diethyl acetal, was treated with titanium tetrachloride to give 2-tetralone in good yield. This highly efficient transformation involves tandem oxonium formation, intramolecular Friedel–Crafts alkylation, deethoxylation, and tautomerization in the same flask.

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Substituted 2-tetralones have played an important role in organic synthesis because they are highly reactive and suitable as starting materials for a wide range of compounds with biological activities, as well as being the precursors of several biologically active natural products.¹ However, in comparison with 1-tetralones, 2-tetralones are often very expensive, less stable, and much more difficult to be synthesized. We have used 4-methoxy-1,3-dioxolan-2-one as a new and unique functionality in organic synthesis.² 5-Arylethyl-4-methoxy-1,3-dioxolan-2-one **1** was treated with 2 equiv of TiCl_4 to give 2-tetralone in good yield. A plausible mechanism of 2-tetralone formation is via a key intermediate **A** derived from the decomposition of cyclic carbonate **1** by TiCl_4 .³ Intrigued by this mechanistic hypothesis, we proposed that 1,1-dialkoxy-4-arylbutan-2-ol **2** should also be a useful precursor of the oxonium intermediate **A** (Fig. 1). Here we describe our synthesis of 2-tetralone from the acetal of 4-aryl-2-hydroxybutanal **2**.

1,1-Dialkoxy-4-arylbutan-2-ol **2** was retrosynthesized by breaking its C(3)–C(4) bond. The synthetic design included glycidaldehyde dialkylacetal **4**⁴ and benzylic Grignard reagent **5'** (Fig. 1 and Eq. 1).⁵

The epoxide **4a** was treated with benzylmagnesium chloride (**5a'**) in the presence of CuBr catalyst at 0 °C to give 2-hydroxy-4-phenylbutanal diethyl acetal (**6a**) in 82% yield.⁶ After the diluted solution of diethyl acetal **6a** was treated with 2 equiv of TiCl_4 at 0 °C, 2-tetralone (**7a**) was isolated in 84% yield (Scheme 1). The result indicates that the diethyl acetal **6a** is a useful precursor of 2-tetralone, as elucidated in Figure 1. In comparison with the cyclic carbonate **1** prepared by multiple-step synthesis,² the diethyl acetal **6a** was prepared in one step from Grignard reagent and oxirane **4a** in high yield.

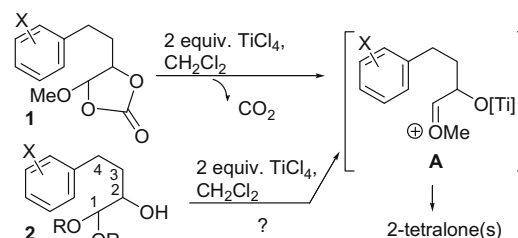
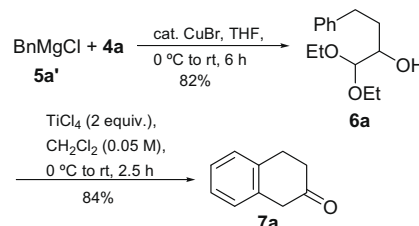
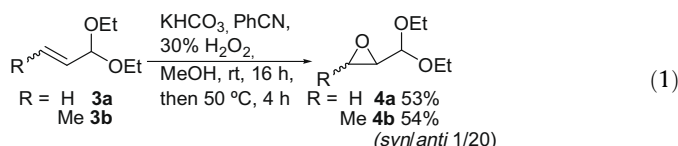


Figure 1. A plausible mechanism for 2-tetralone formation from compound **1** or **2** via the common intermediate **A**.

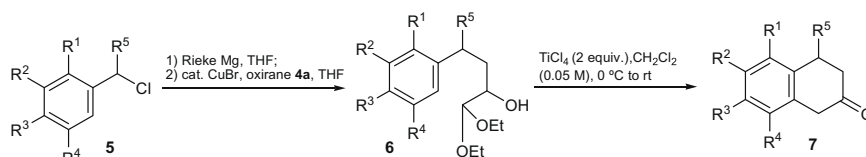


Scheme 1. Synthesis of 2-tetralone (**7a**) by TiCl_4 -promoted intramolecular cyclization of 4-phenyl-2-hydroxybutanal diethyl acetal.



