ORGANIC
LETTERS

2011
Vol. 13, No. 1
158−160

Stereodefined Homopropargyl Amines by Tandem Nucleophilic Addition/Fragmentation of Dihydropyridone Triflates

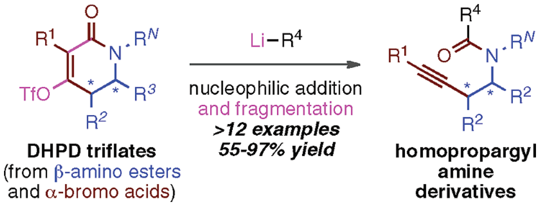
Jumreang Tummatorn and Gregory B. Dudley*

Department of Chemistry and Biochemistry, Florida State University, Tallahassee, Florida 32306-4390, United States

gdudley@chem.fsu.edu

Received November 14, 2010

ABSTRACT



Dihydropyridone (DHPD) triflates undergo nucleophile-triggered fragmentation to provide homopropargyl amine derivatives, the stereochemistry of which is defined by starting from readily available *β*-amino esters.

This work is focused on the synthesis of functionalized homopropargyl amines. Conceptually, three strategic C−C bond construction alternatives (A, B, and C, Figure 1) are available. The first two, [A] propargyl addition to imines[1,2] and [B] acetylide opening of aziridines,[3] involve pre-existing acetylenic substrates and often present unresolved stereo- and regioselectivity issues. The third, [C] *de novo* construction of nonstereogenic alkynes, is largely unexplored.[4,5] Strategy [C] offers the advantage of starting from readily available β-amino acid derivatives of prescribed stereochemistry[6] but requires installation of the C≡C triple bond. The nucleophile-triggered fragmentation of dihydropyridone (DHPD) triflates described herein will enable development of strategy [C].

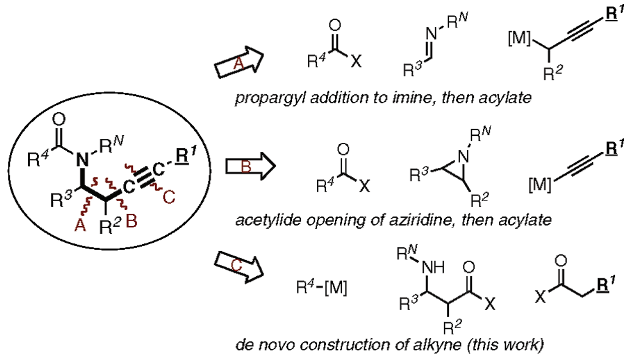


Figure 1. Strategies for the assembly of functionalized homopropargyl amine derivatives. Strategies [A] and [B] make use of pre-existing alkynes but pose stereo- and regiocontrol problems. Strategy [C] exploits pre-existing stereochemistry but presents the challenge of generating the C≡C triple bond.

---

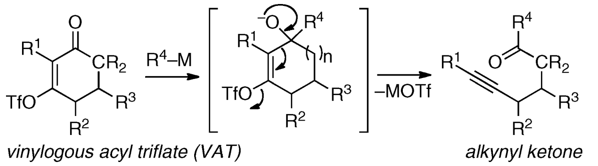
(1) Reviews: (a) Vilaivan, T.; Bhanthumnavin, W.; Sritana-Anant, Y. *Curr. Org. Chem.* **2005**, *9*, 1315–1392. (b) Zhou, P.; Chen, B. C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003–8030. (c) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984–995.

(2) Recent examples: (a) Fandrick, D. R.; Johnson, C. S.; Fandrick, K. R.; Reeves, J. T.; Tan, Z.; Lee, H.; Song, J. J.; Yee, N. K.; Senanayake, C. H. *Org. Lett.* **2010**, *12*, 748–751. (b) Brawn, R. A.; Panek, J. S. *Org. Lett.* **2009**, *11*, 4362–4365. (c) Prajapati, D.; Laskar, D. D.; Gogoi, B. J.; Devi, G. *Tetrahedron Lett.* **2003**, *44*, 6755–6757.

(3) Ding, C.-H.; Dai, L.-X.; Hou, X.-L. *Tetrahedron* **2005**, *61*, 9586–9593.

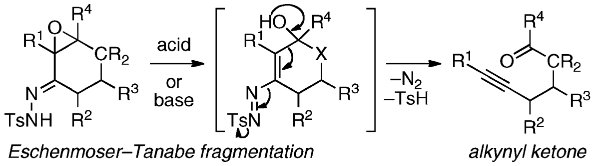
(4) (a) Larock, R. C. *Comprehensive Organic Transformations*, 2nd ed.; Wiley & Sons: New York, 1999; pp 563−583. (d) Brandsma, L. *Preparative Acetylenic Chemistry*, 2nd ed.; Elsevier: Amsterdam, 1988.

