

Gal₃ Catalyzed Tetrahydropyranylation of Alcohols and Phenols

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In dichloromethane, the nucleophilic addition of alcohols or phenols to 3,4-dihydro-2H-pyran (DHP) was catalyzed effectively by gallium triiodide which was generated *in situ* by the reaction of gallium metal and iodine to give the corresponding tetrahydropyranyl acetals in good to excellent yields.

Keywords gallium triiodide, alcohol or phenol, 2-alkoxy(aryloxy)tetrahydropyran, the protection of hydroxyl group

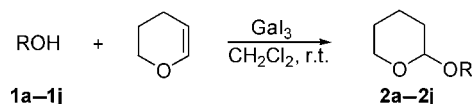
Introduction

Tetrahydropyranylation is an efficient method for the protection of hydroxyl group in organic synthesis due to the stability of the tetrahydropyranyl acetals because they are stable under a variety of reaction conditions such as alkaline media, Grignard reagents, lithium alkyls, metal hydrides, oxidative reagents, alkylating and acylating reagents.¹ Tetrahydropyranyl acetals are generated by a nucleophilic addition of alcohols or phenols to 3,4-dihydro-2H-pyran (DHP). A variety of reagents have been reported to catalyze the procedure, such as protic acids,¹ clay materials (such as montmorillonite K-10, HY-zeolite),² zirconia,³ ion-exchange resins⁴ as well as other miscellaneous catalysts.⁵ Another type of useful catalyst is Lewis acid.⁶ BF₃·OEt₂, AlCl₃, LiClO₄, aluminum sulfate on silica gel and zinc chloride on alumina *etc.* have been found to be effective for this transformation. Recently, metal triflate⁷ such as In(OTf)₃ and LiOTf have also been employed in this reaction. However, many of these methods have several disadvantages, such as expensive reagents, complicated procedure for the preparation of catalyst, tedious work up procedure, long reaction time, elevated reaction conditions, and also, the product yields are not satisfactory to some of the reactions. So it is interesting to develop new reagents with great efficiency, convenient procedures and better yields.

In our research of organic reactions catalyzed by Lewis acid, gallium triiodide has aroused more and more our interests. One of the most evident advantages of this reagent is that it can be prepared *in situ* by a simple inorganic reaction of gallium with iodine.⁸ And more importantly, it has a very high catalytic activity. For example, it catalyzed Sakurai reaction with very high yield.⁹ But to our knowledge, there are very few

reports about the synthetic use of this reagent. We presumed that it maybe have a great potential to be used in organic synthesis. So we decided to use it to catalyze the tetrahydropyranylation of alcohols and phenols. The results showed that in dichloromethane, gallium triiodide catalyzed reaction of 3,4-dihydro-2H-pyran with alcohols or phenols giving the corresponding 2-alkoxy(aryloxy)-tetrahydropyrans in good to excellent yields (Scheme 1).

Scheme 1 GaI₃ catalyzed tetrahydropyranylation of alcohols and phenols



Results and discussion

Gallium triiodide was prepared easily *in situ* by the reaction of gallium metal with iodine in the reaction medium, and a small excess of either Ga or I₂ did not make any difference to the reaction. The tetrahydropyranylation was accomplished very easily and cleanly on alcohols, as well as on phenols. Characteristic reaction conditions include short reaction time and room temperature. Optimized reaction conditions and results of the reaction are summarized in Table 1. It showed that GaI₃ exhibited a powerful catalytic activity in an amount as low as 5 mol%, which was enough to complete the reaction within less than 1 h at ambient temperature. Prolonging reaction time might lower the yields, besides, no noticeable changes occurred by increasing the amount of the catalyst. Three solvents such as acetonitrile, nitromethane and dichloromethane were examined and dichloromethane was found to be the

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Table 1 Tetrahydropyranylation of alcohols and phenols

