A Thermally Induced Hydride Transfer from an Amine to an Allene Triggers an Annulation Reaction giving Dihydrofuropyridinones

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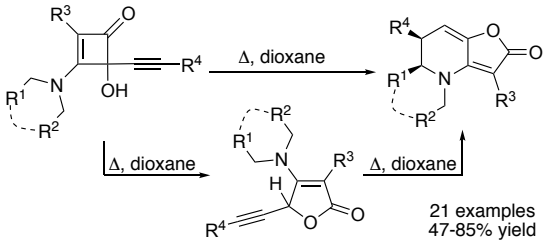
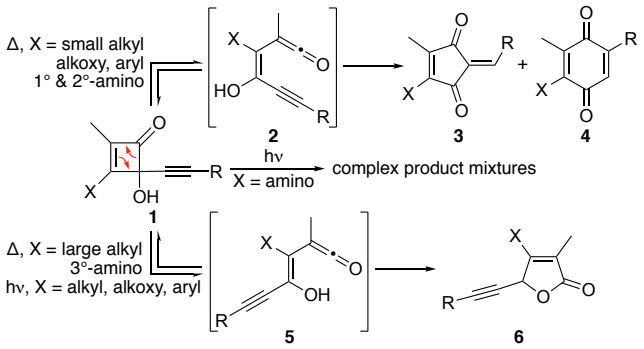
Supporting Information Placeholder



ABSTRACT: A thermal rearrangement leading to dihydrofuropyridinones and related polycyclic ring systems from furanones and cyclobutenones is described. A key feature of the reaction is the thermally induced hydride transfer from a 3°-amine to a conjugated allene to trigger cyclisation.

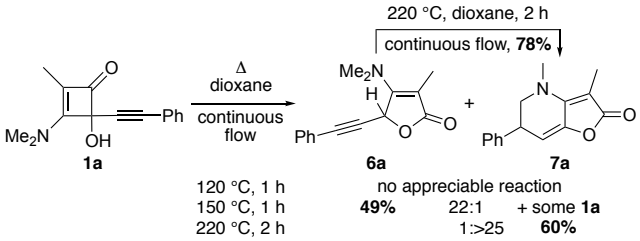
Thermal rearrangements of alkynylcyclobutenones to quinones and cyclopentenediones, *e.g.* **1** → **3** + **4**, have been widely used and studied since their introduction by Moore *et al.* in 1985 (Scheme 1).[1-5] Reactions generally proceed via vinylketene **2** and favor quinone **4** formation.[2-5] They are diverted toward cyclopentenedione **3** when the alkyne carries a radical stabilizing group,[1,4-6] and toward furanone **6** when the cyclobutenone bears large alkyl or 3°-amino residues.[7,8] The formation of furanone **6** is also observed in the photochemical rearrangement of cyclobutenones **1**,[9] with reactions proceeding via the less stable isomeric vinylketene **5**. This switch of reaction course occurs when the collapse of vinylketene **2** to quinone **4** and/or cyclopentenedione **3** is outpaced by its equilibration to vinylketene **5** and near spontaneous collapse to furanone **6**.[7]

Scheme 1. Thermal and photochemical rearrangements of alkynylcyclobutenones



During a study of alkynylcyclobutenone rearrangements leading to furanones,[7] we found the optimization of **1a** → **6a** to be particularly sensitive to changes in reaction time and temperature. Thus, while furanone **6a** was the major product formed on thermolysis of a dioxane solution of **1a** at 150 °C for 1 h under continuous flow, prolonged reaction times and elevated temperatures produced dihydrofuropyridinone **7a** as a significant by-product. Indeed, when the solution was heated at 220 °C for 2 h, **7a** was given in 60% yield (Scheme 2). Similarly, thermolysis of furanone **6a** in dioxane at 220 °C for 2 h gave **7a** in an improved 78% yield.

