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$TiCl_4$-promoted intramolecular cyclization of 4-methoxy-5-arylethyl-1,3-dioxolan-2-ones: an expedient method to prepare 2-tetralones

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ABSTRACT

DABCO is a very effective catalyst in the formation of 4-methoxy-5-arylethyl-1,3-dioxolan-2-ones **12** from the corresponding α-carbonatoaldehyde. Intramolecular cyclization of cyclic carbonates **12** promoted by $TiCl_4$ affords 2-tetralones **13** containing a variety of substituents in high yields.

2-Tetralones **A** are important precursors in the synthesis of biologically active compounds and natural products.[1,2] In comparison with 1-tetralones, 2-tetralones often are less stable, more expensive, and more difficult to be synthesized. Synthetic methods for generating 2-tetralones are categorized as direct building of tetralines, transformations in a pre-formed tetralinic ring or naphthalene precursor, and ring-expansion of 1-indanone *exo*-methylene derivatives.[1] Among them, the most efficient method is to build 2-tetralone via a direct intramolecular cyclization, such as Rh(II)-catalyzed decomposition of α-diazocarbonyl **1**,[3] intramolecular cyclization of iodonium ylides **2** with CuCl,[4] the Friedel–Crafts acylation–cycloalkylation sequence from the reaction of acyl chloride **3** and simple alkene,[5] or Pummerer rearrangement–mediated cyclization of aryl β-ketosulfoxides **4** (Fig. 1).[6] We previously reported that DABCO is an excellent catalyst in the formation of 4-methoxy-5-alkyl-1,3-dioxolan-2-one **5** from the corresponding α-carbonatoaldehyde. In the presence of $TiCl_4$, compound **5** is useful to prepare either α,α-diarylethanol **6** or α-arylmethyl alkyl ketones **7** depending on the electron richness of the aryl nucleophiles. Compound **5** can be considered as a synthetic equivalent of either synthon **I** or **II** (Fig. 2).[7] Following this line of work, we are interested in the intramolecular aromatic electrophilic substitution of cyclic carbonates tethered with an aryl group. Herein, we report our results of 2-tetralone formation from 4-methoxy-5-arylethyl-1,3-dioxolan-2-ones promoted by $TiCl_4$.

The allyl methyl carbonates (**11a–k**) were prepared in modest to good yields by the one-pot reaction of methyl chloroformate

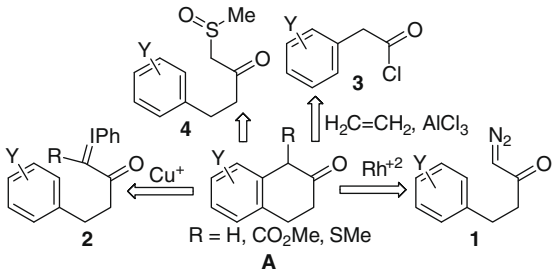

Figure 1. Typical methods used to prepare 2-tetralone **A** from the intramolecular cyclization of compounds **1–4**.

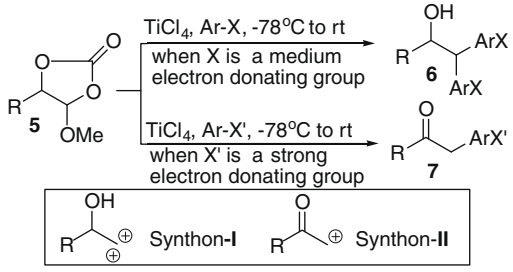

Figure 2. Cyclic carbonate **5** is a synthetic equivalent of either synthon-**I** or **II** depending on the electron richness of the aromatic nucleophiles.

with allyloxylmagnesium bromides, which were prepared in situ by either the reaction of vinylmagnesium bromide (**9**) with aryl-substituted aldehydes (**8a–b** and **8d–k**)[8] or the reaction of