Entry	ROH	Time/h	Yield ^a /%
1	Benzyl alcohol (1a)	0.5	98
2	2-Phenylethanol (1b)	0.6	92
3	Cyclohexanol (1c)	1.0	90
4	Allyl alcohol (1d)	0.6	85
5	Cinnamyl alcohol (1e)	0.8	94
6	Phenol (1f)	0.8	92
7	4- <i>t</i> -Butylphenol (1g)	0.8	88
8	4-Nitrophenol (1h)	1.0	88
9	4-Chlorophenol (1i)	0.8	86
10	2-Naphthol (1j)	0.8	91

^a Yield of pure, isolated product.

most effective medium for this reaction. Because the catalyst was dissolved in it to form a homogeneous solution, which made the reaction take place smoothly. And also, commercial dichloromethane can be used directly.

In summary, we have developed a new and efficient procedure for the tetrahydropyranylation of alcohols and phenols catalyzed by GaI₃. The method offers several advantages such as mild reaction conditions, short reaction time, high yields, and simple experimental operation leading to a useful and attractive process for the preparation of 2-alkoxy(aryloxy)tetrahydropyrans. It is also revealed that GaI₃ is an effective and useful Lewis acid catalyst. Its further application to organic synthesis is currently being explored in our laboratory.

Experimental

General procedure: Gallium metal (0.0035 g, 0.05 mmol) and iodine (0.019 g, 0.075 mmol) were added to 2 mL of dichloromethane. The mixture was stirred and refluxed under nitrogen atmosphere till the reaction was complete, *i.e.*, the reactants disappeared, which needed about 0.5 h, then cooled to room temperature. To this solution was added 3,4-dihydro-2H-pyran (0.135 mL, 1.5 mmol) followed by alcohol or phenol (1 mmol). The resulting mixture was stirred at room temperature for an appropriate time (see Table 1, monitored by TLC) and quenched with water. The mixture was then extracted with CH₂Cl₂ for three times. After being combined and washed with saturated brine the organic layers were dried over anhydrous Na₂SO₄. The solvent was removed and the residue was subsequently purified by column chromatography on silica gel with hexane/ethyl acetate (6 : 1) as eluent to yield the product.

2a^{2a}: Colorless oil. ¹H NMR (CDCl₃, 300 MHz) δ : 1.55—1.80 (m, 6H), 3.56—3.62 (m, 1H), 3.92—3.99 (m, 1H), 4.53 (d, *J*=12.0 Hz, 1H), 4.75 (t, *J*=3.3 Hz, 1H), 4.82 (d, *J*=12.0 Hz, 1H), 7.35—7.42 (m, 5H); IR (neat) ν : 3025, 2938, 1620, 1532, 1178, 1120, 1075 cm⁻¹.

2b^{7b}: Colorless oil. ¹H NMR (CDCl₃, 300 MHz) δ :

1.52—1.85 (m, 6H), 2.78—2.85 (m, 2H), 3.56—3.62 (m, 1H), 3.89—3.95 (m, 1H), 4.02—4.06 (m, 1H), 4.20—4.25 (m, 1H), 4.78 (t, *J*=3.3 Hz, 1H), 7.20—7.28 (m, 5H); IR (neat) ν : 3015, 2936, 1622, 1532, 1165, 1133, 1082 cm⁻¹.

2c^{2a}: Colorless oil. ¹H NMR (CDCl₃, 300 MHz) δ : 1.15—2.01 (m, 16H), 3.48—3.53 (m, 1H), 3.50—3.56 (m, 1H), 3.90—3.96 (m, 1H), 4.72 (t, *J*=3.3 Hz, 1H); IR (neat) ν : 2938, 2934, 1220, 1175, 1133, 1072 cm⁻¹.