10.1021/ol102760q



(1)

Our laboratory has been investigating fragmentation[7] reactions that deliver functionalized alkynes by means of nucleophilic addition to vinylogous acyl triflates (VATs, eq 1).[8] Note that most organic fragmentation processes produce alkenes;[7c] "alkynogenic" fragmentations require a better nucleofuge[9] (typically triflate or molecular nitrogen; cf. eqs 1 and 2) than is needed to generate alkenyl carbonyls. Our ongoing methodology is reminiscent of the classic Eschenmoser−Tanabe alkynyl ketone synthesis (eq 2),[10] but VAT fragmentations deliver a wider array of products including alkynyl ketones, alcohols, and β-keto phosphonates.[11]



(2)

Related methods deliver homopropargyl alcohols,[12] allenyl ketones,[13] and alkynyl aldehydes.[14] Homopropargyl amines, an excellent entry point into the synthesis of complex alkaloids, have remained elusive until now.

Our hypothesis was that DHPD triflates derived from β-amino esters (e.g., **1a**, Scheme 1) would undergo nucleophile-triggered fragmentation to homopropargyl amine derivatives. However, lactam carbonyls are less electrophilic than lactones or ketones, and reaction conditions that had proven optimal in our earlier studies[8,11,12] were not applicable in this new system.

Scheme 1. Synthesis of Dihydropyridone (DHPD) Triflate **1a**

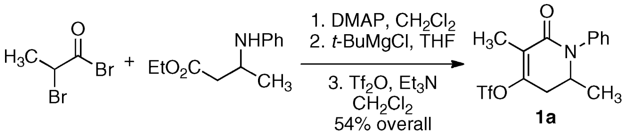
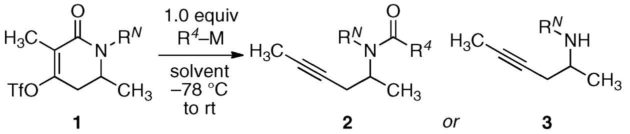


Table 1 comprises illustrative data from a large body of exploratory experiments aimed at establishing the appropriate combination of nitrogen substituent, external nucleophile, solvent, and reaction temperature profile to provide control

Table 1. Selected Experiments from the Optimization of Nucleophile-Triggered Fragmentation of Dihydropyridone (DHPD) Triflates (**1**)



entry	R^N	R^4−M	solvent	yield (%)
1	Ph	Ph−Li[a]	THF	56
2	Ph	Ph−Li[a]	toluene	76
3	Ph	Ph−MgBr[a]	toluene	—[b]
4	Ph	BnNH−Li	THF	0
5	Ph	BnNH−Li	toluene	0
6	Ph	Me−Li[c]	THF	—[b]
7	Ph	Me−Li[c]	toluene	90 (**2**)
8[d]	Ph	Me−Li[c]	toluene	48 (**3**)
9	Ph	Me−MgCl[e]	toluene	—[b]
10	***Ph***	***n-Bu−Li***[f]	***toluene***	***97 (2)***
11	Ph	*t*-Bu−Li[g]	toluene	38 (**2**)
12	Ph	*t*-Bu−Li[g]	toluene	64 (**2**)
13	Bn	*n*-Bu−Li[f]	toluene	46 (**2**)
14	Octyl	*n*-Bu−Li[f]	toluene	54 (**2**)

[a] 1.0 M in butyl ether. [b] Trace quantities of **2** and/or **3** observed in the crude reaction mixture by ^{1}H NMR spectroscopy. [c] 1.0 M in ether. [d] 2.0 equiv of MeLi, −78 to +80 °C. [e] 3.0 M in ether. [f] 2.4 M in hexanes. [g] 0.7 M in pentane.

---

(5) We found two examples of ethynylation of β-amino aldehydes (using the Seyferth−Gilbert/Ohira−Bestmann and Corey−Fuchs homologation protocols, respectively). The reagents involved are fundamentally one-carbon synthons for making terminal alkynes; see: (a) Carballo, R. M.; Ramírez, M. A.; Rodríguez, M. L.; Martín, V. S.; Padrón, J. I. *Org. Lett.* **2006**, *8*, 3837–3840. (b) Kazuta, Y.; Tsujita, R.; Uchino, S.; Kamiyama, N.; Mochizuki, D.; Yamashita, K.; Ohmori, Y.; Yamashita, A.; Yamamoto, T.; Kohsaka, S.; Matsuda, A.; Shuto, S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1199–1212.