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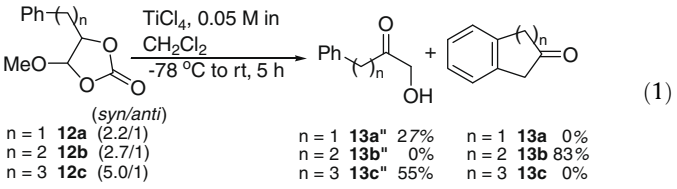
3-phenylpropylmagnesium bromide (**10**) with acrolein (**8c**). When the methyl allyl carbonates **11** in CH_2Cl_2 were sequentially treated with O_3 and Ph_3P, the corresponding α-carbonatoaldehyde intermediates were formed. When 0.2 equiv of DABCO (1,4-diazabicyclo[2.2.2]octane) was added to this solution of crude aldehydes in MeOH and the mixture was stirred for 8 h, the cyclic carbonates **12** were formed as a mixture of two diastereomers in excellent yields (Scheme 1).[7,9] In general, the *syn*-isomer was the major and less polar product. The relative stereochemistry of the two diastereomers was confirmed using the 2D-NOESY technique. The C-4 protons of the *syn*- and *anti*-isomers have well-separated chemical shifts, and the latter one usually appears more downfield. The *syn*- and *anti*-ratio are easily determined by ^1H NMR integration. Both diastereomers are separable by silica gel column chromatography. However, their separation was not needed because both isomers yielded the same product in this study.

When the diluted solution (about 0.05 M) of benzyl-substituted cyclic carbonate **12a** in CH_2Cl_2 was treated with 2 equiv of $TiCl_4$, benzyl hydroxymethyl ketone **13a**″ was formed in 27% yield. The 3-phenylpropyl-substituted analogue **12c** also produced hydroxymethyl ketone **13c**″ in 55% yield (Eq. 1). Interestingly, under similar conditions 2-phenylethyl-substituted cyclic carbonate **12b** produced 2-tetralone **13b** in 83% yield and no hydroxymethyl ketone 13b″ was isolated (Eq. 1). These results indicate that the intramolecular cyclization is applicable only to six-membered ring formation and not to five- or seven-membered ring formation.



(1)

The cyclic carbonates **12a–c** were treated with $TiCl_4$ to generate the oxonium intermediates **12a-1–12c-1,** respectively (Fig. 3). Among them, only intermediate **12b-1** underwent cyclization to give 2-tetralone (**13b**). The other two intermediates (**12a-1** and **12c-1**) were decomposed by water during workup to produce the α-hydroxyaldehydes, which then underwent ene-diol rearrangement to give the corresponding α-hydroxymethyl ketones (**13a**″ and **13c**″), respectively (Fig. 3).[10]

To determine the optimal condition for 2-tetralone formation, compound **12b** was treated with different amounts of $TiCl_4$ at −78 °C. We found that 2 mol equiv of $TiCl_4$ produced the best yield of the desired product (Table 1, entries 1–3).[11] Using this optimized condition, we tested a variety of the 2-arylethyl-substituted cyclic carbonates (Eq. 2); Table 1 lists out the results. Phenyl groups with

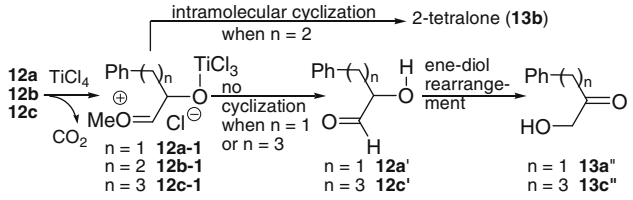


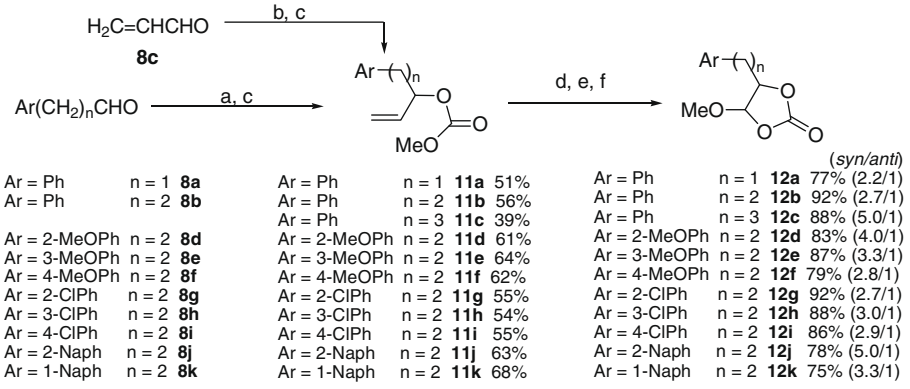
Figure 3. The reaction pathway of the intermediates **12a-1**, **12b-1**, and **12c-1** depends on the spacer length (i.e., *n* value).