2d^{2a}: Colorless oil. ¹H NMR (CDCl₃, 300 MHz) δ : 1.55—1.98 (m, 6H), 3.48—3.54 (m, 1H), 3.86—3.92 (m, 1H), 3.98—4.05 (m, 1H), 4.20—4.27 (m, 1H), 4.70 (t, *J*=3.3 Hz, 1H), 5.18—5.30 (m, 2H), 5.88—5.97 (m, 1H); IR (neat) ν : 3025, 2936, 1642, 1232, 1168, 1120, 1075 cm⁻¹.

2e³: Yellowish oil. ¹H NMR (CDCl₃, 300 MHz) δ : 1.45—1.85 (m, 6H), 3.52—3.58 (m, 1H), 3.88—3.95 (m, 1H), 4.28—4.37 (m, 2H), 4.76 (t, *J*=3.3 Hz, 1H), 6.20—6.31 (m, 1H), 6.64 (d, *J*=14.4 Hz, 1H), 7.26—7.45 (m, 5H); IR (neat) ν : 3015, 2938, 1670, 1625, 1538, 1175, 1120, 1068 cm⁻¹.

2f^{2a}: Colorless oil. ¹H NMR (CDCl₃, 300 MHz) δ : 1.55—2.09 (m, 6H), 3.60—3.66 (m, 1H), 3.92—3.99 (m, 1H), 5.45 (t, *J*=3.3 Hz, 1H), 7.10 (d, *J*=9.0 Hz, 2H), 7.23—7.33 (m, 3H); IR (neat) ν : 3018, 2936, 1622, 1542, 1170, 1132, 1065 cm⁻¹.

2g: Colorless oil. ¹H NMR (CDCl₃, 300 MHz) δ : 1.32 (s, 9H), 1.50—2.10 (m, 6H), 3.62—3.65 (m, 1H), 3.96—4.02 (m, 1H), 5.43 (t, *J*=3.0 Hz, 1H), 7.03 (d, *J*=9.0 Hz, 2H), 7.30 (d, *J*=9.0 Hz, 2H); IR (neat) ν : 3033, 2950, 2865, 1612, 1515, 1180, 1112, 1078 cm⁻¹; MS (70 eV) *m/z* (%): 234 (M⁺, 15), 150 (76), 135 (100). Anal. calcd for C₁₅H₂₂O₂: C 76.88, H 9.46; found C 76.65, H 9.50.

2h^{2a}: Yellow solid, m.p. 58—60 °C (lit.^{2a} 59—60 °C). ¹H NMR (CDCl₃, 300 MHz) δ : 1.58—2.06 (m, 6H), 3.62—3.68 (m, 1H), 3.83—3.89 (m, 1H), 5.54 (t, *J*=3.0 Hz, 1H), 7.15 (d, *J*=9.0 Hz, 2H), 8.12 (d, *J*=9.0 Hz, 2H); IR (CHCl₃) ν : 3028, 2938, 1620, 1532, 1340, 1180, 1124, 1070 cm⁻¹.

2i^{6a}: Colorless oil. ¹H NMR (CDCl₃, 300 MHz) δ : 1.50—2.02 (m, 6H), 3.62—3.68 (m, 1H), 3.88—3.93 (m, 1H), 5.53 (t, *J*=3.0 Hz, 1H), 7.05—7.35 (m, 4H); IR (neat) ν : 3035, 2936, 1610, 1520, 1185, 1125, 1076, 740 cm⁻¹.

2j^{6a}: Yellowish oil. ¹H NMR (CDCl₃, 300 MHz) δ : 1.55—2.06 (m, 6H), 3.62—3.66 (m, 1H), 3.87—3.92 (m, 1H), 5.54 (t, *J*=3.0 Hz, 1H), 7.15 (d, *J*=9.0 Hz, 1H), 7.40—7.60 (m, 4H), 7.85 (d, *J*=9.3 Hz, 1H), 8.06 (d, *J*=9.0 Hz, 1H); IR (neat) ν : 3059, 2938, 1622, 1600, 1523, 1183, 1120, 1078 cm⁻¹.

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