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Synthesis of Stable 2*H*-Pyran-5-carboxylates via a Catalyzed Propargyl-Claisen Rearrangement/ Oxa-6π Electrocyclization Strategy

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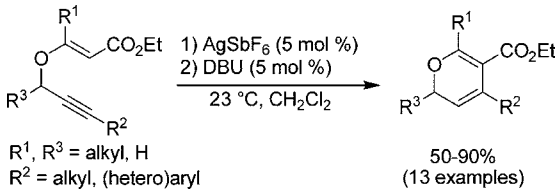
ABSTRACT



The application of easily accessed propargyl vinyl ethers for the synthesis of monocyclic 2*H*-pyrans was achieved. Under the reaction conditions, highly substituted heterocycles were obtained in moderate to excellent yields. The one-pot sequence proceeds via a Ag(I)-catalyzed propargyl-Claisen rearrangement, followed by a base-catalyzed isomerization, and 6π-oxaelectrocyclization, leading to the formation of stable 2*H*-pyrans.

The synthesis of stable 2*H*-pyrans is an ongoing challenge in organic synthesis.[1] Since 2*H*-pyrans undergo a reversible electrocyclic ring-opening to 1-oxatrienes,[2] classical strategies toward monocyclic 2*H*-pyrans generally afford an equilibrating mixture.[3] Typically, the substrate-dependent equilibrium is dominated by 1-oxatrienes,[3d,g] while the 2*H*-pyran form is favored only in a few cases due to increased steric interactions.[4,5] Although there are numerous applications of 1-oxatrienes,[6,7] the synthetic utility of monocyclic 2*H*-pyrans is somewhat limited.[8,9]

Recently, we reported that acceptor substituted propargyl vinyl ethers **1** can be transformed into highly substituted furans by a gold(I)-catalyzed propargyl-Claisen rearrangement/heterocyclization cascade.[10] In this reaction, the catalyst promotes a 5-*exo-dig* heterocyclization of the ketone (or its tautomeric enol form) onto the allene (Scheme 1). On the

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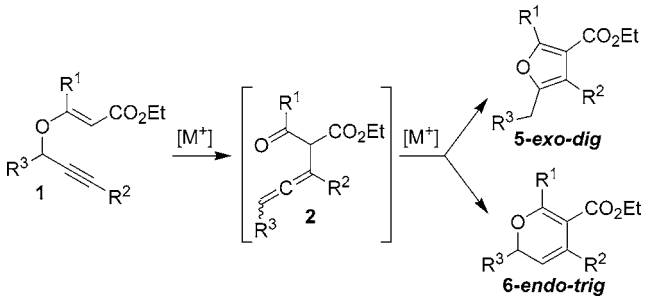
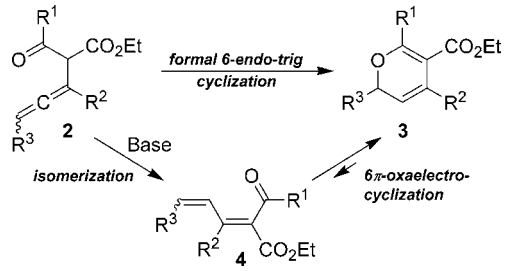
Scheme 1. Synthesis of Furans and 2*H*-Pyrans from Propargyl Vinyl Ethers



basis of these results, we became interested in the possibility of constructing 2*H*-pyrans by a preferential 6-*endo-trig* cyclization of allenes. We report herein that highly substituted 2*H*-pyrans, which only occasionally undergo ring-opening, can be efficiently obtained from propargyl vinyl ethers via a cascade reaction of a propargyl-Claisen rearrangement and a formal 6-*endo-trig* cyclization. $AgSbF_6$ and DBU are sequentially utilized to catalyze this simple one-pot approach to racemic[11] 2*H*-pyrans.

Our initial attempts failed to define a transition metal catalyst system that would promote a straight and regioselective heterocyclization of allenic ketone **2** to the desired 2*H*-pyrans.[11] Owing to the ability of 1-oxatrienes to be in equilibrium with 2*H*-pyrans, we then envisioned a process that proceeds through the sequence shown in Scheme 2. On

Scheme 2. 6π-Electrocyclization Approach to 2*H*-Pyrans **3**



the basis of our observation that cationic silver(I) salts catalyze the rearrangement of propargyl vinyl ethers **1** to the corresponding allenylcarbonyl compounds **2**,[12,13] we planned to utilize $AgSbF_6$ as a catalyst to obtain allenic ketones, which then should undergo base-catalyzed isomerization, and the sequence concludes with a 6π-electron electrocyclic ring-closure of **4** to give the 2*H*-pyrans **3**. The overall process can be considered formally an equivalent of a propargyl-Claisen rearrangement/6-*endo-trig* cyclization domino reaction.

