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EFFICIENT ONE-POT SYNTHESIS OF 2-SUBSTITUTED FURANS FROM 3,3-DIETHOXYPROPENE AND ALDEHYDES USING A Ti(O-*i*-Pr)₄ / 2 *i*-PrMgCl REAGENT

Deok Ki Eom, Seong Jib Choi, and Duk Keun An*

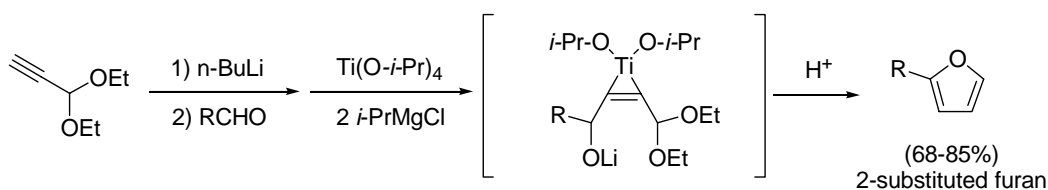
Department of Chemistry, Kangwon National University, Chunchon 200-701,
Korea. E-mail address : dkan@kangwon.ac.kr

Abstract – A new, efficient and direct synthetic method for synthesizing 2-substituted furans using titanium-alkyne complex from easily preparable lithium propargyl alcohol derivatives derived from commercially available 3,3-diethoxypropene, *n*-butyllithium and aldehydes by a Ti(O-*i*-Pr)₄ / 2 *i*-PrMgCl reagent in 68-85% yields.

INTRODUCTION

Furans are important heterocyclic compounds broadly used in material science and found in naturally occurring and biologically important molecules.¹ And, one-pot process has recently gained a considerable and steadily increasing academic, economic, and ecological interest because they address very fundamental principles of organic synthetic efficiency and reaction design. Most known methods for the construction of the furan ring proceed via various types of cycloaddition or cycloisomerization of acyclic precursors.² Additionally, Sato and co-workers have reported on the synthesis of 2-substituted and 2,3-disubstituted furans from 2-alkynyl tetramethylethylene acetals using a Ti(O-*i*-Pr)₄ / 2 *i*-PrMgCl reagent.³ The reaction of the titanium-acetylenic complex generated in situ from acetylenic acetals with Ti(O-*i*-Pr)₄ / 2 *i*-PrMgCl reagent furnished propargyltitaniums which, in turn, reacted with aldehydes to yield furans. This work is a convenient way to synthesize 2,3-disubstituted furans from cyclic acetals and aldehydes in a one-flask operation. However, such a reaction requires cyclic acetals derived from 2-alkynyl to accomplish the reaction.

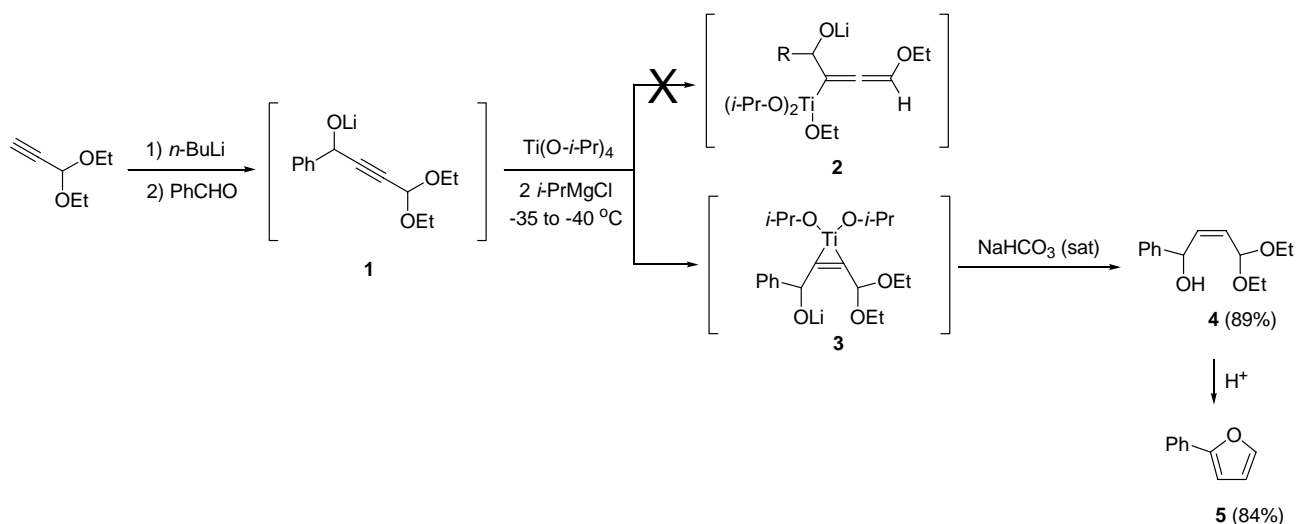
Reported here is a new, efficient and direct synthetic method for synthesizing 2-substituted furans using titanium-alkyne complex from easily preparable lithium propargyl alcohol derivatives derived from commercially available 3,3-diethoxypropene, *n*-butyllithium and aldehydes by a Ti(O-*i*-Pr)₄ / 2 *i*-PrMgCl reagent (Scheme 1).



