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Synthesis of Furans and 2,5-Dihydrofurans by Ag(I)-Catalyzed Isomerization of Allenones, Alkynyl Allylic Alcohols, and Allenylcarbinols

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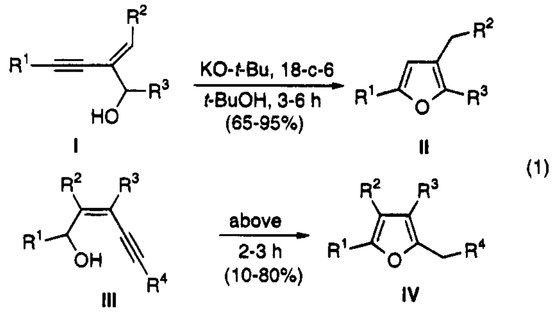
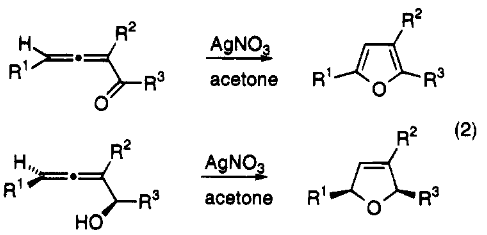
In connection with a program directed toward the synthesis of 2,5-furanocyclic natural products,[1,2] we undertook studies to develop efficient routes to 2,3,5-trisubstituted furans. One variant to emerge from this initiative was a method involving the base-catalyzed isomerization of α- and β-alkynyl allylic alcohols as illustrated in eq 1.[2g,3]



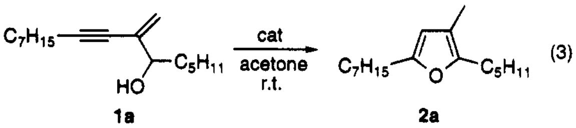
This approach employs starting materials **I** and **III** readily accessible through Pd(0)-catalyzed Castro−Stephens coupling of appropriate vinylic halides and terminal alkynes.[4] However, the strongly basic reaction conditions preclude its use for functionalized furans containing base-sensitive groupings.

In related work we have shown that $AgNO_3$ catalyzes the isomerization of allenones to furans and allenylcarbinols to 2,5-dihydrofurans.[2f,5] These reactions were conducted in anhydrous acetone with *ca.* 10 mol % of $AgNO_3$, which is virtually insoluble in this medium (eq 2).[6]



Although the allene methodology is highly efficient and exceptionally mild, the starting materials are not readily available. It was therefore of interest to explore alternative methodology for the conversion of alkynyl allylic alcohols such as **I** and **III** to furans.

As a starting point we subjected the β-alkynyl allylic alcohol **1a** to our standard $AgNO_3$/acetone conditions.[5,6] A clean, but relatively slow, reaction ensued, leading to furan **2a** in 86% yield (eq 3). Comparable results were observed with AgOTf as the catalyst. Both silver fluoroborate and trifluoroacetate proved more effective, leading to furan **2a** in 97% and 93% yield, respectively, after only 2 h reaction time. Most interestingly, we found that the commercially available 10% $AgNO_3$ on silica gel[7] could serve as a catalyst. Use of a catalytic amount equal to 10 mol % of the alcohol led to furan **2a** in 92% yield upon stirring overnight.[8]



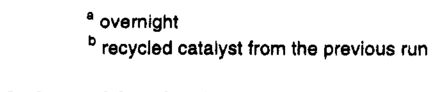
1a **2a**

cat (eq)	t, h	yield, %
$AgNO_3$ (0.2)	12	86
AgOTf (0.2)	12	91
$AgBF_4$ (0.2)	2	97
AgOTFA[a] (0.2)	2	93
$AgNO_3$/silica[b] (0.1)	12	92

[a] TFA = CF_3CO

[b] 10% $AgNO_3$ on silica gel;

In an effort to shorten reaction times, we surveyed a number of solvents for the isomerization of alcohol **1a** with the $AgNO_3$/silica gel system (eq 4). In methanol and methylene chloride, furan **2a** was secured in high yield but overnight stirring was still required. The reaction was significantly slower in Et_2O, THF, or MeCN. Reasoning that a nonpolar solvent would increase the affinity of the polar alcohol toward the silica gel surface, we turned to hexane. A dramatic increase in rate was



1a **2a**

solvent	t, h	eq Ag	yield, %
Me_2CO	12[a]	0.2	92
MeOH	12[a]	0.2	96
CH_2Cl_2	12[a]	0.2	87
hexane	1	0.1	96
hexane	2[b]	0.1	91