To realize the isomerization step, preliminary studies have been carried out on allenic ketone **2a**, which was prepared by treatment of propargyl vinyl ether **1a** with 5 mol % of $AgSbF_6$ in CH_2Cl_2. Initial results indicated that KO*t*Bu (10 mol %, 30 min, 15%), $EtN(iPr)_2$ (10 mol %, 30 min, 17%), NEt_3 (10 mol %, 30 min, 50%), DBU (5 mol %, 30 min, 100%), and DMAP (50 mol %, 12 h, 100%) all afford highly substituted 2*H*-pyran **3a**. Among these bases, however, DBU is the most efficient catalyst based on reaction time. When the reaction was performed in the absence of DBU or in the presence of a catalytic amount of protic acid, no isomerization product **3a** was obtained at all. We were pleased to find that the substitution pattern favors the exclusive formation of the cyclic 2*H*-pyran **3a**. The corresponding 1-oxatriene **4a** was not seen by ^1H NMR analysis of both the crude reaction mixture and the pure product after column chromatography.

The complete synthetic protocol was performed by linking the Ag(I)-catalyzed rearrangement with the cycloisomerization catalyzed by DBU in a one-pot manner [(1) substrate **1**, 5 mol % of $AgSbF_6$, 23 °C, 60 min, CH_2Cl_2; (2) 5 mol % of DBU].[14] Table 1 illustrates the scope of this sequence. Propargyl vinyl ether **1a** readily reacted to give 2*H*-pyran **3a** in good yield. Other propargyl vinyl ethers underwent smooth transformation (entries 2−13); however, the yields varied, depending on the substituents employed. The relatively low yields for substrates derived from primary propargylic alcohols ($R^3 = H$) were due to concomitant furan formation through 5-*exo* cyclization (entries 10−12). Of primary importance, the corresponding 1-oxatrienes **4a**−**m** were not seen by ^1H NMR analysis of crude reaction mixtures (entries 1−13); in these cases, the cyclic 2*H*-pyran form **3** was obtained as the sole product. However, substrate **1n** in which R^1 is a phenyl group gave the corresponding 1-oxatriene **4n** as the predominant product, as did propargyl vinyl ether **1o** with $R^3 = Ph$.

(9) For reaction with 2*H*-pyrans formed in situ, see: (a) Belosludtsev, Y. Y.; Borer, B. C.; Taylor, R. J. K. *Synthesis* **1991**, 320. (b) Obrecht, D. *Helv. Chim. Acta* **1991**, *74*, 27. (c) Charoenying, P.; Davies, D. H.; McKerrecher, D.; Taylor, R. J. K. *Tetrahedron Lett.* **1996**, *37*, 1913. (d) Tius, M. A.; Hu, H.; Kawakami, J. K.; Busch-Petersen, J. *J. Org. Chem.* **1998**, *63*, 5971. (e) Obrecht, D.; Zumbrunn, C.; Müller, K. *J. Org. Chem.* **1999**, *64*, 6182.

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(11) During the course of this work, a gold(I)-catalyzed synthesis of enantioenriched dihydropyrans via chirality transfer utilizing a propargyl-Claisen rearrangement/6-*endo-trig* heterocyclization was reported. Our protocol gives racemic 2*H*-pyrans: Sherry, B. D.; Maus, L.; Laforteza, B. N.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 8132.

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(14) **General Procedure.** Synthesis of **3a**: $AgSbF_6$ (38 mg, 0.11 mmol, 5 mol %) was added to a solution of **1a** (570 mg, 2.1 mmol) in CH_2Cl_2 (10 mL), and the reaction vial was sealed, protected from light, and stirred at room temperature for 60 min. Then, a solution of DBU (17 mg, 0.11 mmol, 5 mol %) in CH_2Cl_2 (0.5 mL) was added, and the reaction mixture was stirred at room temperature for 30 min (until TLC analysis indicated complete conversion). The mixture was concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (pentanes/EtOAc = 80/20) gave 2*H*-pyran **3a** as a colorless oil (432 mg, 1.59 mmol, 76%). R_f 0.65 (pentanes/EtOAc = 80/20); ^1H NMR (360 MHz, $CDCl_3$) δ 0.72 (t, J = 7.1 Hz, 3 H), 1.04 (t, J = 7.4 Hz, 3 H), 1.74−1.96 (m, 2 H), 2.35 (s, 3 H), 3.81−3.87 (m, 2 H), 4.63 (dt, J = 3.8, 6.4 Hz, 1 H), 5.29 (d, J = 3.8 Hz, 1 H), 7.31−7.34 (m, 3 H), 7.44−7.48 (m, 2 H); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 9.6, 13.8, 19.0, 27.3, 60.0, 77.9, 108.3, 116.3, 126.8, 127.3, 128.3, 137.4, 141.1, 166.0, 167.6. LRMS (EI) 272 (10%) [M^+], 199 (100%); HRMS 272.1420 [272.1412 calcd for $C_{17}H_{20}O_3Cl$ (M^+)].