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Some benzyl Grignard reagents can be difficult to be prepared or inaccessible through the conventional treatment of magnesium

Table 1Preparation of 2-tetralone **7** from 4-aryl-2-hydroxyacetal **6**, which is derived from the reaction of glycidaldehyde diethyl acetal (**4a**) with benzylmagnesium chloride **5'**

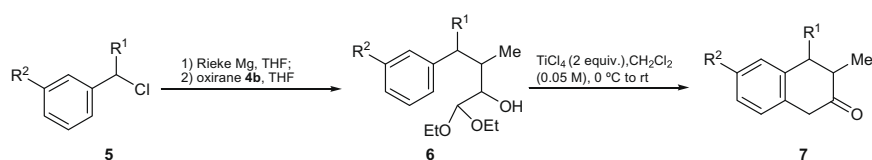
Entry	Benzyl chloride					Metalation			Epoxide 4a ring opening			2-Tetralone formation	
	R ¹	R ²	R ³	R ⁴	R ⁵	Temp. (°C)	Time (h)	Temp. (°C)	Time (h)	Yield (%)	Time (h)	Yield (%) ^a	
1	OMe	H	H	H	H	5b	−20 to −10	1	−40–rt	2.5	82 6b	2	88 7b
2	H	OMe	H	H	H	5c	−40	1	−40–rt	4	89 6c	2	83 7c
3	H	H	OMe	H	H	5d	−40	1	−40–rt	3.5	86 6d	2	85 7d
4	Me	H	H	H	H	5e	−80 to −50	3	−50–rt	2	83 6e	3	87 7e
5	H	Me	H	H	H	5f	−80 to −50	3	−50–rt	2.5	85 6f	3	65 7f ; 25 7f'
6	H	H	Me	H	H	5g	−80 to −50	3	−50–rt	2	78 6g	3.5	86 7g
7	H	Cl	H	H	H	5h	−50	0.5	−50–rt	3	69 6h	5	71 7h ; 3 7h'
8	H	H	Cl	H	H	5i	−50	0.5	−50–rt	3.5	77 6i	8	68 7i
9	H	Me	Me	H	H	5j	−80 to −50	2	−50–rt	3	95 6j	2.5	64 7j ; 25 7j'
10	Me	H	Me	H	H	5k	−80 to −50	1	−50–rt	2.5	75 6k	2.5	79 7k
11	Me	H	H	Me	H	5l	−10 to 0	3	−10–rt	4	79 6l	2.5	96 7l
12	H	H	H	H	Me	5m	−50	1	−50–rt	2	77 6m	3	86 7m
13	H	H	H	H	Et	5n	−50	1	−50–rt	2	76 6n	2.5	79 7n
14	H	H	H	H	Ph	5o	−50	0.5	−50–rt	2	72 6o	2.5	86 7o

^a 8-Methyl-2-tetralone (**7f'**) was formed as a minor product which was inseparable from **7f**; 8-chloro-2-tetralone (**7h'**) was formed as a minor product; and 7,8-dimethyl-2-tetralone (**7j'**) was formed as a minor product which was inseparable from **7j**.

powder or turnings with benzyl halide.⁷ Nevertheless, they can be prepared in situ by the reaction of highly reactive Rieke Mg with the corresponding benzyl chlorides **5** in tetrahydrofuran (THF) at lower temperature (Table 1).⁸ The resulting benzylmagnesium chlorides react regioselectively with glycidaldehyde diethyl acetal (**4a**) in the presence of CuBr to give the corresponding diethyl acetal **6**, with yields of 69–95% (Table 1). 4-(2-Methoxyphenyl)butanal diethyl acetal (**6b**) was treated with TiCl₄ at 0 °C to give 5-methoxy-2-tetralone (**7b**) in 88% yield (entry 1, Table 1). When the C(4)-aryl group of the diethyl acetal **6** was 4-methoxyphenyl (i.e., **6d**), 4-methylphenyl (i.e., **6g**), or 4-chlorophenyl (i.e., **6i**), it was treated with TiCl₄ to give the corresponding 7-substituted 2-tetralone in excellent yields (entries 3, 6, and 8). When the C(4)-aryl group of the diethyl acetal **6** was 2-methylphenyl (i.e., **6e**), 2,4-dimethylphenyl (i.e., **6k**), or 2,5-dimethylphenyl (i.e., **6l**), it was treated with TiCl₄ to give the corresponding 2-tetralone in excellent yields (entries 4, 10, and 11). The results indicate that the intramolecular Friedel–Crafts reaction can be used in the preparation of 7-chloro-, 7-methyl-, 7-methoxy-, 5,7-dimethyl-, and 5,8-dimethyl-2-tetralones in good yields.

In order to introduce the substituent at C(4) of 2-tetralone, the Grignard reagent derived from secondary benzyl halide is needed. α -Methylbenzyl chloride (**5m**) was treated with Rieke Mg by the standard protocol, and the resulting Grignard reagent was reacted with oxirane **4a** in the presence of CuBr to give the acetal **6m** in 77% yield. Further treatment with TiCl₄ gave 4-methyl-2-tetralone (**7m**) in 86% yield (entry 12). Similarly, 4-ethyl-2-tetralone (**7n**) and 4-phenyl-2-tetralone (**7o**) were prepared in good yields starting from the corresponding α -ethylbenzyl chloride (**5n**) and α -phenylbenzyl chloride (**5o**), respectively (entries 13–14). Thus, this method allows the introduction of a C(4)-substituent on 2-tetralone.

