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Ring Opening/Fragmentation of Dihydropyrones for the Synthesis of Homopropargyl Alcohols

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Homopropargyl alcohols (HPAs) are fundamental building blocks for the synthesis of complex polyketide and macrolide structures. In principle, HPAs are available by means of nucleophilic propargyl addition to aldehydes or ketones (Figure 1), but one can generally expect good stereo- and regioselectivity only in pairings of aldehydes with allenylmetal reagents under carefully prescribed conditions.[1,2] In practice, HPAs **2** are often reached by alternative methods, such as acetylide opening of epoxides or alkynylation of β-hydroxy aldehydes.[3]

A new carbonyl extrusion strategy for preparing HPAs is outlined herein: tandem ring-opening/carbon–carbon (C–C) bond cleavage (**1** → **2**, Figure 1). Despite significant advances in acyclic stereocontrol, synthetic chemists remain better equipped to manipulate rigid cyclic systems. Mechanisms for unraveling cyclic systems in a controlled manner provide complex acyclic synthons (e.g., HPAs **2**) that otherwise may be difficult to prepare.

A classic example of ring-opening C–C bond cleavage is the Eschenmoser–Tanabe fragmentation of ene-hydrazone oxides (**A**, Scheme 1).[4] Alternative entry into this mechanistic pathway has been demonstrated,[5] most notably through the use of cyclic vinylogous acyl triflates (**B**).[6a] This latter entry, a tandem nucleophilic addition/C–C bond cleavage reaction, provides efficient access to carbon-tethered alkynyl ketones,[6b] amides, β-keto esters,[6c] alcohols, and other functional groups.[6d,e]

This Communication describes the nucleophile-triggered decomposition of 5,6-dihydro-2-pyrone (DHP) triflates for the synthesis of homopropargyl alcohols (HPAs) (**1** → **2**, Figure 1).[7] For the stereoselective synthesis of chiral HPAs, this carbonyl extrusion strategy changes the nature of the challenge, from (*a*) the difficult, specific task of controlling addition of propargyl nucleophiles to aldehydes and ketones[1b] to (*b*) the more general exercise of preparing 4-oxygenated-5,6-dihydro-2-pyrones (i.e., **1**).[8–14]

DHP triflate **1a** served as the prototype for testing the new bond cleavage strategy. Table 1 shows the efficiency with which **1a** unravels under the action of 2.0 equiv of various carbanionic nucleophiles.[15] Toluene was a better solvent than THF (entries 2 and 3),[6d] and Grignard nucleophiles outperformed organolithiums (entries 1 and 2; entries 6 and 7). Methylmagnesium bromide (MeMgBr, entry 6) emerged as the optimal choice. DHP triflate **1a** was prepared by triflation[6,16] of 6-phenyl-2,4-oxanedione.[17,18]

The need for 2.0 equiv of nucleophile is informative with respect to the reaction mechanism (Scheme 2). Nucleophilic addition to **1** provides a tetrahedral intermediate (**I**) that can either break down along the conventional lines (*path a*) or undergo immediate fragmentation (*path b*, not observed). The former path (*path a*) gives rise to *acyclic* triflate **II**, which is then subject to addition/

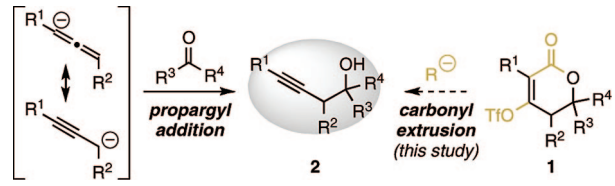
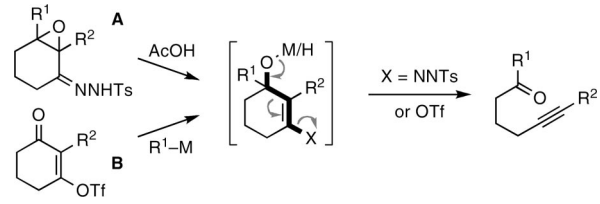


Figure 1. Strategies for the synthesis of homopropargyl alcohols (HPAs).

Scheme 1. Ring-Opening C–C Bond Cleavage (Fragmentation) of Ene-Hydrazone Oxides (**A**) and Vinylogous Acyl Triflates (**B**)



Scheme 2. Postulated Reaction Pathway

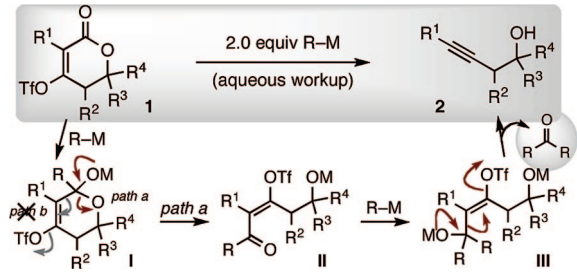
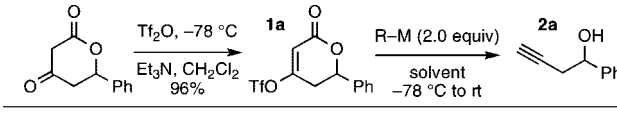