Table 1. Formation of 2*H*-Pyrans **3** from Propargyl Vinyl Ethers **1**[a]

	3				yield	ratio
entry	R^1	R^2	R^3	no.	[%][b]	(**3**:**4**)[c]
1	Me	Ph	Et	**a**	76	>99:1
2	Me	4-*t*Bu(C_6H_4)	Et	**b**	77	>99:1
3	Me	4-PhO(C_6H_4)	Et	**c**	63	>99:1
4	Me	3-thienyl	Et	**d**	90[d]	>99:1
5	Me	CH_2CH_2OTBS	Et	**e**	82	>99:1
6	Me	CH_2(*c*-C_6H_{11})	Et	**f**	75	>99:1
7	Me	Ph	Me	**g**	72	>99:1
8	Me	Ph	*i*Pr	**h**	80	>99:1
9	Me	Ph	CH_2Ph	**i**	50	>99:1
10	Me	Ph	H	**j**	61[d]	>99:1
11	Me	2-MeO(C_6H_4)	H	**k**	59[d]	>99:1
12	Me	3-thienyl	H	**l**	53[d]	>99:1
13[e]	*n*Pent	Ph	Et	**m**	72	>99:1
14	Ph	Ph	Et	**n**	90	20:80[f]
15	Me	CH_2(*c*-C_6H_{11})	Ph	**o**	36	<1:99[g]

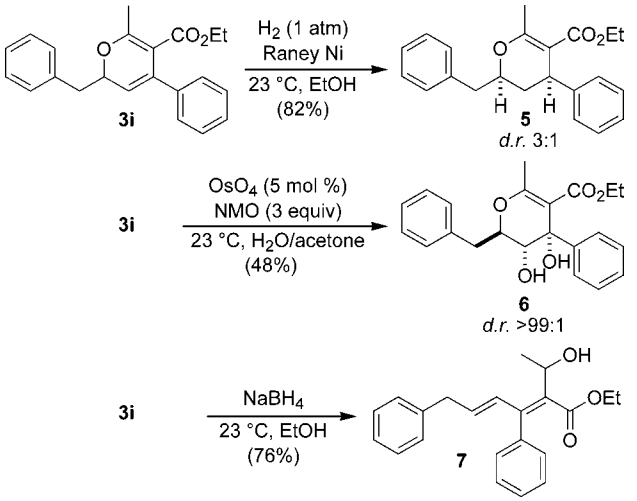
[a] Conditions: (1) substrate **1**, 5 mol % of $AgSbF_6$, 23 °C, 60 min, CH_2Cl_2; (2) 5 mol % of DBU. [b] Yield of pure product after column chromatography. [c] Determined by ^{1}H NMR. [d] The product contains traces of unidentified impurities. [e] The methyl ester was used. [f] **3n**:*trans*-**4n**:*cis*-**4n** = 20:30:50. [g] **3o**:*trans*-**4o**:*cis*-**4o** = 0:100:0.

Since 2*H*-pyrans **3** are prone to slow decomposition at room temperature, extensive storage should occur at −20 °C. Nevertheless, 2*H*-pyrans **3a**−***l*** can be stored at room temperature for several days without diminishing their purity.

We have also investigated further transformations of the 2*H*-pyran products using known chemistry (Scheme 3). For example, hydrogenation (**3i** → **5**),[3h] dihydroxylation (**3i** → **6**),[15] and nucleophilic addition (**3i** → **7**) have afforded the anticipated products in modest to good yields.

In conclusion, we have described a convenient method for the synthesis of monocyclic 2*H*-pyrans. Due to their particular substitution pattern, the resulting heterocyclic compounds show high stability to electrocyclic ring-opening. Additionally, these results underscore the potential of propagyl vinyl ethers as easily accessible starting compounds[16] for the formation of different classes of heterocycles, using a rearrangement−heterocyclization strategy.[10,12] Work is now in progress to extend the synthetic value of monocyclic 2*H*-pyrans.

Scheme 3. Synthetic Utility of 2*H*-Pyrans



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Supporting Information Available: Representative experimental procedures for catalytic 2*H*-pyran formation, compound characterization data for **3a**−**o**, and copies of ^{1}H and ^{13}C NMR spectra of **3** and **5**−**7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Zehnder, L. R.; Wie, L.; Hsung, R. P.; Cole, K. P.; McLaughlin, M. J.; Shen, H. C.; Skenicka, H. M.; Wang, J.; Zificsak, C. A. *Org. Lett.* **2001**, *14*, 2141.

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