ORGANIC LETTERS

2006
Vol. 8, No. 18
4027−4029

Olefination of Ketones Using a Gold(III)-Catalyzed Meyer–Schuster Rearrangement

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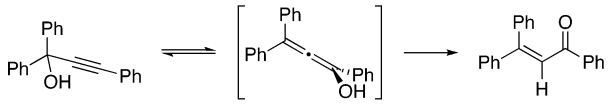
Received July 7, 2006

ABSTRACT

An atom-economical and efficient olefination strategy for ketones is described. Ethoxyacetylide addition followed by a gold-catalyzed Meyer–Schuster rearrangement affords α,β-unsaturated esters, generally in excellent overall yield from the starting ketones. The alkynophilicity of Au^{3+} promotes an interaction with the electron-rich acetylenes that catalyzes the Meyer–Schuster rearrangement selectively over other conceivable pathways.

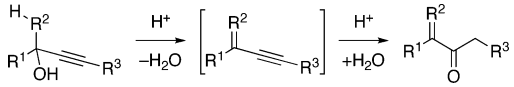
The Meyer−Schuster reaction is a little-known but potentially powerful rearrangement that converts propargyl alcohols into α,β-unsaturated carbonyl compounds.[1] The process formally involves a 1,3-shift of the hydroxyl moiety (Scheme 1), followed by tautomerization of the presumed allenol intermediate, **I**.[2] The reactions first reported by Meyer and Schuster[3] were conducted in acidic media at elevated temperatures. Transition metals[4] and metal oxide[5] catalysts promote the rearrangement via more targeted activation of the acetylenic alcohol, but limited scope, harsh conditions, and a prevalence of side reactions have detracted from the utility of the Meyer−Schuster rearrangement.

Scheme 1. Meyer and Schuster's Rearrangement



Closely related to the Meyer−Schuster is the Rupe rearrangement of propargyl alcohols,[1] which yields an isomeric α,β-unsaturated carbonyl compound via an intermediate enyne.[6] For the Meyer−Schuster reaction to succeed, the initial dehydration leading to the Rupe rearrangement must be blocked[7] or otherwise suppressed.

(1) Swaminathan, S.; Narayanan, K. V. *Chem. Rev.* **1971**, *71*, 429.
(2) (a) Edens, M.; Boerner, D.; Chase, C. R.; Nass, D.; Sciavelli, M. D. *J. Org. Chem.* **1977**, *42*, 3403. (b) Andres, J.; Cardenas, R.; Silla, E.; Tapia, O. *J. Am. Chem. Soc.* **1988**, *110*, 666.
(3) Meyer, K. H.; Schuster, K. *Chem. Ber.* **1922**, *55*, 819.
(4) (a) Erman, M. B.; Aul'chenko, I. S.; Kheifits, L. A.; Dulova, V. G.; Novikov, J. N.; Vol'pin, M. E. *Tetrahedron Lett.* **1976**, 2981. (b) Chabardes, P. *Tetrahedron Lett.* **1988**, *29*, 6253. (c) Choudary, B. M.; Durga Prasad, A.; Valli, V. L. K. *Tetrahedron Lett.* **1990**, *31*, 7521. (d) Narasaka, K.; Kusama, H.; Hayashi, Y. *Chem. Lett.* **1991**, 1413. (e) Lorber, C. Y.; Osborn, J. A. *Tetrahedron Lett.* **1996**, *37*, 853. (f) Picquet, M.; Fernández, A.; Bruneau, C.; Dixneuf, P. H. *Eur. J. Org. Chem.* **2000**, 2361. (g) Suzuki, T.; Tokunaga, M.; Wakatsuki, Y. *Tetrahedron Lett.* **2002**, *43*, 7531.
(5) Chabardes, P.; Kuntz, E.; Varagnat, J. *Tetrahedron* **1977**, *33*, 1775.
(6) The Rupe rearrangement (Rupe, H.; Kambli, E. *Helv. Chim. Acta* **1926**, *9*, 672):

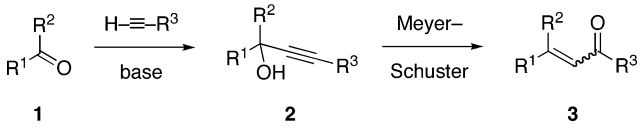


(7) For example, per-phenyl propargyl alcohol **2a** cannot undergo the Rupe rearrangement without breaking aromaticity. Most early examples of the Meyer−Schuster reaction were on substrates with aryl or *tert*-butyl substituents. See ref 1.