Table 1. Decomposition of DHP Triflate **1a** under Various Protocols[18]



entry	R–M	solvent	yield
1[a]	Ph–Li[b]	THF	48%
2	Ph–MgBr[c]	THF	54%
3	Ph–MgBr[c]	toluene	84%
4	*p*-MeO–C_6H_4–MgBr[d]	toluene	51%
5	*n*-Bu–MgCl[e]	toluene	70%
6	**Me–MgBr**[c]	**toluene**	**>95%**
7	Me–Li[f]	toluene	42%
8	*i*-Pr–Li[g]	toluene	15%

[a] –78 °C → 60 °C. [b] 2.0 M in butyl ether. [c] 3.0 M in ether. [d] 0.5 M in THF. [e] 2.0 M in ether. [f] 1.6 M in ether. [g] 0.7 M in pentane.

C–C bond cleavage[6] (**II** → **III** → **2**).[19] Ultimately, HPAs **2** arise stereospecifically from cyclic dihydropyrones **1**.[20]

Whereas propargyl addition to aldehydes (cf. Figure 1) is affected by substituents on the carbonyl group, unraveling of DHP triflates proceeds with high efficiency regardless of the substituent geminal

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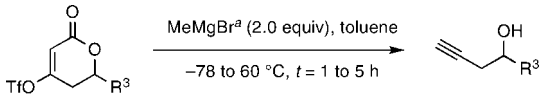
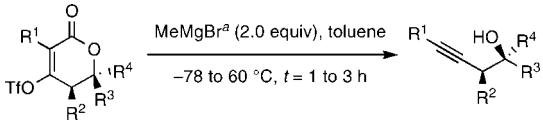
Table 2. Decomposition of DHP Triflates with MeMgBr[18]



entry	1	R^3	2	yield
1[b]	**1a**	Ph	**2a**	quant
2[b]	**1b**	*p*-Br−C_6H_4	**2b**	99%
3[b]	**1c**	*p*-MeO-C_6H_4	**2c**	95%
4[c]	**1d**	3-furyl	**2d**	92%
5[b]	**1e**	cinnamyl	**2e**	84%
6	**1f**	$PhCH_2CH_2$	**2f**	quant
7	**1g**	cyclohexyl	**2g**	85%
8[c]	**1h**	*t*-butyl	**2h**	91%

[a] 3.0 M in ether. [b] −78 °C to rt, 1 h. [c] Overnight reaction (t = 12 h).

Table 3. Decomposition of Substituted DHP Triflates[18]



entry	1	R1	R2	R3	R4	2	yield
1	**1i**	H	H	$PhCH_2CH_2$	Me	**2i**	82%
2	**1j**	Me	H	Ph	H	**2j**	quant
3	**1k**	Bn	H	Ph	H	**2k**	92%
4[c]	**1l**	H	Me	Cy[b]	H	**2l**	76%
5[c]	**1m**	H	Me	H	Cy[b]	**2m**	78%
6	**1n**	H	Bn	H	Ph	**2n**	83%

[a] 3.0 M in ether. [b] Cy = cyclohexyl. [c] Overnight reaction (t = 12 h).

to the oxygen atom (Table 2). Aryl substituents were well-tolerated (entries 1–4), whether electron-rich (entries 3 and 4, 95 and 92%) or electron-poor (entry 2, 99%). Fragmentation of cinnamyl-substituted **1e** furnished HPA **2e** in 84% yield (entry 5). Alcohols **2f–h**—formally the products of propargyl addition to linear, branched, and tertiary aliphatic aldehydes—were produced in excellent yields through this ring-opening/C–C bond cleavage methodology (entries 6–8).

Table 3 presents experiments aimed at unraveling differentially substituted DHP triflates **1**. Geminal disubstitution was tolerated in the synthesis of tertiary alcohol **2i** (entry 1, 82%). Entries 2 and 3 illustrate the formation of internal alkynes (**2j** and **2k**). The nucleophile-promoted fragmentations yield **2** in a stereodefined manner: 5,6-*cis*-DHP triflate **1l** gives rise to *syn*-HPA **2l** (entry 4, 76%), whereas *trans*-isomers **1m** and **1n** provide *anti*-HPAs **2m** and **2n** (entries 5 and 6, 78 and 83%).

In conclusion, nucleophilic addition of methylmagnesium bromide to 5,6-dihydro-2-pyrone (DHP) triflates induces a ring-opening/fragmentation process to furnish homopropargyl alcohols. The unified strategy of preparing and unraveling DHP triflates provides chiral homopropargyl alcohols that may be difficult to access by other means. The full scope and applications of this process in chemical synthesis will be reported in due course.

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

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(18) See Supporting Information for details.

(19) As in previous reports,[6] slow fragmentation of **IV** ensures consumption of R–M (2 equiv) prior to formation of the ketone.

(20) A symmetrical ketone (i.e., acetone for R–M = MeMgBr) is an expected byproduct. Indeed, benzophenone (diphenyl ketone) was identified by NMR spectroscopy following an experiment in which phenylmagnesium bromide was employed as the nucleophile (Table 1, entry 3).

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