Tetrahedron Letters 49 (2008) 6009–6012

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# One-pot synthesis of highly substituted tetrahydrofurans from activated propargyl alcohols using $Bu_3P$

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ARTICLE INFO

*Article history:*
Received 9 June 2008
Revised 28 July 2008
Accepted 31 July 2008
Available online 7 August 2008

*Keywords:*
Tandem conjugate addition
Double Michael addition
Tributylphosphine
Tetrahydrofuran ring

ABSTRACT

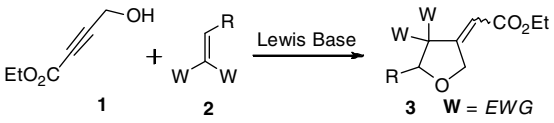
General and robust synthesis of highly functionalized tetrahydrofuran ring was accomplished with activated propargyl alcohol and reactive Michael acceptors in the presence of catalytic $Bu_3P$.



Highly substituted tetrahydrofurans are ubiquitous in many natural and unnatural products of biological importance.[1,2] Methylenetetrahydrofurans form a very useful class of skeletal building blocks, and are derived from extensive synthetic protocols.[2,3] Among the methods developed, a formal [3+2] cycloaddition reaction of propargyl alcohols to electrophilic alkene received considerable attention.[3] Initially, a typical tandem reaction involving conjugate (Michael) additions of activated propargyl alcohol to α-nitroalkene was reported by Ikeda and others using $^t$BuOK.[4a,4b] Lately, Morikawa et al. re-examined the reaction with Lewis acid catalyst to overcome the instability of activated propargyl alcohol with limited substrate scope.[4c]

Phosphine-catalyzed reactions using electrophilic alkenes have emerged as powerful synthetic tool for the construction of N,O-heterocycles such as tetrahydropyrroles, tetrahydropyridines, dioxanes, and pyrones.[9] We anticipated similar [3+2] cycloaddition to methylenetetrahydrofurans using $Bu_3P$ from activated propargyl alcohol of type **1** with Michael acceptor **2** (Scheme 1). Accordingly, we have investigated this useful reaction to increase the substrate scope and compatibility.

Herein, we report our preliminary results using ethyl 4-hydroxybut-2-ynoate **1** and electrophilic alkenes such as alkylidene malonate **2**. Our early efforts focused on alkene **2a** to define the optimal reaction conditions (Scheme 2). Addition of substrate **2a** to propargyl alcohol **1** in the presence of tertiary amines (TEA, DBU, DABCO, and DMAP) furnished the expected tetrahydrofuran with slow conversion rate. Manipulation of the solvent, catalyst,




**Scheme 1.** Synthesis of highly functionalized tetrahydrofurans by double Michael reaction.

and temperature did not improve the conversion to tetrahydrofuran. In all the cases, minor formation of product was observed, along with a new by-product, **4**. The new by-product was characterized as dioxane **4,** and was formed by self conjugate addition of propargyl alcohol **1**.[5] In addition, reactions conducted at elevated temperature (>100 °C) led to a considerable decomposition of starting materials. Interestingly, use of highly nucleophilic tributylphosphine eliminated the formation of this side product and gave the tetrahydrofuran **3a** exclusively. The catalytic nature of the reaction was investigated by varying the solvent to find the optimum loading of $Bu_3P$ (10 mol % for complete conversion under solvent free conditions).[6a] More importantly, a high compatibility of tributylphosphine to the electrophilic alkene and propargyl alcohol **1** was observed under these reaction conditions. Our attempts to replace $Bu_3P$ catalyst with other phosphines, such as triphenylphosphine, were not successful.

Having identified the suitable reaction conditions, the scope of reaction was explored with a range of alkylidene-, arylidene-, and heteroarylidene malonate/Meldrum's acid based alkene derivatives (Table 1). The required Michael acceptors (**2a–j**) were prepared by following known literature methods.[7] Tandem conjugate addition of alkylidene and branched alkylidene malonate