Scheme 2. Discovery of a new rearrangement pathway



To demonstrate the generality of the method, the same conditions were applied to various 4-amino-5-alkynylfuranones, **6b-h**. Each, on thermolysis at 220 °C in dioxane under flow, gave the corresponding dihydrofuropyridinone **7b-h** in good to excellent yield (Table 1, Figure 1). As expected, analogues with an *N*,*N*-dimethylamino residue (**6b**,**e**) gave rise to a single product, while higher homologues (**6c**,**d**) and those bearing cyclic 3°-amines (**6f-h**) displayed useful diastereoselectivity.[10]

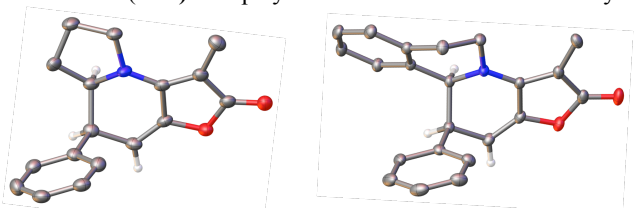
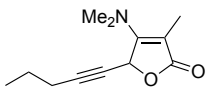
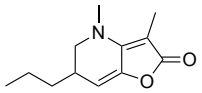
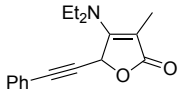
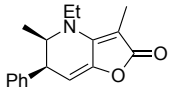
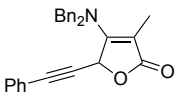
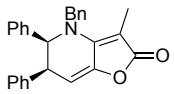
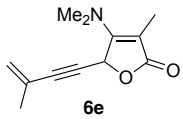
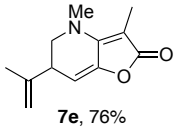
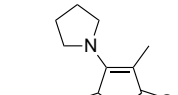
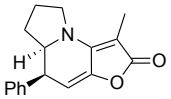
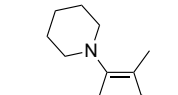
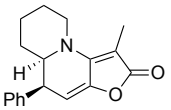
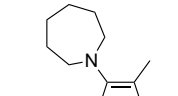
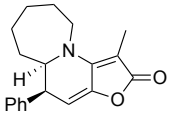


Figure 1. X-ray crystal structures of dihydrofuropyridinones **7f** and **7i**

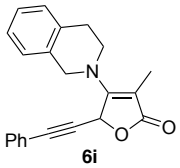
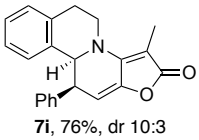
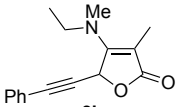
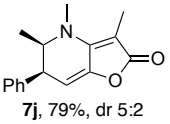
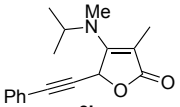
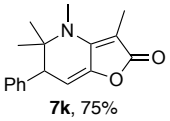
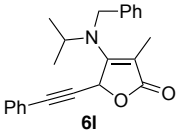
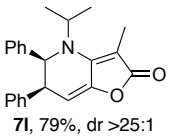
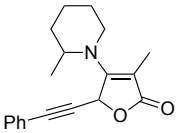
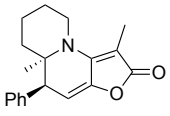
Table 1. Further examples of the rearrangement highlighted in Scheme 1

starting material	product, yield, dr	conditions
 **6b**	 **7b**, 67%	220 °C, 4 h dioxane, continuous flow
 **6c**	 **7c**, 82%, dr 4:1	220 °C, 2 h dioxane, continuous flow
 **6d**	 **7d**, 76%, dr 6:1	220 °C, 1 h dioxane, continuous flow
 **6e**	 **7e**, 76%	220 °C, 2 h dioxane, continuous flow
 **6f**	 **7f**, 85%, dr 25:1	220 °C, 1 h dioxane, continuous flow
 **6g**	 **7g**, 69%, dr 16:1	220 °C, 1 h dioxane, continuous flow
 **6h**	 **7h**, 79%, dr 7:1	220 °C, 1 h dioxane, continuous flow

