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# 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.



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.

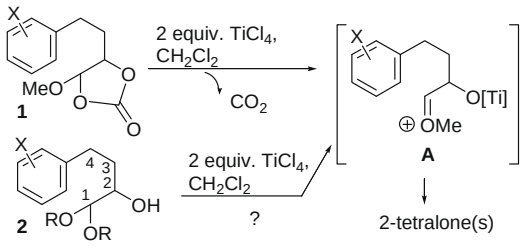
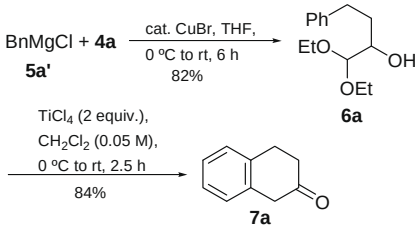
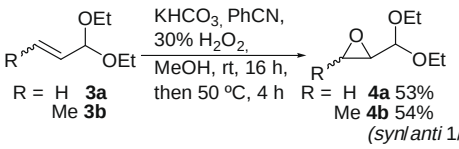



**Figure 1.** A plausible mechanism for 2-tetralone formation from compound **1** or **2** via the common intermediate **A**.




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




(1)

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

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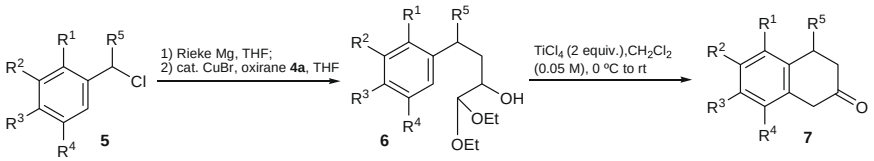
**Table 1**
Preparation of 2-tetralone **7** from 4-aryl-2-hydroxyacetal **6**, which is derived from the reaction of glycidaldehyde diethyl acetal (**4a**) with benzylmagnesium chloride **5′**




| 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** |

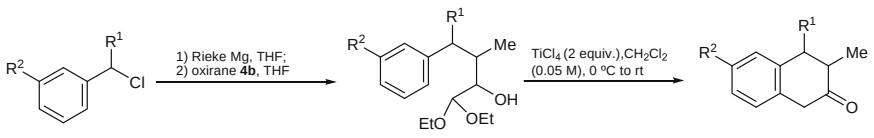
[a] 8-Methyl-2-tetralone (**7f′**) was formed as a minor product which was inseparable from **7f**; 8-chloro-2-tetralone (**7h′**) was formed as a minor product; and 7,8-dimethyl-2-tetralone (**7j′**) was formed as a minor product which was inseparable from **7j**.

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 $TiCl_4$ 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 $TiCl_4$ 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 $TiCl_4$ 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 $TiCl_4$ 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 $TiCl_4$, 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 2**
Preparation 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″** (*syn*/*anti* 1/2.8) |

[a] Commercially available benzyl magnesium chloride (**5a′**) was used.

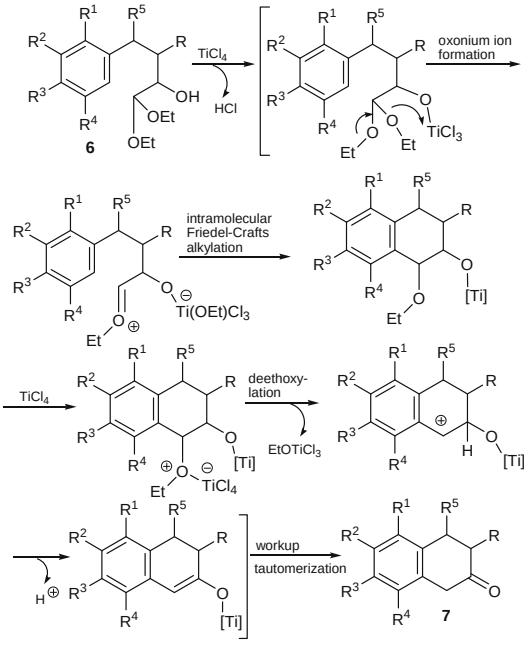



**Figure 2.** A plausible mechanism for 2-tetralone **7** formation from compounds **6**.

**4b** followed by $TiCl_4$-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 $TiCl_4$ 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 $TiCl_4$ 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.

## Acknowledgments

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