Synthesis and Thermal Rearrangement of *C,N*-Dialkynyl Imines: A Potential Aza-Bergman Route to 2,5-Didehydropyridine

Wendi M. David and Sean M. Kerwin*

*Division of Medicinal Chemistry, College of Pharmacy, The University of Texas at Austin Austin, Texas 78712*

Although 2,5-didehydropyridine (Scheme 1, **B**, X = N) has been the subject of numerous computational studies,[1] there has not yet been any experimental evidence for the existence of this elusive intermediate.[2] In 1972 Robert Bergman and co-workers[3] reported the thermal rearrangement of dideuterated (*Z*)-3-hexene-1,5-diyne (Scheme 1, **A**, X = CH) and established the existence of a 1,4-didehydrobenzene intermediate (**B**, X = CH) in this process. We reasoned that a 2,5-didehydropyridine intermediate might be generated from a *C,N*-dialkynyl imine (**A**, X = N) in the course of a rearrangement analogous to the Bergman rearrangement of hex-3-ene-1,5-diyne (**A**, X = CH). We report here a rapid and convenient synthesis of *C,N*-dialkynyl imines and the high-yielding conversion of these compounds to (*Z*)-β-alkynylacrylonitriles under very mild thermolysis conditions. Our preliminary studies of this isomerization are in agreement with a proposed mechanism involving the aza-Bergman rearrangement of the imines to β-alkynylacrylonitriles; however, we have not been able to trap the putative diradical 2,5-didehydropyridine intermediate. Thus, the 2,5-didehydropyridine species, if generated in this rearrangement, behaves very differently than 1,4-didehydrobenzene.

Although *C*-alkynyl-,[4] *N*-alkynyl-,[5] and *C,C*-dialkynyl imines[6] have previously been prepared, *C,N*-dialkynylimines have not been reported. Our synthesis of the requisite *C,N*-dialkynylimines **1a,b** (Scheme 2) involves alkynylcuprate substitution[5] of the oximinosulfonate esters **6** and **7**, which are prepared from the oxime **5**. Treating the silyl nitronate **4**[7] with 2 equiv of lithium phenylacetylide[8] affords the previously reported[9,10] oxime **5** in modest yield along with variable amounts of 3-methyl-5-phenylisoxazole, which presumably arises from 1,3-dipolar cycloaddition of an intermediate nitrile oxide with phenylacetylene. Addition of the cuprate derived from phenyl-acetylene to the oxime tosylate **6** affords the *C,N*-dialkynyl imine **1a** in 20% yield. The corresponding oxime mesylate **7** undergoes reaction to afford **1a** in 38% yield. The imine **1b** is produced in 20% yield upon addition of the cuprate derived from 6-phenylhex-5-en-1-yne[11] to oxime mesylate **7**. Imines **1a** and **1b** are isolated as relatively stable yellow oils after chromatography. These compounds can be handled in the air for short periods of time, or stored at −10 °C under argon for

Scheme 1

X = CH or N
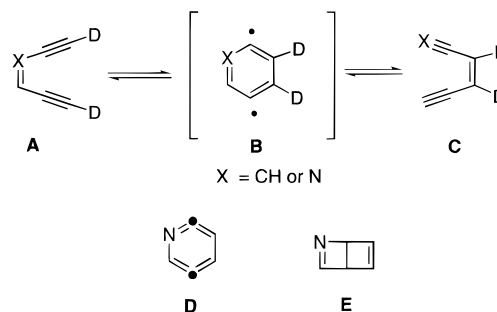
Scheme 2
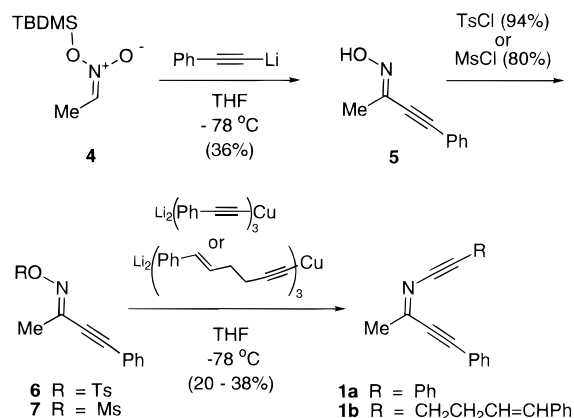
weeks without any signs of decomposition. Both **1a** and **1b** display separate resonances in their ¹H and ¹³C NMR spectra corresponding to (*E*)- and (*Z*)-isomers about the imine double bond (∼1:2 ratio). In the case of imine **1a**, these separate resonances do not coalesce at temperatures up to 60 °C in benzene or THF (500 MHz); however, we have been unable to resolve the C=N double bond isomers by TLC or HPLC.