Table 1
The formation of 2-tetralones from the intramolecular cyclization of 2-arylethyl-substituted cyclic carbonates **12b–k** promoted by $TiCl_4$

Entry	Carbonate	$TiCl_4$ (equiv)	Time (h)	Product	Yield (%)
1	**12b**	1	8	**13b**	46
2	**12b**	1.5	7	**13b**	57
3	**12b**	2.0	5	**13b**	83
4	**12d**	2.0	4	**13d**	69
5	**12e**	2.0	4	**13e**	75
6	**12f**	2.0	4	**13f**	73
7	**12g**	2.0	5	**13g**	65
8	**12h**	2.0	5	**13h**	63
9	**12i**	2.0	5	**13i**	32[a]
10	**12i**	4.0	5	**13i**	58
11	**12j**	2.0	5	**13j**	89
12	**12k**	2.0	5	**13k**	88

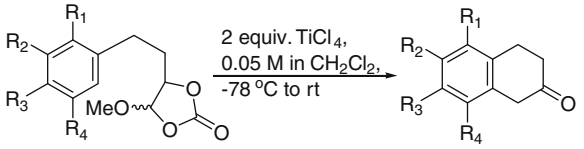
[a] 7-Chloro-1,2,3,4-tetrahydronaphthalene-1,2-diol (**13i**′) was isolated in 23% as a mixture of cis- and trans-isomers.

a 2-methoxy- or 4-methoxy-substituent produced the corresponding 2-tetralones in good yields (entries 4 and 6). The phenyl group with a 3-methoxy substituent generated only 6-methoxy-2-tetralone (**13e**) in good yield; the other regioisomer (8-methoxy-2-tetralone) was not formed (entry 5). We next studied the phenyl group with the chlorine deactivating group. The phenyl group with a 2-chloro- or 4-chloro-substituent produced the corresponding 2-tetralones in good yields (entries 7 and 8). With the 4-chloro-phenyl compound **12i**, we obtained not only 2-tetralone **13i** but also 7-chloro-1,2,3,4-tetrahydronaphthalene-1,2-diol (**13i**′) (entry 9). When the reaction mixture was treated with 4 equiv of $TiCl_4$, the yield of 2-tetralone **13i** increased to 58% (entry 10). Presumably, the precursor of compound **13i**′ is convertible to 2-tetralone **13i** by the extra amount of $TiCl_4$. When we replaced the aryl group of 2-arylethyl-substituted cyclic carbonate with 2-naphthyl and 1-naphthyl, we obtained 1,2-dihydrophenanthren-3(4*H*)-one (**13j**) and 3,4-dihydrophenanthren-2(1*H*)-one (**13k**) in 89% and 88% yields, respectively (entries 11 and 12). In the intermolecular reaction, we found that the electron richness of the aromatic compound is crucial to the success of its reaction with cyclic carbonate **5**.[7] Interestingly,



Scheme 1. Reagents and conditions: (a) $H_2C{=}CHMgBr$ (**9**), THF, 0 °C, 1 h; (b) $Ph(CH_2)_3MgBr$ (**10**), THF, 0 °C, 1 h; (c) $ClCO_2Me$, 0 °C to rt, 5 h; (d) O_3, CH_2Cl_2, −78 °C; (e) Ph_3P, −78 °C to rt, 5 h; (f) DABCO (0.2 equiv), MeOH, rt, 8 h.

the results given in Table 1 indicate that the deactivated chlorophenyl group can still be used to form 2-tetralone. This property will make this methodology more versatile and useful in the preparation of 2-tetralone with a variety of substituents.