In order to introduce a C(3) substituent on 2-tetralone, the 1,2-disubstituted oxirane is needed. The oxirane **4b** was treated with benzylmagnesium chloride (**5a'**) at 0 °C to give 1,1-diethoxy-3-methyl-4-phenylbutan-2-ol (**6p**) in 73% yield. Interestingly, no CuBr is needed in this reaction. When the diluted solution of acetal **6p** was treated with TiCl₄, 3-methyl-2-tetralone (**7p**) was isolated in 86% yield (Table 2, entry 1). Similarly, the Grignard reagent derived from 3-methoxybenzyl chloride **5c** was treated with oxirane

Table 2Preparation of 2-tetralone **7** from 4-aryl-2-hydroxyacetal **6**, which was derived from the reaction of oxirane **4b** with benzylmagnesium chloride **5'**

Entry	Benzyl chloride			Metalation		Epoxide 4b ring opening			2-Tetralone formation	
	R ¹	R ²		Temp. (°C)	Time (h)	Temp. (°C)	Time (h)	Yield (%)	Time (h)	Yield (%)
1	H	H	5a	— ^a	— ^a	0–rt	24	73 6p	3	86 7p
2	H	OMe	5c	−40	1	−40–rt	24	58 6q	2.5	79 7q
3	Ph	H	5o	−50	0.5	−50–rt	24	56 6o''	3	58 7o'' (<i>syn/anti</i> 1/2.8)

^a Commercially available benzyl magnesium chloride (**5a'**) was used.

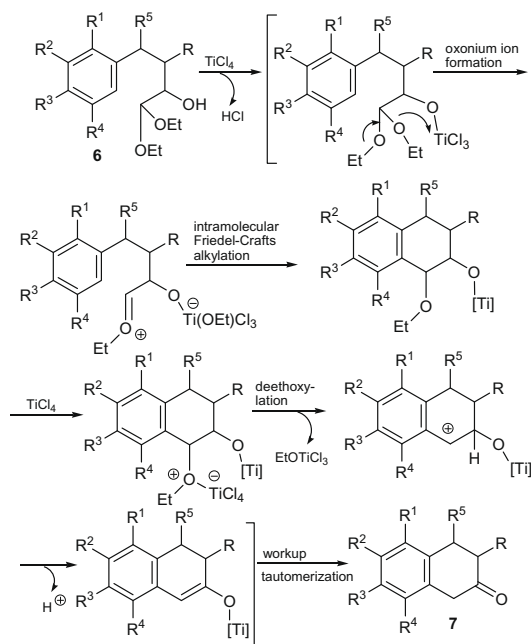


Figure 2. A plausible mechanism for 2-tetralone **7** formation from compounds **6**.

4b followed by TiCl₄-promoted cyclization to give 6-methoxy-3-methyl-2-tetralone (**7q**) in 79% yield (Table 2, entry 2).

In order to introduce the substituents at both the C(3)- and C(4)-positions of 2-tetralone, the α -substituted-benzyl chloride and 1,2-disubstituted oxirane **4b** were used as starting materials. α -Phenylbenzyl chloride (**5o**) was treated with Rieke Mg by the standard protocol, and the resulting Grignard reagent was reacted with oxirane **4b** at -50°C to give α -hydroxy acetal **6o''** in 56% yield. Further treatment with TiCl₄ gave 3,4-dimethyl-2-tetralone (**7o''**) as a mixture of two diastereomers (*syn/anti* 1/2.8) in 58% yield (Table 2, entry 3). The stereochemistry of the major isomer

was determined by 2D-NOESY and from the coupling constant of C(4)-H and C(3)-H. In summary, 4-aryl-2-hydroxybutanal diethyl acetal **6** was easily prepared from the reaction of benzyl organometallic reagent and glycidaldehyde diethyl acetal **4**. The diluted solution of acetal **6** was treated with TiCl₄ to give 2-tetralones in good yields. A variety of substituents can be introduced at all positions of 2-tetralone except C(1) by this method. The 2-tetralone formation involves tandem oxonium ion formation, intramolecular Friedel-Crafts alkylation, deethoxylation, and tautomerization in the same flask (Fig. 2).³ To the best of our knowledge, this two-step synthetic sequence is the most efficient and direct way to prepare 2-tetralone derivatives.

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