Pergamon

Tetrahedron Letters 42 (2001) 5501–5503

TETRAHEDRON
LETTERS

One-pot preparation of 2-substituted and 2,3-disubstituted furans from 2-alkynal tetramethylethylene acetals and aldehydes using a divalent titanium reagent Ti(O-*i*-Pr)$_4$/2 *i*-PrMgX

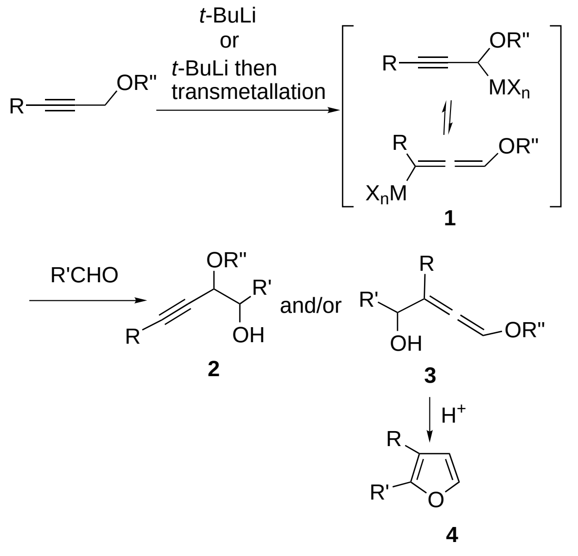
Xin Teng, Takeshi Wada, Sentaro Okamoto and Fumie Sato*

Department of Biomolecular Engineering, Tokyo Institute of Technology, 4259 Nagatsuta-cho, Midori-ku, Yokohama, Kanagawa 226-8501, Japan

Received 28 May 2001; accepted 6 June 2001

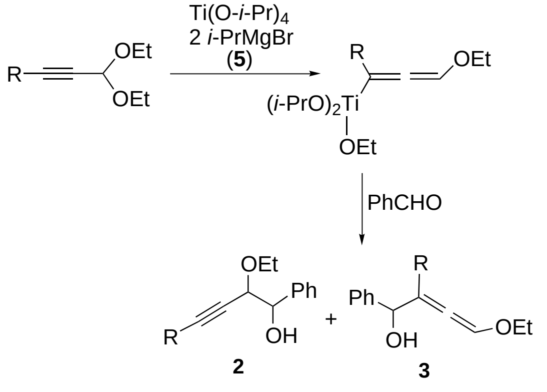
Abstract—Sequential treatment of 2-alkynal tetramethylethylene acetals with a divalent titanium reagent Ti(O-*i*-Pr)$_4$/2 *i*-PrMgX and aldehydes gave, after acidic work-up, furans in good to excellent yields, thus providing a new efficient one-pot access to a variety of 2-substituted and 2,3-disubstituted furans including those having a functionalized substituent(s). © 2001 Elsevier Science Ltd. All rights reserved.

The synthetic utility of propargylic/allenylic metal reagents of the type **1** has been investigated, and it has been revealed that **1** where M is Li, Mg, Zn or Ti affords β-acetylenic alcohols **2** as the major products by its reaction with aldehydes,[1] while the corresponding aluminum reagent provides the α-allenylic alcohols **3** exclusively, that are converted to furans **4** by treatment under acidic conditions (Scheme 1).[2] These organometallic reagents were synthesized from propargyl ethers through deprotonation with *t*-BuLi for the Li-reagent and the following transmetallation for the Mg, Zn, Ti or Al-reagent.



Scheme 1.

Recently, we reported that propargylic/allenylic titanium compounds can be directly prepared from propargylic alcohol derivatives such as acetates, carbonates and ethers, by the reaction with a divalent titanium reagent Ti(O-*i*-Pr)$_4$/2 *i*-PrMgX (**5**) that proceeds via an oxidative addition pathway.[3,4] As expected, the propargylic/allenylic titanium reagent **1** (M = Ti) was readily generated from 2-alkynal dialkyl acetal and **5**, and that, in turn, reacted with an aldehyde to afford the corresponding **2** predominantly as shown in Scheme 2. We



R	2 : 3	Yield, %
SiMe$_3$	76 : 24	99
n-Bu	69 : 31	98

Scheme 2.