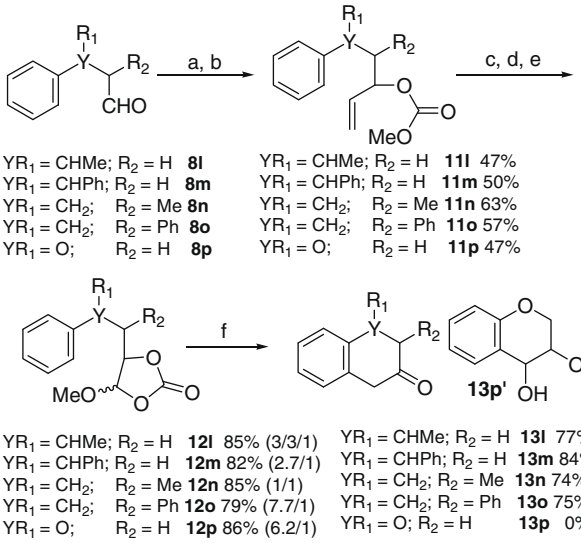


$R_1 = R_2 = R_3 = R_4 = H$	**12b**	$R_1 = R_2 = R_3 = R_4 = H$	**13b**
R_1 = OMe; $R_2 = R_3 = R_4 = H$	**12d**	R_1 = OMe; $R_2 = R_3 = R_4 = H$	**13d**
R_2 = OMe; $R_1 = R_3 = R_4 = H$	**12e**	R_2 = OMe; $R_1 = R_3 = R_4 = H$	**13e**
R_3 = OMe; $R_1 = R_3 = R_4 = H$	**12f**	R_3 = OMe; $R_1 = R_3 = R_4 = H$	**13f**
R_1 = Cl; $R_2 = R_3 = R_4 = H$	**12g**	R_1 = Cl; $R_2 = R_3 = R_4 = H$	**13g**
R_2 = Cl; $R_1 = R_3 = R_4 = H$	**12h**	R_2 = Cl; $R_1 = R_3 = R_4 = H$	**13h**
R_3 = Cl; $R_1 = R_3 = R_4 = H$	**12i**	R_3 = Cl; $R_1 = R_3 = R_4 = H$	**13i**
R_2, R_3 =  $R_1 = R_4 = H$	**12j**	R_3, R_4 =  $R_1 = R_2 = H$	**13j**
R_1, R_2 =  $R_3 = R_4 = H$	**12k**	R_1, R_2 =  $R_3 = R_4 = H$	**13k**

(2)

We next turned our attention to the possibility of functionalizing the C-3 and C-4 positions of 2-tetralone. The cyclic carbonates (**12l–o**) were prepared from aryl-substituted aldehydes (**8l–o**) following the method described above. They were treated with $TiCl_4$ to produce 4-methyl-2-tertralone (**13l**), 4-phenyl-2-tetralone (**13m**), and 3-methyl-2-tetralone (**13n**), respectively, in excellent yields (Scheme 2). 2-Tetralone **13m** is an important compound in the synthesis of 4-phenyl-2-amidotetralins as a melatonin-receptor agent.[12] The cyclic carbonate **12o** contains two phenyl groups. When it was treated with $TiCl_4$, we obtained 3-phenyl-2-tetralone (**13o**) exclusively in 75% yield. This result indicates that only the 3-phenyl group participates in the Friedel–Crafts reaction because the reaction favors six-membered ring formation instead of five-membered ring formation. We also prepared phenoxymethyl-substituted cyclic carbonate **12p** following our standard protocol. When it was treated with $TiCl_4$, chroman-3,4-diol (**13p′**) was isolated in 52% yield as a mixture of two diastereomers; no chroman-3-one (**13p**) was observed.

Figure 4 describes the rationale for the formation of compounds **13** and **13p′** from cyclic carbonate **12**. The cyclic carbonate **12** is decomposed by the first equivalent of $TiCl_4$ to give oxonium intermediate **B**, which undergoes the Friedel–Crafts reaction to produce



Scheme 2. Reagents and conditions: (a) $H_2C{=}CHMgBr$ (**9**), THF, 0 °C, 1 h; (b) $ClCO_2Me$, 0 °C to rt, 5 h; (c) O_3, CH_2Cl_2, −78 °C; (d) Ph_3P, −78 °C to rt, 5 h; (e) DABCO (0.2 equiv), MeOH, rt, 8 h; (f) $TiCl_4$, (2 equiv), CH_2Cl_2 (0.05 M), −78 °C to rt, 3–5 h.

intermediate **C**. The benzylic methoxy group of **C** is removed with the help of the second equivalent of $TiCl_4$ to generate intermediate **D** or **F-1**. Intermediate **D** then undergoes deprotonation to give 2-tetralone **13**. In contrast, intermediate **F-1** is quenched by water to produce diol **13p′**.

In summary, the arylethyl-substituted cyclic carbonate **12** can be prepared using a very straightforward method, and it can be considered as a synthetic equivalent of synthon-**III** to synthesize the 2-tetralone derivatives (Fig. 4). Further studies are in progress to determine the applicability of this method to ring annulation with heteroaromatic rings and natural product synthesis.