[a] overnight

[b] recycled catalyst from the previous run

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(2) For recent synthetic approaches to these natural products, see: (a) Kando, A.; Ochi, T.; Tokoroyama, T.; Siro, M. *Chem. Lett.* **1987**, 1491. (b) Paterson, I.; Gardner, M.; Banks, B. J. *Tetrahedron* **1989**, *45*, 5283. (c) Marshall, J. A.; Wang, X.-j. *J. Org. Chem.* **1991**, *56*, 6264. (d) Astley, M. P.; Pattenden, G. *Synlett* **1991**, 335. (e) Paquette, O. A. *Chemtracts—Org. Chem.* **1992**, *5*, 141 and references cited therein to original papers from the Paquette group. (f) Marshall, J. A.; Yu, B.-c. *J. Org. Chem.* **1994**, *59*, 324. (g) Marshall, J. A.; DuBay, W. J. *J. Org. Chem.* **1994**, *59*, 1703. (h) Marshall, J. A.; Wallace, E. M.; Coan, P. S. *J. Org. Chem.* **1995**, *60*, 796.

(3) Marshall, J. A.; DuBay, W. J. *J. Org. Chem.* **1993**, *58*, 3435.

(4) *Cf.* (a) Sonogashira, K. in *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 3, Chapter 2.4. (b) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.

(5) (a) Marshall, J. A.; Wang, X.-j. *J. Org. Chem.* **1991**, *56*, 960. (b) Marshall, J. A.; Pinney, K. G. *J. Org. Chem.*, **1993**, *58*, 7180.

(6) Marshall, J. A.; Bartley, G. S. *J. Org. Chem.* **1994**, *59*, 7169.

(7) Aldrich Chemical Co., Milwaukee, WI.

(8) We are aware of only one other application of this type in which $AgNO_3$ on silica gel is used to catalyze a heterocyclization reaction. In that case, the product is a substituted proline methyl ester: Kinsman, R.; Lathbury, D.; Vernon, P.; Gallagher, T. *J. Chem. Soc., Chem. Commun.* **1987**, 243.

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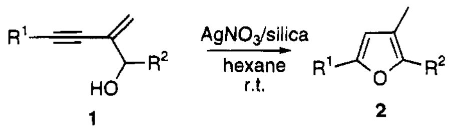
observed. With only 10 mol % of $AgNO_3$, the reaction was complete within 1 h, giving furan **2a** in 96% yield. Furthermore, the catalyst could be reused. A second run on the same scale with the recovered $AgNO_3$/silica gel required only 2 h for completion and proceeded in 91% yield. We were also able to perform this conversion repeatedly by using a HPLC apparatus for elution of alcohol **1a** with hexane through a stainless steel column packed with the catalyst.

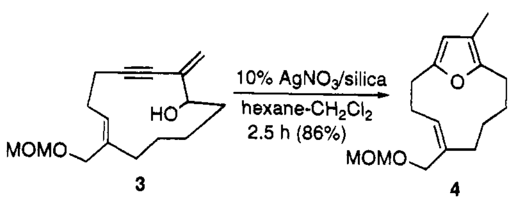
Comparable results were obtained with the β-alkynyl allylic alcohols **1b** and **1c** (eq 5).



(5)

R¹	R²	series	t, h	eq Ag	yield, %
C_7H_{15}	C_5H_{11}	a	1	0.1	96
$MOMO(CH_2)_4$	Et	b	0.25	0.2	99
$MOMO(CH_2)_4$	H	c	0.25	0.2	89

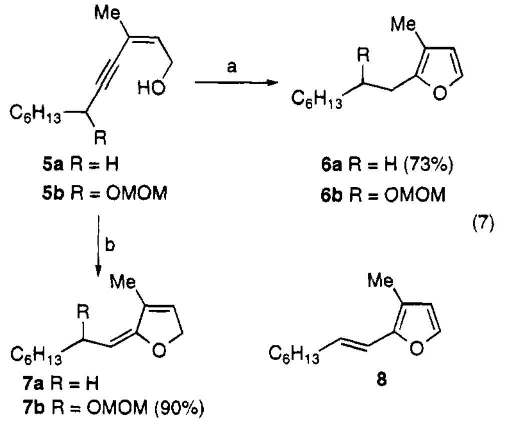
The 12-membered pseudopterane prototype[1a] **4** was prepared from β-alkynyl allylic alcohol **3** in 86% yield (eq 6). Previously this transformation had been effected in 64% yield through treatment of alcohol **3** with a 5-fold excess of KO-*t*-Bu/18-crown-6 in THF for 10 h.[2g]