Keywords: furan; allenyl; propargyl; titanium.

* Corresponding author. Tel.: +81-45-924-5787; fax: +81-45-924-5826; e-mail: fsato@bio.titech.ac.jp

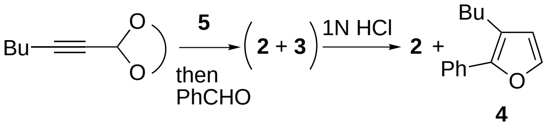
PII: S0040-4039(01)01068-1

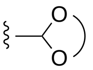
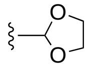
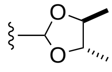
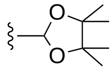
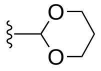
then carried out the synthesis of a titanium reagent of the type **1** from 2-alkynal cyclic acetal and its reaction with an aldehyde in expectation of synthesizing the corresponding furan via **3**. This anticipation was based on our recent finding that, while the allylic titanium reagent derived from **5** and acrolein diethyl acetal reacts with an aldehyde at the γ-position exclusively, the titanium complex obtained from acrolein cyclic acetal reacts at both the α- and γ-positions.[5]

Table 1 summarizes the results of the reaction of the titanium reagent derived from several different cyclic acetals of 2-heptynal with benzaldehyde. As anticipated, the reaction provided the corresponding furan **4** (through **3**), after acidic work-up, as the major product in a variable ratio depending on the acetal, and to our satisfaction, the pinacol derivative (2-heptynal tetramethylethylene acetal) afforded **4** exclusively and in excellent yield (entry 3 in Table 1).

With this finding, we carried out the reaction using various combinations of 2-alkynal tetramethylethylene acetals[6] and aldehydes, and the results are summarized in Table 2. As can be seen from Table 2, furans having various kinds of substituents at the C-2 and C-3 positions can be readily prepared. Noteworthy is the fact that, when trimethylsilylpropynal tetramethylethylene acetal was used as the starting acetal, the trimethylsilyl group present at the C-3 position in the initially formed furan was desilylated during acidic work-up, and thus, eventually, the reaction allows an access to monosubstituted furans at the C-2 position (entries 9 and 10). Several characteristic features of the reaction can be seen from the table. Since an organotitanium reagent shows high chemoselectivity, it is possible to carry out the reaction with aldehydes having a functional group (entries 2, 3 and 5). Preparation of furans with a functionalized substituent at the C-3 position is also feasible starting from the acetals containing a functional group (entries 6 and 7). Thus, furans having a variety of functionalized substituents at the C-2 and/or C-3 position can be readily synthesized by a one-pot reaction. The preparation of *p*-difurylbenzenes starting with terephtalaldehyde (entries 10 and 11) is also noteworthy, because the compounds having such structure have attracted interest as a starting material for the preparation of conjugated polymers.[7]

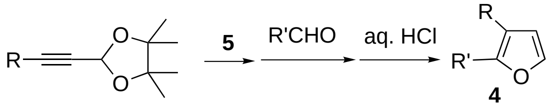
Table 1.[a]

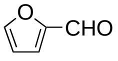
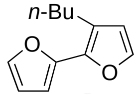
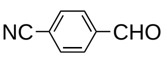
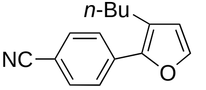
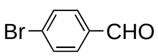
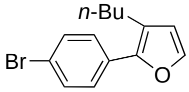
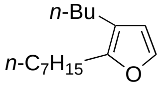
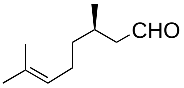
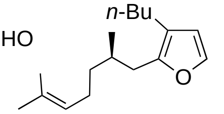
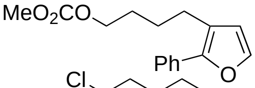
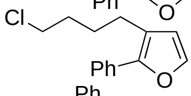
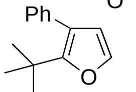
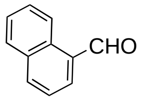
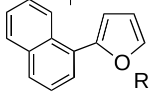
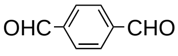
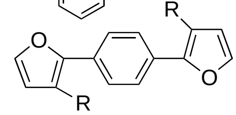