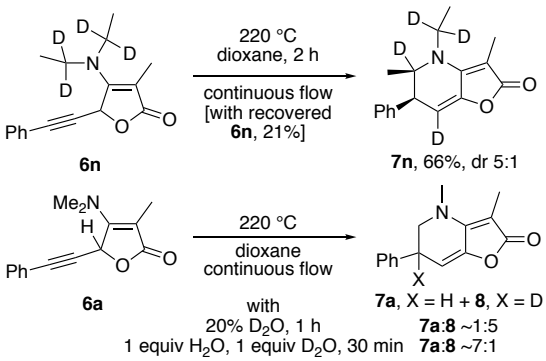
Next, an examination of substrates with differentially substituted 3°-amine residues (**6i-m**) showed that the reaction displayed excellent regioselectivity (Table 2). In each case studied, the newly created ring was formed to the residue bearing the weakest CH bond such that insertion followed the sequence Bn > 3°-alkyl > 2°-alkyl > 1°-alkyl > Me.

To better understand the mechanistic course of the reaction, three isotope labeling experiments were conducted (Scheme 3). In the first, tetradeuterated aminofuranone **6n** (>99% isotopomer) was heated in dioxane at 220 °C for 2 h and gave tetradeuterated dihydrofuropyridinone **7n** in 67% yield (>99% isotopomer). In the second and third, dimethylaminofuranone **6a** was heated for a limited time in dioxane doped respectively with 20% D_2O, and with a 1:1 mixture of H_2O and D_2O. Both experiments gave the mono-deuterated dihydrofuropyridinone **8** and its isotopomer **7a** in ratios of ~1:5 and ~7:1 respectively. The isotope patterns observed in the products provided strong evidence that the reaction involved alkyne to allene isomerisation as the rate determining step,[11] followed by hydride transfer from the amine residue to the newly formed allene (Figure 2).[12]

Table 2. Regioselectivity in respect of the amine substituents

starting material	product, yield, dr	conditions
 **6i**	 **7i**, 76%, dr 10:3	220 °C, 1 h dioxane, continuous flow
 **6j**	 **7j**, 79%, dr 5:2	220 °C, 2 h dioxane, continuous flow
 **6k**	 **7k**, 75%	220 °C, 2 h dioxane, continuous flow
 **6l**	 **7l**, 79%, dr >25:1	220 °C, 1 h dioxane, continuous flow
 **6m**, dr ~ 1 : 1	 **7m**, 79%, dr 15:1	220 °C, 1 h dioxane, continuous flow

Scheme 3. Deuterium labelling studies designed to shed light on the mechanistic course of the rearrangement



DFT calculations were then performed to assess whether our proposed mechanism for the rearrangement was reasonable.[13] They showed that the hydride transfer (**10** → [**11**] → **12**) and ring closure (**12** → [**13**] → **7a**) steps had similar energy requirements,[12] with both being lower than that for the alkyne to allene isomerisation step (**6a** → **10**).[11] Computationally, the latter was found to be prohibitive until water was made available to catalyse proton transfer (Figure 2).[14] Experimentally, reactions conducted in dioxane that had been distilled from sodium or dried over molecular sieves were slowed, but not prevented.[15]