(6)

3 4

The γ-alkynyl allylic alcohol **5a**[2g] also isomerized readily to the corresponding furan **6a**[9] upon exposure to 10% $AgNO_3$ on silica gel in hexane at rt (eq 7). A second run with the recovered catalyst gave identical results. We had previously found that propargylic ethers such as **5b** were converted to vinylfurans with elimination of the OMOM moiety upon treatment under the aforementioned strongly basic reaction conditions.[2g,10] When **5b** was stirred with the supported catalyst in hexane, the elimination product **8** along with furan **6b** and diene **7b**,[11] an obvious precursor of furan **6b**, were present after consumption of starting material was complete. These three products were easily separable by column chromatography on silica gel deactivated with Et_3N. When the reaction was allowed to proceed for several hours, diene **7b** gave way to furan **6b** and increased amounts of vinylfuran **8**. Addition of 5% Et_3N to the hexane solvent essentially shut down the isomerization and elimination steps, as evidenced by the isolation of diene **7b** as the sole product after 6 h.

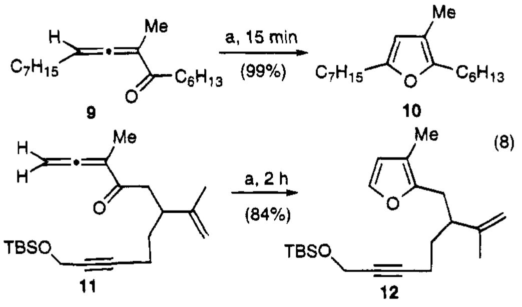


(7)

a) 0.2 eq of 10% $AgNO_3$ on silica gel, hexane
b) 0.2 eq of 10% $AgNO_3$ on silica gel, 5% Et_3N-hexane

Interestingly, alkynyl allylic alcohol **5a** exhibited parallel behavior but the reaction was much slower. After 48 h, an approximately equal mixture of diene **7a** and starting alcohol **5a** was present, according to the ^1H NMR spectrum of the crude reaction mixture. Use of Et_3N with alcohol **1a** led to negligible cyclization after 3 da.

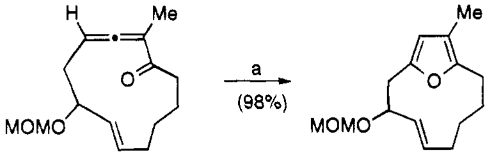
As expected, allenones such as **9** and **11** were readily converted to furans **10** and **12** by the supported $AgNO_3$ catalyst (eq 8).[5] Again, the recovered catalyst could be reused with no decrease in yield.



(8)

a) 0.2 eq of 10% $AgNO_3$ on silica gel, hexane, rt

Of particular interest, the pseudopterane prototype[1a] **14** was obtained nearly quantitatively from allenone **13** in only 3.5 h (eq 9). By our previously reported procedure, this transformation was effected in 92% yield after a reaction time of 12 h.[12]



(9)

13 14

a) 0.2 eq of 10% $AgNO_3$ on silica gel, hexane, r.t., 3.5 h

In a final application, we subjected the nonracemic allenylcarbinol **15** to the catalyst system.[13] Cyclization to the *cis*-2,5-dihydrofuran **16** proceeded in 95% yield within 10 min (eq 10).

The foregoing methodology offers a unified approach for the synthesis of a variety of furans. It is particularly attractive for relatively strained 2,5-furanocycles such as **4** and **14**. In view of our previous findings,[2f,5b] the methodology should also be applicable to 2,5-dihydro-

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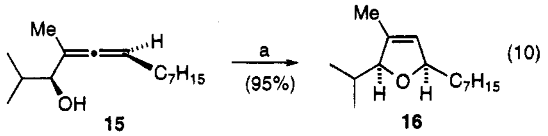
[9] Kotake, H.; Inomata, K.; Kinoshita, H.; Aoyama, S.; Sakamoto, Y. *Heterocycles* **1978**, *10*, 105.

[10] Marshall, J. A.; Bennett, C. E. *J. Org. Chem.* **1994**, *59*, 6110.

[11] The stereochemistry of the exocyclic double bond was assigned by a NOESY experiment showing an interaction between the CH_2 protons of the OMOM grouping and the vinylic Me and an absence of one between this Me and the side chain vinylic H. We thank Dr. Ron Garber and Ms. Helga Cohen for assistance with this experiment.