Entry	Acetal: 	Regioselectivity 2^b : 4	Combined Yield, %
1		39 : 61	98
2		11[c] : 89	78
3		0 : 100	84 (84)[d]
4		19 : 81	82

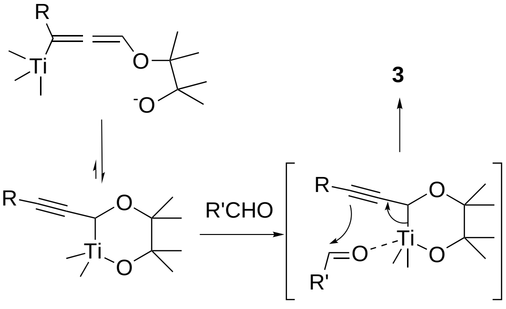
[a]Reactions were carried out using the acetal (1.6 eq.), Ti(O-*i*-Pr)$_4$ (1.4 eq.), *i*-PrMgBr (2.8 eq.), and PhCHO (1 eq.). [b]Ratio of diastereomers of **2** was 54 : 46 for entry1 and 54 : 46 for entry 4. [c]Diastereomeric ratio was not determined. [d]*i*-PrMgCl was used instead of *i*-PrMgBr.

Table 2.[a]



Entry	R	R'CHO	4	Isolated Yield, %
1	*n*-Bu			74
2				71
3				68
4		*n*-C_7H_{15}CHO		76
5				99
6	MeO_2CO-$(CH_2)_4$	PhCHO		75
7	Cl-$(CH_2)_4$	PhCHO		82
8	Ph	*t*-BuCHO		83
9	TMS			80
10[b]	TMS		 R = H	75
11[b]	*n*-Bu		R = *n*-Bu	55

[a]Unless otherwise indicated, all reactions were carried out using acetal (1.6 eq.), Ti(O-*i*-Pr)$_4$ (1.4 eq.), *i*-PrMgBr (2.8 eq.), and aldehyde (1 eq.). [b]0.5 equiv of the aldehyde was added.



Scheme 3.

The predominant production of α-allenyl alcohols **3**, i.e. furans **4**, may be explained by assuming that the titanium complex derived from a cyclic acetal of 2-alkynal would exist mainly as a propargyltitanium, that can be stabilized by chelation,[8] rather than an allenyl derivative, and the reaction with aldehydes proceeds preferentially via the six-membered transition structure depicted in Scheme 3. Although an explanation of the result that 2-alkynal tetramethylethylene acetal afforded the highest selectivity compared with other cyclic acetals must await further study, it was fortunate that the acetal prepared from inexpensive pinacol shows the highest selectivity.

In conclusion, the present one-pot reaction[9] opens up an easy access to a variety of 2-substituted and 2,3-disubstituted furans including those having functionalized substituent(s), that will find widespread use in organic synthesis such as preparation of furan-containing natural products[10] and poly-aromatic macromolecules.[7]

Acknowledgements

We thank the Ministry of Education, Culture, Sports, Science and Technology (Japan) for financial support.