When a benzene solution of **1a** is heated under reflux overnight, nitrile **3a** is produced in 88% yield after chromatography (Scheme 3). Nitrile **3a** is produced as the (*Z*)-stereoisomer (>95%), as judged from the ¹H NMR of the crude thermolysis product and comparison to authentic (*E*)-**3a**.[12] Heating a solution of imine **1a** in benzene containing a large excess of 1,4-cyclohexadiene (1,4-chd) as a hydrogen atom trap, or in neat 1,4-chd at 150 °C for 2 h, affords the nitrile **3a** as the only isolable product. The imine **1b** contains a pendent double bond that could serve as an intramolecular trap for the putative diradical intermediate **2** (Scheme 3). Such a cyclization should proceed at a rapid rate (ca. 10⁶ s⁻¹);[13] indeed, a similar technique has been used to trap 1,4-didehydrobenzene intermediates formed from Bergman cyclizations.[14] We find that heating a benzene solution of **1b** containing a large excess of 1,4-chd affords only the nitrile **3b** in nearly quantitative yield. Nitrile **3b** is produced as a single isomer with (*Z*)-stereochemistry about the tetrasubstituted double bond. In none of these reactions were any products (e.g., **8** or **10**) which would arise from trapping of the putative 2,5-didehydropyridine intermediate **2** detected.

Heating solutions of **1a** in either acetonitrile or heptane at 110 °C and monitoring the rate of the disappearance of **1a** and

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(10) Morrocchi, S.; Ricca, A.; Zanarotti, A.; Bianchi, G.; Gandolfi, R.; Grünanger, P. *Tetrahedron Lett.* **1969**, 3329−3332.
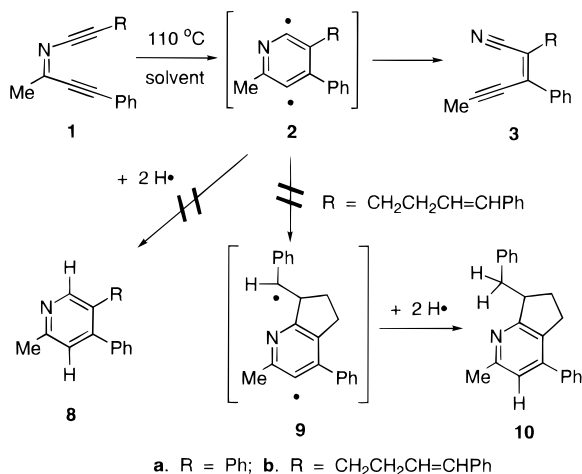
(11) Keinan, E.; Peretz, M. *J. Org. Chem.* **1983**, *48*, 5302−5309.

(12) Authentic (*E*)-**3a** was synthesized by the palladium-catalyzed coupling of 1-propynyltributyltin and the (*E*)-enol triflate of 2-cyano-2-phenylacetophenone.

(13) This value is estimated from that reported for the corresponding cyclization involving a secondary *sp³* radical center: Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317−323.

(14) Wisniewski Grissom, J.; Calkins, T. L. *Tetrahedron Lett.* **1992**, *33*, 2315−2318.

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Scheme 3

a. R = Ph; **b**. R = CH₂CH₂CH=CHPh

Table 1. Kinetic Parameters for the Thermal Isomerization of **1a** and **11**[a]

starting material (solvent)	k, s$^{-1 \, b}$	$t_{1/2} (\tau)^b$	product
1a (CH₃CN)	2.43×10^{-4}	47 min	**3a**
1a (heptane)	2.70×10^{-4}	43 min	**3a**
11[c] (CH₃CN + 1,4-chd[d])	3.24×10^{-7e}	24.4 days[e]	o-terphenyl

[a] See Supporting Information for experimental details. [b] Average value for two runs. [c] (Z)-1,6-Diphenylhex-3-ene-1,5-diyne. [d] 1,4-Cyclohexadiene. [e] Estimate from a single run of 12 days duration.

the production of **3a** gave the *first-order* rate constants shown in Table 1. The $t_{1/2}$ for the thermal isomerization of **1a** to **3a** is between 40 and 50 min at 110 °C, regardless of solvent polarity. The $t_{1/2}$ for the Bergman cyclization of the corresponding (Z)-1,6-diphenylhex-3-ene-1,5-diyne (**11**) to o-terphenyl is reported to be 71 min at 280 °C.[15] We find that prolonged heating of **11** in acetonitrile containing excess 1,4-chd affords a first order rate of conversion to o-terphenyl that is about 1000-fold slower than the rearrangement of **1a** to **3a**.