[12] Marshall, J. A.; Wang, X.-j. *J. Org. Chem.*, **1992**, *57*, 3387.

[13] This material was prepared through use of an improved procedure based on previously published work: Marshall, J. A.; Perkins, J. *J. Org. Chem.* **1994**, *59*, 3509.



a) 0.2 eq of 10% $AgNO_3$ on silica gel, hexane, r.t., 10 min

furans, as exemplified by the efficient heterocyclization of allenylcarbinol **15**.

In some ongoing studies we have found that allenic and propargylic acids are nearly quantitatively converted to butenolides by the supported catalyst system.[14] These finding will be reported in due course.

Experimental Section[15]

Representative Experimental Procedure for $AgNO_3$/ Silica Gel Cyclizations: 2-Pentyl-3-methyl-5-heptylfuran (2a). A. Batch Process. To a stirred solution of 0.250 g (1.00 mmol) of allylic alcohol **1a** in 4.0 mL of hexane was added 0.17 g (0.10 mmol) of 10% $AgNO_3$ on silica gel.[7] The mixture was allowed to stir protected from light for 1 h at rt. The mixture was then diluted with ether, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (deactivated with 5% Et_3N−hexane) afforded 0.240 g (96%) of furan **2a** as a clear colorless oil: IR (cm^{-1}, film) 2927, 2856, 1577, 1467; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.77 (s, 1H), 2.57 (t, J = 7.3 Hz, 2H), 2.54 (t, J = 7.3 Hz, 2 H), 1.94 (s, 3 H), 1.67−1.57 (m, 4 H), 1.45−1.23 (m, 12 H), 0.94 (t, J = 6.8 Hz, 3 H), 0.93 (t, J = 6.8 Hz, 3 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) 153.4, 149.3, 113.7, 107.6, 31.8, 31.4, 29.6, 29.1, 28.4, 28.2, 28.0, 25.9, 22.6, 22.4, 14.0, 14.0, 9.8. Anal. Calcd for $C_{17}H_{30}O$: C, 81.53; H, 12.07. Found: C, 81.42; H, 11.99.

B. Flow Process. A Waters Prep LC System 500 was equipped with a 1 × 12 in. stainless steel semiprep column packed half with silica gel (deactivated with 5% Et_3N−hexane) and half with 10% $AgNO_3$ on silica gel. The column was flushed with hexane, and a solution of 0.50 g (2.00 mmol) of alcohol **1a** in 2 mL of hexane was introduced with the aid of hexane. The column was eluted with 800 mL of hexane, and the eluant was concentrated under reduced pressure to afford 0.45 g (90%) of furan as a clear light yellow oil. A repeat run yielded 0.445 g (89%) and a third run with 1.00 g (4.00 mmol) of alcohol **1a** gave 0.84 g (84%) of furan **2a**.

Diene 7b. To a stirred solution of 25.0 mg (0.10 mmol) of allylic alcohol **5b**[2g] in 1.0 mL of 5% Et_3N−hexane was added 33.0 mg (0.02 mmol) of 10% $AgNO_3$ on silica gel.[7] The mixture was allowed to stir protected from light for 5 h at rt. The mixture was then diluted with ether, filtered, and concentrated under reduced pressure to afford 24.5 mg (98%) of diene **7** as a clear yellow oil. Owing to the acid lability of this substance, it proved necessary to use $CDCl_3$ passed through activity II basic alumina as solvent for determination of the ^{1}H NMR spectrum: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.99 (br s, 1 H), 4.78 (d, J = 1.8 Hz, 2 H), 4.76 (d, J = 6.5 Hz, 1 H), 4.59−4.52 (m, 1 H), 4.48 (d, J = 6.5 Hz, 1 H), 4.18 (br d, J = 9.3 Hz, 1 H), 3.37 (s, 3 H), 1.78 (dt, J = 2.0, 1.6 Hz, 3 H), 1.67 (m, 10 H), 0.85 (t, J = 7.0 Hz, 3 H).

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Supporting Information Available: ^{1}H NMR spectra for furans **2a** and **6a**, alcohol **5a**, and dienes **7a** and **7b**; contour plot for NOESY experiment (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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[14] For an example employing $AgNO_3$ in acetone, see ref 2h.

[15] For typical experimental protocols, see: Marshall, J. A.; Wang, X.-j. *J. Org. Chem.* **1991**, *56*, 960.