(6) *Enantioselective Synthesis of b-Amino Acids*, 2nd ed.; Juaristi, E., Soloshonok, V. A., Eds.; Wiley-VCH: New York, 2005.

(7) Fragmentation reactions as defined by Grob: (a) Grob, C. A.; Schiess, P. W. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 1–15. Seminal paper: (b) Eschenmoser, A.; Frey, A. *Helv. Chim. Acta* **1952**, *35*, 1660–1666. Recent review: (c) Prantz, K.; Mulzer, J. *Chem. Rev.* **2010**, *110*, 3741–3766. Leading references: (d) Kürti, L.; Czakó, B. Grob Fragmentation. In *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier: New York, 2003; pp 190−191 and references cited. (e) Kürti, L.; Czakó, B. Wharton Fragmentation. In *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier: New York, 2003; pp 480−481 and references cited.

(8) (a) Kamijo, S.; Dudley, G. B. *J. Am. Chem. Soc.* **2005**, *127*, 5028–5029. (b) Kamijo, S.; Dudley, G. B. *J. Am. Chem. Soc.* **2006**, *128*, 6499–6507.

(9) (a) Lepore, S. D.; Mondal, D. *Tetrahedron* **2007**, *63*, 5103–5122. (b) Creary, X.; Burtch, E. A. *J. Org. Chem.* **2004**, *69*, 1227–1234. (c) Su, T. M.; Sliwinski, W. F.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1969**, *91*, 5386–5388. (d) Streitwieser, A., Jr.; Wilkins, C. L.; Kiehlmann, E. *J. Am. Chem. Soc.* **1968**, *90*, 1598–1601.

(10) Seminal papers: (a) Eschenmoser, A.; Felix, D.; Ohloff, G. *Helv. Chim. Acta* **1967**, *50*, 708–713. (b) Tanabe, M.; Crowe, D. F.; Dehn, R. L. *Tetrahedron Lett.* **1967**, 3943–3946. Leading references: (c) Kürti, L.; Czakó, B. Eschenmoser−Tanabe Fragmentation. In *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier: New York, 2003; pp 158−159 and references cited.

(11) (a) Kamijo, S.; Dudley, G. B. *Org. Lett.* **2006**, *8*, 175–177. (b) Jones, D. M.; Kamijo, S.; Dudley, G. B. *Synlett* **2006**, 936–938. (c) Kamijo, S.; Dudley, G. B. *Tetrahedron Lett.* **2006**, *47*, 5629–5632. (d) Jones, D. M.; Dudley, G. B. *Synlett* **2010**, 223–226. (e) Jones, D. M.; Lisboa, M. P.; Kamijo, S.; Dudley, G. B. *J. Org. Chem.* **2010**, *75*, 3260–3267. (f) Jones, D. M.; Dudley, G. B. *Tetrahedron* **2010**, *60*, 4860–4866.

(12) Tummatorn, J.; Dudley, G. B. *J. Am. Chem. Soc.* **2008**, *130*, 5050–5051.

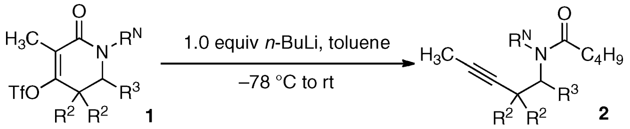
(13) Kolakowski, R. V.; Manpadi, M.; Zhang, Y.; Emge, T. J.; Williams, L. J. *J. Am. Chem. Soc.* **2009**, *131*, 12910–12911.

(14) (a) Draghici, C.; Brewer, M. *J. Am. Chem. Soc.* **2008**, *130*, 3766–3767. (b) Draghici, C.; Huang, Q.; Brewer, M. *J. Org. Chem.* **2009**, *74*, 8410–8413. (c) Bayir, A.; Draghici, C.; Brewer, M. *J. Org. Chem.* **2010**, *75*, 296–302.

over the desired addition/fragmentation pathway. It is clear from Table 1 that *N*-arylated DHPD triflates (R^N = Ph) undergo optimal ring opening by the addition/fragmentation pathway upon treatment with 1.0 equiv of alkyllithium reagents in hydrocarbon solvents (entry 10). *N*-Alkyl DHPD triflates (entries 13 and 14) were less effective, probably due to greater electron density at the lactam nitrogen as compared to the *N*-aryl substrates. Other organolithium nucleophiles were suitable (entries 2, 7, and 12), but Grignard reagents were not (entries 3 and 9). Toluene typically provides better results than ethereal solvents (cf. entries 6 and 7).