As highlighted in Scheme 1, there are structural similarities between the Bergman rearrangement of hexenediynes and the rearrangement of *C,N*-dialkynyl imines to β-alkynylacrylonitriles. In addition, there are other similarities between these two reactions. Both reactions occur at rates that are first-order with respect to starting material and are relatively unaffected by the polarity of the solvents employed.[3] Thus, it appears that both processes proceed though nonpolar, unimolecular reaction mechanisms. In addition, both reactions appear to be stereospecific, in that the Bergman reaction requires (Z)-enediynes, and the rearrangement of **1** produces (Z)-β-acetylenic acrylonitriles specifically.[16]

Despite the similarities noted above, there are key differences between the Bergman reaction and the rearrangement of *C,N*-

(15) Schmittel, M.; Kiau, S. *Chem. Lett.* **1995**, 953−954.

dialkynylimines. First, the rearrangement of **1** occurs much more readily than the Bergman reaction of simple hexenediynes.[17] Electron withdrawing substituents on the phenyl rings of **11** have been shown to accelerate its Bergman rearrangement,[15] perhaps by decreasing the degree of repulsion of the in-plane π-orbitals in the transition state.[18] The substitution of an sp^2 carbon in **11** with a nitrogen, as in **1**, may facilitate the rearrangement by a similar effect. The overall conversion of **1** to **3** is highly exothermic.[19] To the extent that ground state stabilization of the product of the reaction is reflected in the transition state, this may also play a role in enhancing the rate over that of the Bergman reaction. A more important difference between the Bergman reaction and the rearrangement of *C,N*-dialkynylimines involves the evidence for a diradical intermediate in the former. In contrast, we have been unable to obtain any evidence for a diradical intermediate in the rearrangement of **1** to **3**.[20] This inability to trap diradical species **2** may be related to the theoretical predictions of a very low energy barrier for the ring opening reaction of **B** (Scheme 1, X = N) to nitrile **C** (X = N).[1] Alternatively, the intermediate 2,5-didehydropyridine may not exist as a diradical species but may be more closely represented by alternative structures, such as **D** or **E** (Scheme 1).

In conclusion, *C,N*-dialkynyl imines undergo a facile thermal rearrangement to β-alkynylacrylonitriles that is structurally related to the Bergman rearrangement of (Z)-hexenediynes. Despite similarities between the Bergman reaction of hexenediynes and the rearrangement of *C,N*-dialkynylimines to (Z)-β-alkynylacrylonitriles, which lead us to speculate that these two processes are related mechanistically, there is a clear dichotomy between the Bergman rearrangement and the rearrangement of *C,N*-dialkynylimines concerning the nature of the intermediates that are involved.

Supporting Information Available: Experimental details, spectral data for all new compounds reported in the text, and plots of the kinetic data (12 pages). See any current masthead page for ordering and Internet access instructions.

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(16) For imine **1**, only the isomer with (Z)-stereochemistry about the imine double bond would be expected to undergo an aza-Bergman reaction. As the isomeric mixture of imine **1a** (∼2:1 Z/E) undergoes first-order isomerization to nitrile **3a**, there is presumably a rapid equilibration between (E)- and (Z)-imines under the thermolysis reaction conditions. The nature of this E to Z isomerization remains to be elucidated.

(17) Enediynes which undergo a release of strain upon Bergman cyclization react at a much faster rate than simple acyclic enediynes such as **11**. See, for example: Magnus, P.; Fortt, S.; Pitterna, T.; Snyder, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 4986−4987.

(18) Koga, N.; Morokuma, K. *J. Am. Chem. Soc.* **1991**, *113*, 1907−1911.

(19) Semi-empirical calculations using the AM1 Hamiltonian have been used to predict the relative heats of formation for the nitrile **C** (Scheme 1, X = N) and the imine **A** (X = N). These calculations predict that nitrile **C** lies 34 kcal/mol lower in energy than the imine **A**.

(20) Nicolaou and co-workers have reported a potential Bergman rearrangement in which the intermediate 1,4-didehydrobenzene does not undergo intermolecular trapping: Nicolaou, K. C.; Smith, A. L. *Acc. Chem. Res.* **1992**, *25*, 497−503.