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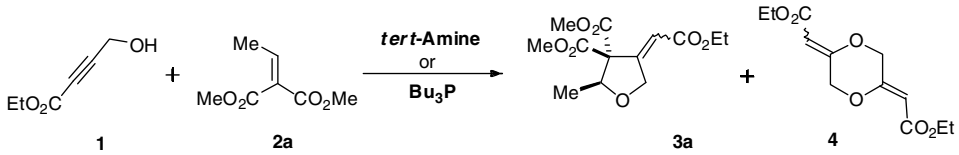
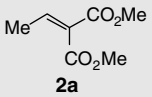
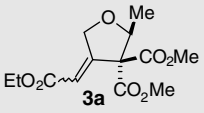
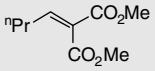
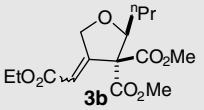
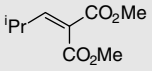
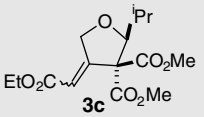
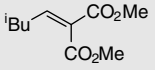
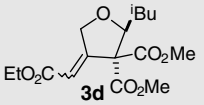
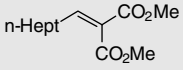
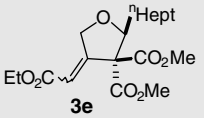
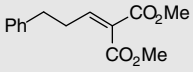
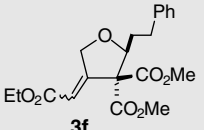
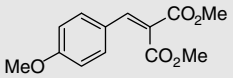
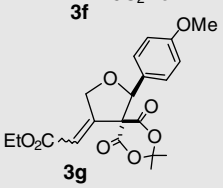
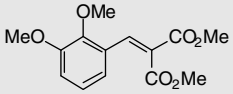
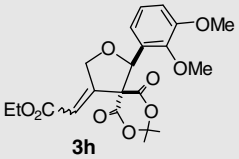
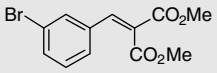
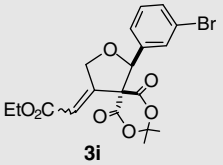
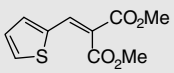
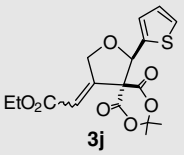
doi:10.1016/j.tetlet.2008.07.180



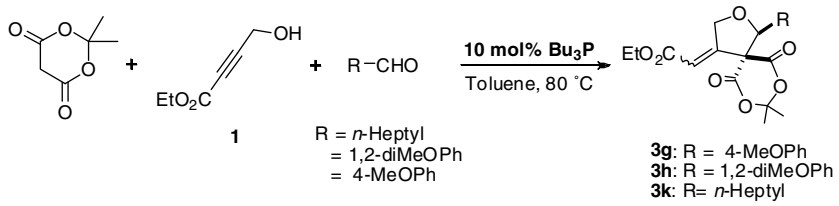

1 2a 3a 4

**Scheme 2.** Synthesis of tetrahydrofuran using alkene **2a** and propargyl alcohol **1**.

**Table 1**

| Entry | Michael acceptor | Product | Solvent (temp.) | Time (h) | Yield[a] (*E*:*Z*) |
|---|---|---|---|---|---|
| 1 |  **2a** |  **3a** | Neat (rt) | 4 | 86% (1:1.7) |
| 2 |  **2b** |  **3b** | Neat (rt) | 6 | 80% (1:1.6) |
| 3 |  **2c** |  **3c** | Neat (rt) | 8 | 80% (1:1.6) |
| 4 |  **2d** |  **3d** | Neat (rt) | 8 | 92% (1:2) |
| 5 |  **2e** |  **3e** | Neat (rt) | 8 | 75% (1:1.5) |
| 6 |  **2f** |  **3f** | Toluene (80 °C) | 6 | 78% (1:1.6) |
| 7 |  **2g** |  **3g** | Toluene (80 °C) | 4 | 89% (1:4.1) |
| 8 |  **2h** |  **3h** | Toluene (80 °C) | 8 | 83% (1:3.1) |
| 9 |  **2i** |  **3i** | Toluene (80 °C) | 6 | 85% (1:5.1) |
| 10 |  **2j** |  **3j** | Toluene (80 °C) | 4 | 87% (1:3.1) |

[a] Isolated yields.