The results in Table 1 are significant in that they enable the synthesis of functionalized, internal homopropargyl amine derivatives from nonacetylenic starting materials.[5] Thus, we turned our attention to other substituted DHPD triflates to verify the generality of the method (Table 2). Variation in the *N*-aryl protecting group (entries 1−3) was tolerated, as were branched alkyl (entry 4), aryl (entries 5−6), and geminal dimethyl (entry 6) substituents, indicating that changes in sterics and/or electronic features around the periphery of the DHPD triflate are of minimal impact.

Table 2. Preliminary Scope of the Tandem Addition/Fragmentation of DHPD Triflates **1** to Homopropargyl Amines **2**

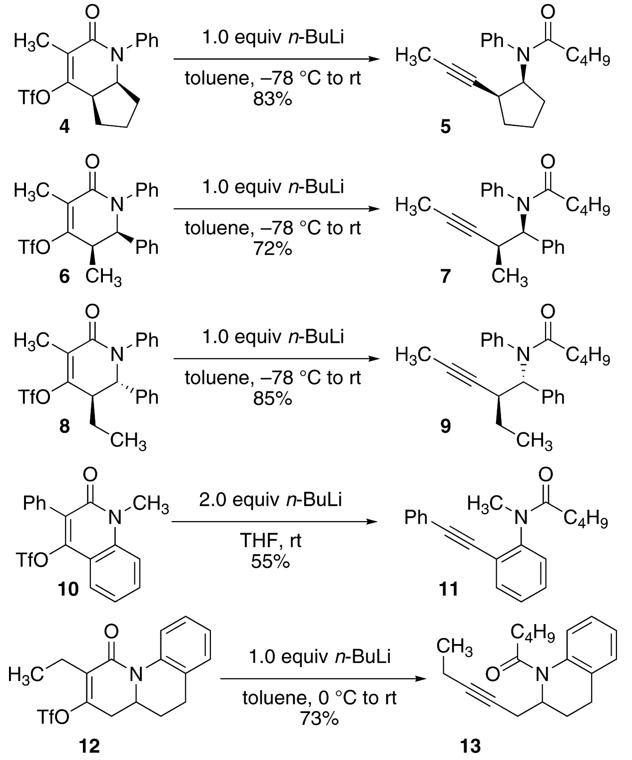


entry	R^2	R^3	R^N	yield (%)
1 (**1a**)	H	Me	Ph	97 (**2a**)
2 (**1b**)	H	Me	p-MeO-C$_6$H$_4$	81 (**2b**)
3 (**1c**)	H	Me	p-Cl-C$_6$H$_4$	88 (**2c**)
4 (**1d**)	H	*i*-Pr	Ph	80 (**2d**)
5 (**1e**)	H	Ph	Ph	77 (**2e**)
6[a] (**1f**)	Me	Ph	Ph	84 (**2f**)

[a] 2.0 equiv of *n*-BuLi, 0 °C to rt.

A diverse collection of DHPD triflates was assembled[15] and examined next (Scheme 2), with each substrate designed to probe a particular concept of interest to the methodology. The first example (**4** → **5**) is notable because the *cis*-cyclopentane stereochemistry would be difficult to access by *syn*-selective imine cyclization or by (stereoretentive) aziridine opening (cf. strategies A and B, Figure 1). The next two examples illustrate the stereospecificity of the addition/fragmentation process: *cis*-DHPD triflate **6** gives rise to *syn*-homopropargyl amine **7**, and the *trans*-DHPD triflate **8** provides *anti*-homopropargyl amine **9**. Quinolone **10** presents different stereoelectronic properties, but under slightly modified conditions the target *o*-alkynyl-aniline (**11**) was produced in a reasonable yield. Finally, tricyclic DHPD triflate **12** underwent ring-opening fragmentation to yield propargylated tetrahydroquinoline **13**.

Scheme 2. Synthesis of Functionalized Homopropargyl Amine Derivatives from Diverse DHPD Triflates



In summary, we report the nucleophile-triggered fragmentation of dihydropyridone (DHPD) triflates, which provides multifunctional homopropargyl amine core structures of great potential value in organic synthesis. The focus of this strategy for the synthesis of homopropargyl amines is on the formation of the nonstereogenic alkyne, which enables one to avoid many of the synthetic challenges associated with other approaches. Further development of this methodology, including for application in the synthesis of complex alkaloids from *β*-amino ester building blocks, is now underway.

Acknowledgment. This research is supported by a grant from the National Science Foundation (NSF-CHE 0749918). We thank Dr. Vithaya Ruangpornvisuti (Chulalongkorn University, Thailand) for assisting J.T. with computational analysis of DHPD triflates that helped guide her experimental efforts.

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.

OL102760Q

---

[15] The DHPD triflates used in this methodology were prepared by annulation of *β*-amino esters with carboxylic acid derivatives (cf. Scheme 1). See Supporting Information for details.