Scheme 1.

RESULTS AND DISCUSSION

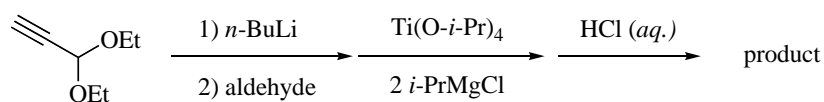
Recently, we carried out the synthesis of a titanium-alkynyl complex (**3**) without an allenyltitanium moiety (**2**) from lithium propargyl alcohol derivatives including the acetal group (**1**) by its reaction with a divalent titanium reagent $\text{Ti}(\text{O}-i\text{-Pr})_4 / 2 i\text{-PrMgCl}$ at -35 to -40 °C. Fortunately, we gave the corresponding *cis*-allyl alcohols (**4**) in good yield (89%) after hydrolysis. Subsequent hydrolysis under acid condition (0.5N HCl) then provided the desired 2-substituted furan (**5**) in 84% yield.⁴ The result suggests the titanium-alkynyl complex (**3**) was stabilized at low reaction temperature (-35 to -40 °C) (Scheme 2).



Scheme 2.

With these results in hand, we anticipated that treatment of the reaction product of 3,3-diethoxypropyne and a $\text{Ti}(\text{O}-i\text{-Pr})_4 / 2 i\text{-PrMgCl}$ reagent with various aldehydes might afford one-pot access to 2-substituted furans. Table 1 summarizes the results of successive treatment of various aldehydes with the $\text{Ti}(\text{O}-i\text{-Pr})_4 / 2 i\text{-PrMgCl}$ reagent.

Table 1. One-pot synthesis of 2-substituted furans from 3,3-diethoxypropyne and aldehydes using $\text{Ti}(\text{O}-i\text{-Pr})_4 / 2 i\text{-PrMgCl}$ reagent.^a



Entry	Aldehyde	Product	Yield, % ^b
1			84
2			77
3			68
4			72
5			85
6			78
7			75
8			77
9			82
10			68

^a3,3-Diethoxypropyne : *n*-BuLi : aldehyde : $\text{Ti}(\text{O}-i\text{-Pr})_4$: *i*-PrMgCl = 1 : 1 : 0.8 : 3 : 6. ^bIsolated yield after silica column chromatography.

As shown in Table 1, benzaldehyde was smoothly reacted to produce 2-phenylfuran in an 84% yield (entry 1). Similarly, aldehydes of electron donating substituents such as 4-methylbenzaldehyde and 4-methoxybenzaldehyde, and electron withdrawing substituents such as 4-bromobenzaldehyde were readily reacted with the corresponding 2-substituted furans in 77%, 68% and 72% yields, respectively (entries 2-4). Also, 1-naphthylaldehyde, poly-aromatic aldehyde and 2-furalal, heterocyclic aldehyde gave the corresponding 2-substituted furans in 85% and 78% yields, respectively (entries 5-6). The case of aliphatic aldehydes, namely caproaldehyde, cyclohexanecarboxaldehyde, hydrocinnamaldehyde, and an α,β -unsaturated aldehyde, cinnamaldehyde, provided product 2-substituted furan in 68-82 yields (entries 7-10).