References

1. (a) Mercier, F.; Epsztein, R.; Holand, S. *Bull. Soc. Chim. Fr.* **1972**, 690–696; (b) Chwastek, H.; Epsztein, R.; Le Goff, N. *Tetrahedron* **1973**, *29*, 883–889; (c) Chwastek, H.; Le Goff, N.; Epsztein, R.; Bara-Marszak, M. *Tetrahedron* **1974**, *30*, 603–608; (d) Evans, D. A.; Nelson, J. V. *J. Am. Chem. Soc.* **1980**, *102*, 774–782; (e) Furuta, K.; Ishiguro, M.; Haruta, R.; Ikeda, N.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2768–2776; (f) Hiraoka, H.; Furuta, K.; Ikeda, N.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2777–2780.
2. Ishiguro, M.; Ikeda, N.; Yamamoto, H. *Chem. Lett.* **1982**, 1029–1030.
3. (a) Nakagawa, T.; Kasatkin, A.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 3207–3210; (b) Yoshida, Y.; Nakagawa, T.; Sato, F. *Synlett* **1996**, 437–438; (c) Okamoto, S.; An, D. K.; Sato, F. *Tetrahedron Lett.* **1998**, *39*, 4551–4554; (d) An, D. K.; Okamoto, S.; Sato, F. *Tetrahedon Lett.* **1998**, *39*, 4555–4558; (e) An, D. K.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1998**, *39*, 4861–4864; (f) An, D. K.; Hirakawa, K.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1999**, *40*, 3737–3740; (g) Hanazawa, T.; Okamoto, S.; Sato, F. *Org. Lett.* **2000**, *2*, 2369–2371.
4. Reviews for the synthetic utility of **5**: (a) Sato, F.; Urabe, H.; Okamoto, S. *Pure Appl. Chem.* **1999**, *71*, 1511–1519; (b) Sato, F.; Urabe, H.; Okamoto, S. *J. Synth. Org. Chem. Jpn.* **1998**, *56*, 424–432; (c) Sato, F.; Urabe, H.; Okamoto, S. *Synlett* **2000**, 753–775; (d) Sato, F.; Urabe, H.; Okamoto, S. *Chem. Rev.* **2000**, *100*, 2835–2886.
5. (a) Teng, X.; Okamoto, S.; Takayama, Y.; Sato, F. *J. Am. Chem. Soc.* **1999**, *121*, 11916–11917; (b) Okamoto, S.; Teng, X.; Fujii, S.; Takayama, Y.; Sato, F. *J. Am. Chem. Soc.* **2001**, *123*, 3462–3471.
6. 2-Alkynaltetramethylethylene acetals could be readily prepared from the corresponding diethyl acetals by treatment with pinacol in the presence of a catalytic amount of *p*-TsOH in $\mathrm{CH_2Cl_2}$.
7. (a) Reynolds, J. R.; Child, A. D.; Ruiz, J. P.; Hong, S. Y.; Marynick, D. S. *Macromolecules* **1993**, *26*, 2095–2103; (b) Child, A. D.; Sankaran, B.; Larmat, F.; Reynolds, J. R. *Macromolecules* **1995**, *28*, 6571–6578.
8. A similar stabilization of allenyl/propargyltitaniums by intramolecular chelation or coordination has been reported: (a) Hoppe, D.; Gonschorrek, C.; Schmidt, D.; Egert, E. *Tetrahedron* **1987**, *43*, 2457–2466; (b) Hamada, T.; Mizojiri, R.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **2000**, *122*, 7138–7139.
9. Typical procedure: to a solution of 2-heptynal tetramethylethylene acetal (168 mg, 0.8 mmol) and $\mathrm{Ti(O\text{-}}i\mathrm{\text{-}Pr)_4}$ (207 μL, 0.7 mmol) in $\mathrm{Et_2O}$ (6 mL) was added *i*-PrMgBr (1.18 mL, 1.19 M in $\mathrm{Et_2O}$, 1.4 mmol) at −50°C. After being stirred for 1.5 h at this temperature, the mixture was allowed to warm to 0°C and stirred for an additional 30 min. After addition of benzaldehyde (55.6 μL, 0.5 mmol), the mixture was stirred for 30 min at rt. To this were added aqueous 1N HCl (5 mL), THF (5 mL), and EtOH (5 mL). The resulting mixture was stirred for 3 h and then extracted with $\mathrm{Et_2O}$ (2×5 mL). The combined organic layers were washed with saturated aqueous $\mathrm{NaHCO_3}$ (10 mL), dried over $\mathrm{MgSO_4}$, concentrated in vacuo, and chromatographed on silica gel to give 2-phenyl-3-butylfuran (84 mg) in 84% yield.
10. Leading references for furans in natural products, pharmaceuticals, flavors and fragrances, and for preparation of substituted furans: (a) Ma, S.; Zhang, J. *Chem. Commun.* **2000**, 117-118; (b) Méndez-Andino, J.; Paquette, L. A. *Org. Lett.* **2000**, *2*, 4095–4097.