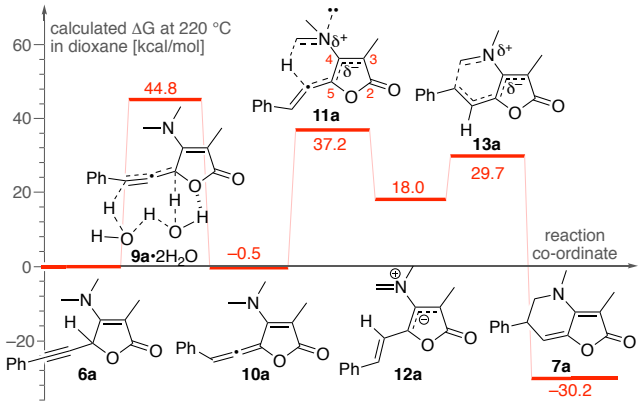
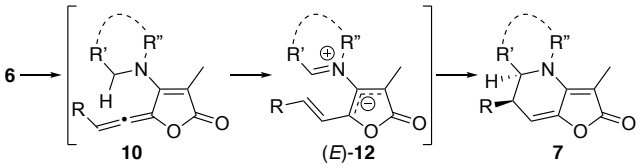


Figure 2. Calculated energy barriers for the rearrangement of 5*H*-furanone **6a** to dihydrofuropyridinone **7a** using M062X/6-311+g(d,p)

Importantly, the mechanism helps to explain the stereochemical course of the rearrangement (Scheme 4) with hydride transfer in allene **10** giving the lowest energy zwitterion, (*E*)-**12**. A disrotatory 6π-electrocyclisation follows, providing dihydrofuropyridinone **7** as the major diastereoisomer.

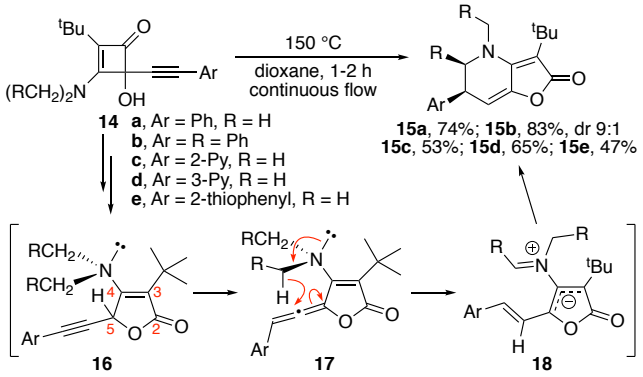
Scheme 4. Explaining the stereochemical course of the rearrangement



Interestingly, the calculated transition state for hydride transfer, **11**, showed significant pyramidalisation of its nitrogen atom (Figure 2 and Supporting Information). Additionally, its 'lone pair' showed minimal interaction with the α,β–unsaturated carbonyl system, as evidenced by a calculated bond order of 1.1 for N-C4. Rather, it was aligned anti to the breaking CH bond. The significance of that conformational preference was evidenced when the rearrangement of *tert*-butylcyclobutenones **14** gave dihydrofuropyridinones **15** directly on thermolysis at 150 °C (Scheme 5). Here, steric bulk at C3 in the furanone intermediates **16** ensures that the C4 amino residue is twisted out of conjugation with the α,β-unsaturated carbonyl. This lessens the vinylogous carbamate character of **16** leading to an acidification at C5 and acceleration of proton transfer to **17**. Pyramidalization of the nitrogen atom in allene **17** then serves to promote reactive conformers that are predisposed to hydride transfer, lowering the energy required to form zwitterion **18**.

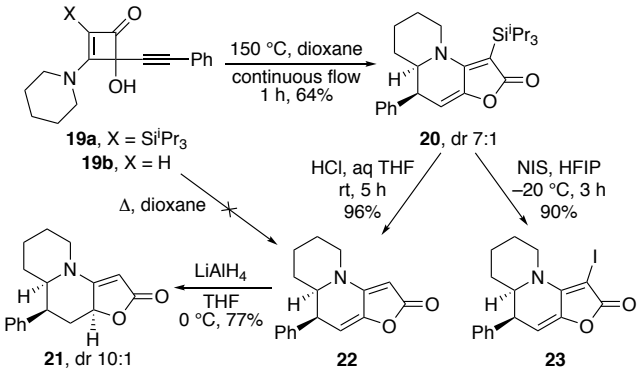
The steric effect was further evidenced in the rearrangements of cyclobutenones (**14c-e**) to dihydrofuropyridinones (**15c-e**) where direct conversion was again observed on thermolysis at 150 °C for 1 h. These experiments additionally showed that the alkyne residue can carry aryl (*e.g.* **6f-n**), heteroaryl (*e.g.* **14c-e**), alkyl (*e.g.* **6b**) and vinyl (*e.g.* **6e**) substituents.[16]