10.1021/ol0616743 CCC: $33.50
Published on Web 08/02/2006

Propargyl alcohols **2** are commonly prepared by addition of acetylide nucleophiles to carbonyl compounds. Compared to many carbanion nucleophiles, acetylides are less basic and less sensitive to steric congestion around the electrophilic carbonyl partner. The idealized sequence of (1) addition of a terminal acetylene and (2) Meyer−Schuster rearrangement results in olefination of the carbonyl with complete atom economy (Scheme 2).[8] This two-step strategy would be

Scheme 2. Atom-Economical HWE-Type Olefination Strategy



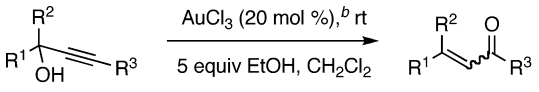
1 **2** **3**

particularly valuable for the Horner−Wadsworth−Emmons (HWE)-type olefination[9] of hindered ketones. It was this potential utility that stimulated our interest in developing a mild and generally efficient protocol for conducting the Meyer−Schuster reaction.

Gold(III) chloride ($AuCl_3$) emerged as the preferred choice from our initial screening of various catalysts and conditions.[10] The high affinity of late transition-metal Lewis acids, particularly gold-based catalysts, for acetylenic π-bonds enables many important processes to be achieved under mild conditions.[11] This mode of activation has become increasingly important in recent years.[12] In contrast, Brønsted, main-group, and early transition-metal Lewis acids bind preferentially to harder Lewis basic sites.[13] Thus, $AuCl_3$ likely promotes the Meyer−Schuster rearrangement through a fundamentally different type of catalyst−substrate interaction than known metal oxide or protic acid catalysts. The alkynophilicity of gold catalysts should be advantageous in improving the selectivity for the Meyer−Schuster reaction in preference to the Rupe or dehydration processes.

Table 1 shows gold catalysis of the Meyer−Schuster rearrangement,[14] with the "original" substrate (**2a**) listed in

Table 1. Initial Screening of Substrates[a]



(1)

2 **3**

entry	R^1	R^2	R^3	**2**	time	**3**	yield (%)[c]
1	Ph	Ph	Ph	**2a**	o/n[d]	**3a**	86
2	Et	Et	Ph	**2b**	o/n[d]	**3b**	<20[e]
3	Ph	H	Ph	**2c**	o/n[d]	**3c**	32
4	Ph	Ph	OEt	**2d**	<5 min	**3d**	>95
5	4-*t*-Bu-cyclohexyl		OEt	**2e**	<5 min	**3e**	82
6	adamantyl		OEt	**2f**	<5 min	**3f**	>95
7	*t*-Bu	Me	OEt	**2g**	<5 min	**3g**	86
8[b]	*t*-Bu	Me	OEt	**2g**	1 h	**3g**	<15[f]

[a] Typical procedure: Gold(III) chloride (0.1 mmol) added to a solution of propargyl alcohol **2** (0.5 mmol), EtOH (2.5 mmol), and CH_2Cl_2 (8 mL) at room temperature. See Supporting Information for details. [b] $TsOH·H_2O$ (0.1 mmol) was employed in lieu of $AuCl_3$ in entry 8. [c] Isolated yield of pure product, unless otherwise indicated. [d] Overnight (12−16 h). [e] The major product of this reaction was the enyne derived from dehydration of **2b** (57% yield). [f] The isolated mixture consisted of three major components—**2g**, **3g**, and an unknown byproduct in a ca. 70:15:15 mole ratio—along with minor decomposition products.

entry 1. The relatively high catalyst loading (20 mol %) provided complete and efficient conversion in a reasonable time frame (12−16 h), affording **3a** in 86% yield. However, the experiments illustrated in entries 2[15] and 3[16] serve as a reminder of the limited scope of the Meyer−Schuster process.