In summary, the present one-pot reaction opens presented here affords easy access to a variety of 2-substituted furans, that will find widespread use in organic syntheses such as in preparation of furan-containing natural products and poly-aromatic macromolecules.¹ This reaction method was proved to be an effective synthetic method for preparation of 2-substituted furans.

EXPERIMENTAL

General. All reported yields are isolated yields after column chromatography. ¹H-NMR and ¹³C-NMR spectra were recorded on a Bruker DPX FT (400MHz) or Bruker Avance (300MHz) spectrometer. The chemical shifts are expressed as units with Me₄Si as the internal standard in CDCl₃.

Typical procedure. To a solution of 3,3-diethoxypropyne (0.144 mL, 1.0 mmol) in Et₂O (10 mL) was added *n*-BuLi (0.4 mL, 2.5M in hexane, 1.0 mmol) at 0 °C. After being stirred for 1h at rt, to this was added benzaldehyde (0.08 mL, 0.8 mmol) at 0 °C and the mixture was stirred for 1h at rt. To this were added dropwise *i*-PrMgCl (4.69 mL, 1.28 M in Et₂O, 6.0 mmol) and Ti(O-*i*-Pr)₄ (0.88 mL, 3.0 mmol) at -40 °C. The resulting clear yellow solution was stirred for 2.5h at -35 to -40 °C. During this period the solution was colored orange to red-brown. The reaction mixture was quenched with saturated aqueous NaHCO₃ (1 mL) and filtered. After addition 0.5N HCl (20 mL), the mixture stirred for 1-2h and extracted with Et₂O (2 X 10 mL). After the mixture dried over MgSO₄, and concentrated in vacuum. The residue was purified by column chromatography on silica gel. All products were characterized by ¹H and ¹³C NMR spectra.

2-Phenylfuran (Entry 1 in Table 1) ¹H-NMR (CDCl₃) δ 6.47 (dd, $J=1.80, 3.31$ Hz, 1H), 6.65 (d, $J=3.62$ Hz, 1H), 7.26 (t, $J=7.48$ Hz, 1H), 7.38 (t, $J=7.71$ Hz, 2H), 7.46 (d, $J=1.21$ Hz, 1H), 7.66-7.68 (m, 2H). ¹³C NMR (CDCl₃) 104.94, 111.63, 123.78, 127.31, 128.66, 130.89, 142.05, 154.03.

2-(4-Methylphenyl)furan (Entry 2 in Table 1) $^1\text{H-NMR}$ (CDCl_3) δ 2.36 (s, 3H), 6.45 (dd, $J=1.76, 3.64\text{Hz}$, 1H), 6.58 (d, $J=3.2\text{Hz}$, 1H), 7.18 (d, $J=7.93\text{Hz}$, 2H), 7.44 (d, $J=1.27\text{Hz}$, 1H) 7.56 (d, $J=8.19\text{Hz}$, 2H), ^{13}C NMR (CDCl_3) 21.25, 104.20, 111.53, 123.75, 128.26, 129.34, 137.14, 141.65, 154.20.

2-(4-Methoxyphenyl)furan (Entry 3 in Table 1) $^1\text{H-NMR}$ (CDCl_3) δ 3.83 (s, 3H), 6.44 (dd $J=1.81, 3.30\text{Hz}$, 1H), 6.51 (d, $J=3.5\text{Hz}$, 1H), 6.92 (d, $J=8.88\text{Hz}$, 2H), 7.42 (d, $J=1.21\text{Hz}$, 1H), 7.60 (d, $J=8.78\text{Hz}$, 2H). ^{13}C NMR (CDCl_3) 55.32, 103.34, 111.52, 114.10, 124.03, 125.23, 141.37, 154.03, 159.00.

2-(4-Bromophenyl)furan (Entry 4 in Table 1) $^1\text{H-NMR}$ (CDCl_3) δ 6.47 (dd, $J=1.75, 3.32\text{Hz}$, 1H), 6.65 (d, $J=3.36\text{Hz}$, 1H), 7.47-7.55 (m, 5H). ^{13}C NMR (CDCl_3) 105.53, 111.80, 121.05, 125.28, 129.78, 131.79, 142.38, 152.94.