Acknowledgments

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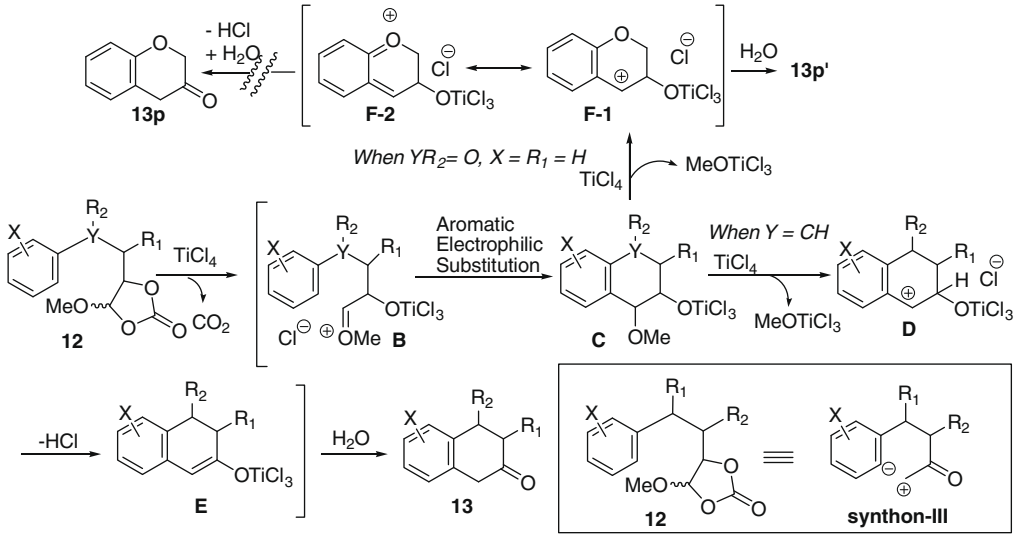

Figure 4. The plausible mechanism for the formation of 2-tetralone **13** or chroman-3,4-diol (**13p′**) from the reaction of cyclic carbonate **12** with $TiCl_4$. The arylethyl-substituted cyclic carbonate **12** can be considered as a synthetic equivalent of synthon-**III**.

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9. *General procedure for the preparation of cyclic carbonate (**12c**)*: A two-necked flask fitted with a glass tube to admit ozone, a $CaCl_2$ drying tube, and a magnetic stirring bar was charged with alkene **11c** (479.2 mg, 2.0 mmol) in CH_2Cl_2 (10 mL). The flask was cooled to −78 °C and O_3 was bubbled through the solution. When the solution turned blue, ozone addition was stopped and N_2 was passed through the solution until the blue color was discharged. To the resulting ozonide in CH_2Cl_2 was added Ph_3P (419.7 mg, 1.6 mmol) at −78 °C, the reaction mixture was warmed slowly to room temperature and was stirred at room temperature for 3 h. The reaction mixture was concentrated to give the crude residue. To a solution of the crude residue in MeOH (6 mL) was added DABCO (44.8 mg, 0.4 mmol) and the reaction mixture was stirred at room temperature for 8 h. The reaction mixture was concentrated to give the crude residue which was purified by silica gel column chromatography to give the carbonate **12c-***syn* (354.5 mg, 1.50 mmol) and **12c-***anti* (70.9 mg, 0.30 mmol) in 88% yield.
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11. *General procedure for the preparation of 2-tetralone (**13b**)*: To a solution of 4-methoxy-5-phenethyl-1,3-dioxolan-2-one (**12b**) (62 mg, 0.29 mmol) in 5 mL of CH_2Cl_2, $TiCl_4$ (0.58 mmol, 0.58 mL, 1 M in CH_2Cl_2) was added dropwise at −78 °C over a period of 5 min. The reaction mixture was warmed slowly to rt in a period of 5 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, concentrated, and chromatographed on silica gel column to give 2-teralone (**13b**, 35.2 mg) as a pale yellow oil in 83% yield. TLC R_f = 0.57 (hexane/EtOAc = 6:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.53–2.57 (t, J = 6.6 Hz, 2H), 3.05–3.08 (t, J = 6.6 Hz, 2H), 3.59 (s, 2H), 7.12–7.23 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.3 (2°), 38.1 (2°), 45.0 (2°), 126.8 (3°), 126.8 (3°), 127.5 (3°), 128.2 (3°), 133.2 (4°), 136.7 (4°), 210.6 (4°); IR (KBr, neat) 3023, 2952, 2849, 1716, 1456, 1238, 749 cm^{-1}; MS m/z (relative intensity): 147 (M^++1, 1), 146 (M^+, 71), 117 (28), 104 (100), 103 (15), 91 (14), 78 (12); HRMS calcd for $C_{10}H_{10}O$: 146.0732. Found: 146.0731.
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