Scheme 5. Sterically induced rate enhancement including an extension to heteroaromatic alkynyl substituents



Extension of the steric effect to triisopropylsilylcyclobutenones additionally gives access to dihydrofuropyridinones bearing a proton or iodide at C3. This is a useful extension, as cyclobutenone **19b** gave rise to a complex product mixture on thermolysis and iodonated cyclobutenones are difficult to prepare and handle. Thus, thermolysis of cyclobutenone **19a** at 150 °C in dioxane gave dihydrofuropyridinone **20** directly in 64% yield (Scheme 6, Figure 3). Its protonation with aq. HCl and its iodination with NIS each proceeded in high yield to give furoquinolizidines **22** and **23** respectively.[17] Interestingly, treatment of **22** with $LiAlH_4$ led to reduction of the enol ether function, producing **21** in good yield and with high diastereoselectivity.[18]

Scheme 6. Using TIPS as a proton and halogen surrogate



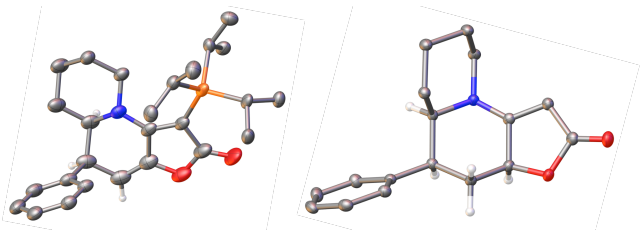


Figure 3. X-ray analysis of **20** and **21**

In summary, 4-amino-5-alkynylfuranones and 3-amino-4-alkynylcyclobutenones undergo a hitherto unknown thermal rearrangement leading to dihydrofuropyridinones. The rearrangement is initiated by an alkyne to allene isomerization, which induces a hydride transfer from the proximal amino-substituent and cyclisation of the resulting zwitterion.

SUPPORTING INFORMATION

Experimental accounts with data, including copies of the NMR spectra and CIF files, are available as Supporting Information. The Supporting Information is available free of charge on the ACS Publications website.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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REFERENCES

(1) Karlsson, J. O.; Nguyen, N. V.; Foland, L. D.; Moore, H. W. *J. Am. Chem. Soc.* **1985**, *107*, 3392.