The use of oxygen-activated alkynes expands the scope to a much wider range of substitution patterns (entries 4−7). The ethoxyacetylene substrates were easily prepared using ethyl ethynyl ether,[17] and the gold-catalyzed Meyer−Schuster rearrangements were complete within minutes. The resulting α,β-unsaturated ethyl esters (**3**, R^3 = OEt) are versatile synthetic intermediates.[18] Entries 7 and 8 illustrate the difference between gold(III) chloride and a catalyst (TsOH) that is less alkynophilic. The acid-catalyzed reaction (entry 8) was sluggish and less selective for the desired Meyer−Schuster product (**3g**).[19]

Table 2 recounts efforts to determine the minimum catalyst loading needed to effect the Meyer−Schuster rearrangement of ethoxyacetylene **2f**: full conversion was achieved at 5 mol % (entries 1−5).[20] These conditions were appropriate

(8) (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259.

(9) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

(10) Metal oxides, protic acids of varying strengths, and silica gel were explored. These oxophilic reagents did not provide good prospects for expanding the scope of the Meyer−Schuster rearrangement.

(11) Recent reviews with leading references: (a) Dyker, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 4237. (b) Hashmi, A. S. K. *Gold Bull.* **2003**, *36*, 3. (c) Ma, S.; Yu, S.; Gu, Z. *Angew. Chem., Int. Ed.* **2006**, *45*, 200.

(12) Selected examples of gold(III) catalysis of organic reactions: (a) Fukuda, Y.; Utimoto, K. *J. Org. Chem.* **1991**, *56*, 3729. (b) Fukuda, Y.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2013. (c) Asao, N.; Takahashi, K.; Lee, S.; Kasahara, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 12650. (d) Yao, T.; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 11164. (e) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 6962. (f) Antoniotti, S.; Genin, E.; Michelet, V.; Genêt, J.-P. *J. Am. Chem. Soc.* **2005**, *127*, 9976. (g) Georgy, M.; Boucard, V.; Campagne, J.-M. *J. Am. Chem. Soc.* **2005**, *127*, 14180 (including two examples of Meyer−Schuster products). (h) Kusama, H.; Miyashita, Y.; Takaya, J.; Iwasawa, N. *Org. Lett.* **2006**, *8*, 289. Examples and leading references on gold(I) catalysis: (i) Johansson, M. J.; Gorin, D. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 18002. (j) Genin, E.; Toullec, P. Y.; Antoniotti, S.; Brancour, C.; Genêt, J.-P.; Michelet, V. *J. Am. Chem. Soc.* **2006**, *128*, 3112.

(13) *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: New York, 2000.

(14) Small amounts of an alcoholic cosolvent (e.g., 5.0 equiv of ethanol) increased the efficiency of the reaction.

(15) Entry 2 highlights the competition between simple dehydration—leading to an undesired enyne in 57% yield—and the formal 1,3-hydroxy shift en route to **3b**.

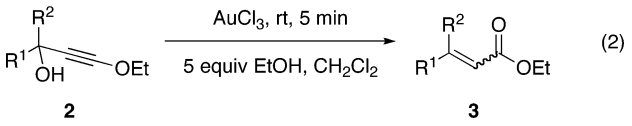
(16) Mixtures of alkene stereoisomers were obtained in entries 3, 7, and 8. No effort was made to optimize selectivity; the *E*:*Z* ratios were nearly 1:1 in some cases (e.g., entry 7). Given the general thermodynamic preference for *E*-isomers, these data suggest the possibility of a kinetic preference for the *Z*-isomers, which will be investigated further.

(17) A commercial 40% solution in hexane was used as received.

(18) Crich, D.; Natarajan, S.; Crich, J. Z. *Tetrahedron* **1997**, *53*, 7139.

(19) Aqueous acidic conditions were also tested for **2e** → **3e** (cf. Table 1, entry 5): reactions in THF−H_2O (1:1) promoted by either AcOH or HCl were incomplete after 1 h. Such acidic conditions are also more likely to promote undesired side reactions.

Table 2. Catalyst Loading and Optimization[a]



(2)

2 **3**

entry	R^1	R^2	**2**	$AuCl_3$	**3**	conversion (%)
1	adamantyl		**2f**	20 mol %	**3f**	>95
2	adamantyl		**2f**	10 mol %	**3f**	>95
3	adamantyl		**2f**	5 mol %	**3f**	>95
4	adamantyl		**2f**	1 mol %	**3f**	ca. 50[b]
5	adamantyl		**2f**	0.1 mol %	**3f**	<5[b]
6	Ph	Ph	**2d**	5 mol %	**3d**	>95
7	*t*-Bu	Me	**2g**	5 mol %	**3g**	>95
8	*n*-Bu	*n*-Bu	**2h**	5 mol %	**3h**	>95

[a] Typical procedure: Gold(III) chloride added to a solution of propargyl alcohol **2** (1 equiv), EtOH (5 equiv), and CH_2Cl_2 in an open flask at room temperature. See Supporting Information for details. [b] After 24 h.