2-Naphthalen-1-ylfuran (Entry 5 in Table 1) $^1\text{H-NMR}$ (CDCl_3) δ 6.59 (dd, $J=1.84, 3.30\text{Hz}$, 1H), 6.73 (d, $J=3.23\text{Hz}$, 1H), 7.48-7.57 (m, 3H), 7.62 (d, $J=1.13\text{Hz}$, 1H), 7.73 (dd, $J=1.12, 8.73\text{Hz}$, 1H), 7.83-7.90 (m, 2H), 8.40 (d, $J=6.29\text{Hz}$, 1H). ^{13}C NMR (CDCl_3) 109.19, 111.35, 125.30, 125.54, 125.90, 126.15, 126.52, 128.49, 128.54, 128.59, 130.30, 133.93, 142.40, 153.46.

2,2'-Bifuran (Entry 6 in Table 1) $^1\text{H-NMR}$ (CDCl_3) δ 6.45 (dd, $J=1.81, 3.39\text{Hz}$), 6.55 (d, $J=3.32\text{Hz}$, 2H), 7.41 (d, $J=1.30\text{Hz}$, 2H). ^{13}C NMR (CDCl_3) 105.07, 111.35, 141.74, 146.62.

2-Pentylfuran (Entry 7 in Table 1) $^1\text{H-NMR}$ (CDCl_3) δ 0.81-0.84 (m, 3H), 1.24-1.32 (m, 4H), 1.53-1.59 (m, 2H), 2.54 (t, $J=7.62\text{Hz}$, 2H), 5.90 (dd, $J=0.83, 3.1\text{Hz}$, 1H), 6.21 (dd, $J=1.91, 3.07\text{Hz}$, 1H), 7.23 (dd, $J=0.72, 1.8\text{Hz}$, 1H). ^{13}C NMR (CDCl_3) 14.40, 22.81, 28.13, 28.35, 31.78, 104.89, 110.41, 141.01, 157.04.

2-Cyclohexylfuran (Entry 8 in Table 1) $^1\text{H-NMR}$ (CDCl_3) δ 1.12-1.23 (m, 2H), 1.27-1.36 (m, 3H), 1.61-1.66 (m, 2H), 1.69-1.74 (m, 2H), 1.93-1.97 (m, 2H), 2.51-2.57 (m, 1H), 5.87 (dd, $J=1.83, 3.16\text{Hz}$, 1H), 6.21 (dd, $J=1.83, 3.16\text{Hz}$, 1H), 7.21 (t, $J=0.96\text{Hz}$, 1H). ^{13}C NMR (CDCl_3) 24.92, 25.10, 30.51, 36.18, 101.50, 108.78, 139.36, 160.02.

2-Phenethylfuran (Entry 9 in Table 1) $^1\text{H-NMR}$ (CDCl_3) δ 2.88 (t, $J=4.90\text{Hz}$, 4H), 5.90 (d, $J=2.98\text{Hz}$, 1H), 6.20 (dd, $J=1.86, 3.12\text{Hz}$, 1H), 7.10-7.12 (m, 4H), 7.19-7.26 (m, 2H). ^{13}C NMR (CDCl_3) 28.90, 33.35, 104.13, 109.09, 125.03, 127.33, 127.34, 139.84, 140.20, 154.35.

2-Styrylfuran (Entry 10 in Table 1) $^1\text{H-NMR}$ (CDCl_3) δ 6.27 (d, $J=3.33\text{Hz}$, 1H), 6.34 (dd, $J=1.82, 3.25\text{Hz}$, 1H), 6.81 (d, $J=16.26\text{Hz}$, 1H), 6.96 (d, $J=16.26\text{Hz}$, 1H), 7.17 (t, $J=7.23\text{Hz}$, 1H), 7.26 (t, $J=7.62\text{Hz}$, 2H), 7.32 (d, $J=1.45\text{Hz}$, 1H), 7.38 (d, $J=7.38\text{Hz}$, 2H), 7.21-7.48 (m, 5H). ^{13}C NMR (CDCl_3) 107.53, 110.60, 115.44, 125.28, 126.09, 126.53, 127.65, 136.00, 141.09, 152.22.

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