(2) (a) Perri, S. T.; Foland, L. D.; Decker, O. H. W.; Moore, H. W. *J. Org. Chem.* **1986**, *51*, 3067. (b) Decker, O. H. W.; Moore, H. W. *J. Org. Chem.* **1987**, *52*, 1174. (c) Foland, L. D.; Decker, O. H. W.; Moore, H. W. *J. Am. Chem. Soc.* **1989**, *111*, 989. (d) Perri, S. T.; Dyke, H. J.; Moore, H. W. *J. Org. Chem.* **1989**, *54*, 2032. (e) Karabelas, K.; Moore, H. W. *J. Am. Chem. Soc.* **1990**, *112*, 5372. (f) Perri, S. T.; Moore, H. W. *J. Am. Chem. Soc.* **1990**, *112*, 1897. (g) Enhsen, A.; Karabelas, K.; Heerding, J. M.; Moore, H. W. *J. Org. Chem.* **1990**, *55*, 1177. (h) Heerding J. M.; Moore, H. W. *J. Org. Chem.* **1991**, *56*, 4048. (i) Xu, S.; Yerxa, B. R.; Sullivan, R. W.; Moore, H. W. *Tetrahedron Lett.* **1991**, *40*, 1129. (j) Xia, H.; Moore, H. W. *J. Org. Chem.* **1992**, *57*, 3765. (k) Gayo, L. M.; Winters, M. P.; Moore, H. W. *J. Org. Chem.* **1992**, *57*, 6896. (l) Sullivan, R. W.; Coghlan, V. M.; Munk, S. A.; Moore, H. W.; Reed, M. W. *J. Org. Chem.* **1994**, *59*, 2276. (m) Xiong, Y.; Xia, H.; Moore, H. W. *J. Org. Chem.* **1995**, *60*, 6460. (n) Xiong, Y.; Moore, H. W. *J. Org. Chem.* **1996**, *61*, 9168. (o) Heileman, M. J.; Tiedemann, R.; Moore, H. W. *J. Am. Chem. Soc.* **1998**, *120*, 3801. (p) Tiedemann, R.; Heileman, M. J.; Moore, H. W.; Schaumann, E. *J. Org. Chem.* **1999**, *64*, 2170. (q) Ezcurra, J. E.; Karabelas, K.; Moore, H. W. *Tetrahedron* **2005**, *61*, 275. (r) Chen, P.; Dong, G. *Chem. Eur. J.* **2016**, *22*, 18290.

(3) (a) Liebeskind, L. S.; Foster, B. S. *J. Am. Chem. Soc.* **1990**, *112*, 8612. (b) Liebeskind, L. S.; Zhang, J. *J. Org. Chem.* **1991**, *56*, 6379. (c) Wipf, P.; Hopkins, C. R. *J. Org. Chem.* **1999**, *64*, 6881. (d) Boullais, C.; Rannou, C.; Reveillere, E. Mioskowski, C. *Eur. J. Org. Chem.* **2000**, 723. (e) Knueppel, D.; Martin, S. F. *Angew. Chem. Int. Ed.* **2009**, *48*, 2569. (f) Knueppel, D.; Martin, S. F. *Tetrahedron* **2011**, *70*, 9765. (g) Nichols, A. L.; Zhang, P.; Martin, S. F. *Org. Lett.* **2011**, *13*, 4696. (h) Nichols, A. L.; Zhang, P.; Martin, S. F. *Tetrahedron* **2012**, *68*, 7591. (i) Yan, X.; Hu, X. *J. Org. Chem.* **2014**, *79*, 5282. (j) Yang, J.; Knueppel, D.; Cheng, B.; Mans, D.; Martin, S. F. *Org. Lett.* **2015**, *17*, 114. (k) Knueppel, D.; Yang, J.; Cheng, B.; Mans, D.; Martin, S. F. *Tetrahedron* **2015**, *71*, 5741. (l) Blumberg, S.; Martin, S. F. *Org. Lett.* **2017**, *19*, 790. (m) Hill-Cousins, J. T.; Pop, I.-A.; Pileio, G.; Stevanato, G.; Håkansson, P.; Roy, S. S.; Levitt, M. H.; Brown, L. J.; Brown, R. C. D. *Org. Lett.* **2015**, *17*, 2150.

(4) (a) Zehr, P. S.; Kayali, R.; Pena-Cabrera, E.; Robles-Resendiz, O.; Villanueva-Rendon, A. D.; Soederberg, B. C. G. *Tetrahedron*, **2008**, *64*, 5336; (b) Packard, E.; Pascoe, D. D.; Maddaluno, J.; Goncalves, T. P.; Harrowven, D. C. *Angew. Chem. Int. Ed.* **2013**, *52*, 13076. (c) Yin, H.; Dantale, S. W.; Akhmedov, N. G.; Soederberg, B. C. G. *Tetrahedron*, **2013**, *69*, 9284.