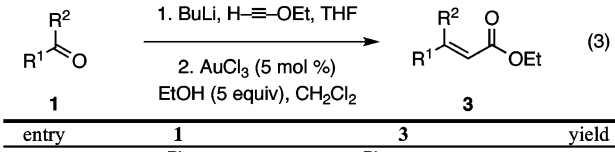
for aliphatic, aromatic, hindered, and unhindered substrates (entries 6−8). In conjunction with addition of ethoxyacetylene to ketones (**1** → **2**, R^3 = OEt), the Meyer−Schuster rearrangement (**2** → **3**) completes, in principle, an efficient HWE-type olefination strategy.

Diverse ketone substrates were subjected to the two-stage olefination process without purification of the intermediate propargyl alcohols (Table 3). Benzophenone (**1d**), adamantanone (**1f**), and pinacolone (**1g**) gave rise to alkenes **3d**, **3f**, and **3g** in good to excellent yields (entries 1−3). Dienonate **3i** was obtained from verbenone (**1i**) in nearly quantitative yield (entry 4). The efficiency of the acetylide addition dropped for camphor (**1j**) and 3,3,5,5-tetramethylcyclohexanone (**1k**), although alkenoates **3j** and **3k** were isolated in reasonable overall yields (entries 5 and 6).

In summary, an atom-economical olefination strategy is realized. The ketones evaluated herein comprise aromatic, aliphatic, and vinyl ketones; cyclic and acyclic ketones; and primary, secondary, tertiary, and methyl ketones. The powerful catalyst−substrate interaction between Au^{3+} and electron-rich acetylenes is selective for the Meyer−Schuster rearrangement over other conceivable pathways. Current and future work includes efforts to control the stereoselectivity of the Meyer−Schuster reaction with respect to *E*- and *Z*-isomers and to apply this olefination strategy to solve problems in chemical synthesis.

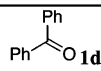
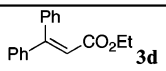
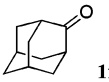
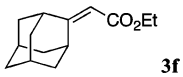
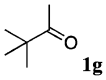
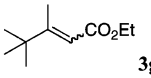
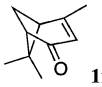
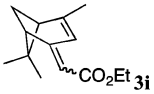
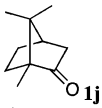
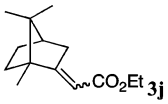
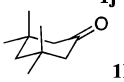
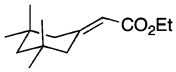
(20) On the basis of qualitative (TLC) monitoring of the experiments using a lower catalyst loading (entries 4 and 5), the reactions appeared to proceed rapidly and then stall at a certain point. Efforts to increase the turnover number will be addressed in future work.

Table 3. Olefination of Hindered Ketones[a]



(3)

1 **3**

entry	**1**	**3**	yield
1	 **1d**	 **3d**	91%
2	 **1f**	 **3f**	99%
3	 **1g**	 **3g**	99%[b]
4	 **1i**	 **3i**	96%[c]
5	 **1j**	 **3j**	68% (84%)[c,d]
6	 **1k**	 **3k**	73% (85%)[d]

[a] See Supporting Information for details. [b] Ca. 4:3 ratio of olefin isomers. [c] Ca. 2:1 ratio of olefin isomers. [d] 10 mol % of $AuCl_3$ employed. Value in parentheses is the calculated yield based on recovered ketone **1**.

Acknowledgment. This research was supported by the James and Ester King Biomedical Research Program, Florida Department of Health, the Donors of the American Chemical Society Petroleum Research Fund, and the FSU Department of Chemistry and Biochemistry. D.A.E. is the recipient of graduate fellowships from FSU and the MDS Research Foundation. We are profoundly grateful to all of these agencies for their support. We thank Dr. Joseph Vaughn (FSU) for assistance with the NMR facilities, Dr. Umesh Goli (FSU) for providing the mass spectrometry data, and the Krafft Lab for the use of their FT-IR instrument.

Supporting Information Available: Experimental procedures, characterization data for all new compounds, and copies of ^1H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0616743