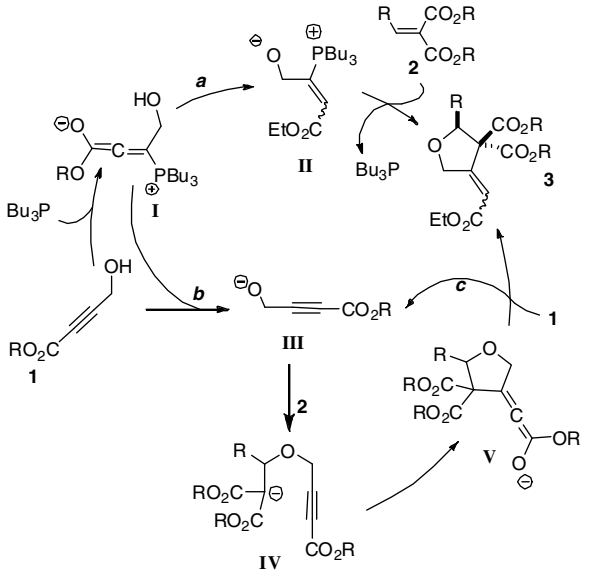



**Scheme 3.** Three component coupling reaction for the synthesis of highly substituted tetrahydrofuran ring.

acceptors underwent clean transformation to provide the 3-alkylidene tetrahydrofurans (**3**), as a separable *E:Z* mixture, in good yield (entries 1–6). The arylidene and heteroarylidene malonate esters were found to be inert under the same reaction conditions, and further optimization of reaction conditions varying the temperature and solvent did not yield the required product. The more reactive arylidene and heteroarylidene alkenes derived from Meldrum's acid provided the tetrahydrofuran ring through modification of reaction conditions (entries 7–10).[6b] The spectral data of each of the products showed a characteristic olefin proton for the *E*-isomer in between $\delta$ 6.01 and 6.50 ppm, whereas the *Z*-olefinic proton appeared in the region of $\delta$ 5.80–6.09 ppm.[3,6c]

Considering the instability and highly reactive nature of alkylidene Meldrum's acids, the anticipated tandem conjugate addition reaction was planned using the in situ generation of alkene from the aldehyde and Meldrum's acid (Scheme 3). The mixture of Meldrum's acid, octanal and ethyl 4-hydroxybut-2-ynoate **1** was treated with $Bu_3P$. Heating the reaction mixture at 80 °C in toluene led to the formation of tetrahydrofuran **3k** as a *E:Z* (2:1) isomeric mixture in 40% yield.[8] Increasing the amount of catalyst $Bu_3P$ and varying the solvent did not improve the yield. This multicomponent reaction was further examined using additional aldehydes including *p*-anisaldehyde and 1,2-dimethoxy benzaldehyde (**3g** and **3h**) where products were found in low yields (42% and 46% respectively, Scheme 3). It is likely that the thermal instability of enolizable Meldrum's acid was the reason for observed lower yields. Further optimization of reaction conditions of this three-component reaction system is currently in progress.

In connection with previous reports, we propose the probable mechanism as a formal [3+2] cycloaddition of zwitterionic intermediate **II** (formed by the initial attack of the nucleophilic $Bu_3P$ on **1**) with electrophilic alkene **2**, leading to methylenetetrahydrofuran **3** (Scheme 4).[3,9] In the proposed mechanistic path, *path* ***a*** accounts for the catalytic nature of reaction. Complementary catalytic cycles (*path* ***b*** *and path* ***c***) are expected to compete with *path* ***a*** in the case of solvent-free reaction conditions. The strong basic nature of enolate intermediates **I** or **V** could trigger the catalytic cycles *path* ***b*** and *path* ***c*** by proton abstraction from propargyl alcohol **1**. The proposed mechanism also explains the observed poor olefin regioselectivity of product **3** by the intermediacy of allene **I** and/or **V**. Absence of Michael addition product **IV** (protonated) further supports the derived mechanism.




**Scheme 4.** Probable mechanism for the tandem conjugate addition reaction.

In conclusion, we have demonstrated efficient and simple methodology to highly functionalized tetrahydrofuran rings from readily available starting materials using catalytic amount of tributylphosphine. In the course of the reaction, we have also developed a promising one-pot, three-component coupling reaction for the same.

## Acknowledgments

The authors would like to thank Drs. Amar Chittiboyina, Mahesh Gundluru, and Paulo Carvalho for their suggestions in editing the manuscript. This work was funded in part by the Center for Disease Control and Prevention (CDC cooperative agreements 1UO1 CI000211-03 and 1UO1 CI000362-01). The preceding investigations were conducted in a facility remodeled with support from a National Center for Research Resources, National Institutes of Health (C06 Rr-14503-01).

## Supplementary data

Supplementary data (spectral data of all the products) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.07.180.

## References and notes

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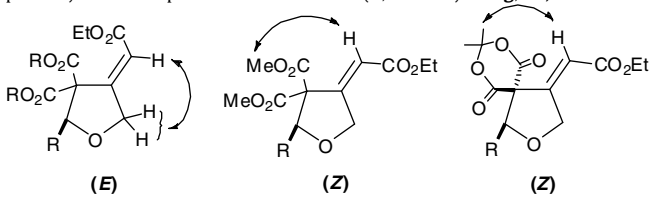
5. *Spectral data of* **4** (major isomer): $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 5.06 (s, 1H), 4.75 (s, 2H), 4.17 (q, $J$ = 7.1, 2H), 1.28 (t, $J$ = 7.1, 3H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 164.50, 160.04, 94.65, 77.29, 77.03, 76.78, 65.52, 59.90, 14.26. HRMS: 279.0852 for $C_{12}H_{16}O_6Na$ (Calcd mass 279.0845). Compound **4** (minor isomer): $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.50 (s, 2H), 5.46 (s, 1H), 5.01 (s, 1H), 4.60 (s, 2H), 4.17 (m, 4H), 1.28 (m, 6H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 166.59, 164.60, 164.31, 160.46, 97.11, 94.17, 77.28, 77.02, 76.77, 64.78, 61.80, 60.10, 59.89, 14.28. HRMS: 279.0839 for $C_{12}H_{16}O_6Na$ (Calcd mass 279.0845).
6. (a) *General procedure A*: To a mixture of olefin (**2a–f**, 0.5 mmol) and alkynoate **1** (0.5 mmol) was added catalytic $Bu_3P$ (0.05 mmol) at room temperature under argon. After the completion of reaction, the crude mixture was dissolved in ethyl acetate, washed with aq $NaHSO_3$, dried, and concentrated. Purification on silica gel gave pure *E* and *Z* isomers of **3a-f**, and were characterized by 1D-NMR ($^1$H, $^{13}$C, DEPT), 2D-NMR (COSY, NOESY, HSQC, HMBC), HRMS and IR.
(b) *General procedure B*: To a degassed solution of olefin (**2g–j**, 0.5 mmol) and alkynoate **1** (0.5 mmol) in toluene (1 mL) was added catalytic $Bu_3P$ (0.05 mmol)

at room temperature under argon. The reaction mixture was heated to 80 °C. After the completion of reaction, crude mixture was diluted with ethyl acetate, washed with aq.$NaHSO_3$, dried, concentrated, and purified on silica gel using ethyl acetate and hexane to give the *E*:*Z* mixture of **3g–j**.

(c) The (*Z*) and (*E*) structures were confirmed by NOE correlations of $OCH_2$ (ring protons) and olefin proton as shown below (A, B and C) for **3g**, **3h,** and **3a**.




7. (a) Bigi, F.; Carloni, S.; Ferrari, L.; Maggi, R.; Mazaccani, A.; Sartori, G. *Tetrahedron Lett.* **2001**, *42*, 5203–5205; (b) Cardillo, G.; Fabbroni, S.; Gentilucci, L.; Gianotti, M.; Tolomelli, A. *Synth. Commun.* **2003**, *33*, 1587–1594.
8. *General Procedure C*: To the degassed solution of aldehyde (0.5 mmol), Meldrum's acid (0.5 mmol) and ethyl 4-hydroxybut-2-ynoate **1** (0.5 mmol) in toluene (2 mL) was added $Bu_3P$ (0.05 mmol) under argon and heated at 80 °C. After the completion, reaction mixture was diluted with ethyl acetate and washed with aq $NaHSO_3$, dried, and concentrated. The isomeric *E*:*Z* mixture of product (**3g**, **3h**, and **3j**) was subjected to silica gel chromatography and characterized by NMR, HRMS, and IR.
9. Zhu, X. F.; Henry, C. E.; Kwon, O. *J. Am. Chem. Soc.* **2007**, *129*, 6722–6723 and references cited therein.