(5) (a) Foland, L. D.; Karlsson, J. O.; Perri, S. T.; Schwabe, R.; Xu, S. L.; Patil, S.; Moore H. W. *J. Am. Chem. Soc.* **1989**, *111,* 975. (b) Gonalves, T. P.; Mohamed, M.; Whitby, R. J.; Sneddon, H. F.; Harrowven, D. C. *Angew. Chem. Int. Ed.* **2015**, *54*, 4531.

(6) (a) Musch, P. W.; Remenyi, C.; Helten, H.; Engels, B. *J. Am. Chem. Soc.* **2002**, *124*, 1823; (b) Niwayama, S.; Kallel, E. A.; Sheu, C. M.; Houk, K. N. *J. Org. Chem.* **1996**, *61*, 2517.

(7) Sun, W.; Wilson, D. C.; Harrowven, D. C. *Synthesis* **2017**, *49*, 3091.

(8) (a) Moore, H. W.; Perri, S. T. *J. Org. Chem.* **1988**, *53*, 996. (b) Birchler, A. G.; Liu, F.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 7737. (c) Yamamoto, Y.; Ohno, M.; Eguchi, S. *Tetrahedron* **1994**, *50*, 7783. (d) Lee K. H.; Moore, H. W. *J. Org. Chem.* **1995**, *60*, 735. (e) Turnbull, P.; Heileman, M. J.; Moore, H. W. *J. Org. Chem.* **1996**, *61*, 2584. (f) Liu, F.; Liebeskind, L. S. *J. Org. Chem.* **1998**, *63*, 2835.

(9) (a) Perri, S. T.; Foland, L. D.; Moore, H. W. *Tetrahedron Lett.* **1988**, *29*, 3529. (b) Yamamoto, Y.; Ohno, M.; Eguchi, S. *Tetrahedron* **1994**, *50*, 7783. (c) Harrowven, D. C.; Mohamed, M.; Gonçalves, T. P.; Whitby, R. J.; Bolien, D.; Sneddon, H. F. *Angew. Chem. Int. Ed.* **2012**, *51*, 4405.

(10) Diastereomer ratios were determined on crude reaction mixtures by HPLC analysis and/or comparison of integrals in the ^{1}H NMR spectra for the alkene CH signals (both at δ_H ~5.6 ppm) and the neighbouring allylic CH (at δ_H ~3.9 ppm for the major isomer and δ_H ~4.2 ppm for the minor isomer).

(11) Hashmi, A. S. K. Synthesis of Allenes by Isomerization Reactions. In *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH Verlag GmbH, Weinheim, 2008; pp 2-50.

(12) (a) Suschitzky, H.; Meth-Cohn, O. *Adv. Heterocycl. Chem.* **1972**, *14*, 211. (b) Meth-Cohn, O.; Taylor, D. L. *Chem. Commun.* **1995**, 1463. (c) Meth-Cohn, O. *Adv. Heterocycl. Chem.* **1996**, *65*, 1. (d) O'Leary, J.; Formosa, X.; Skranc, W.; Wallis, J. D. *Org. Biomol. Chem.* **2005**, *3*, 3273. (e) Zhang, C.; Murarka, S.; Seidel, D. *J. Org. Chem.* **2009**, *74*, 419. (f) Murarka, S.; Zhang, C.; Seidel, D. *Org. Lett.* **2009**, *11*, 129. (g) Földi, A. A.; Ludányi, K.; Bényei, A. C.; Mátyus, P. *Synlett.* **2010**, 2109. (h) Pozharskii, A. F.; Povalyakhina, M. A.; Degtyarev, A. V.; Ryabtsova, O. V.; Ozeryanskii, V. A.; Dyablo, O. V.; Tkachuk, A. V.; Kazheva, O. N.; Chekhlov, A. N.; Dyachenko, O. A. *Org. Biomol. Chem.* **2011**, *9*, 1887.

(13) (a) Niwayama, S.; Kallel, E. A.; Sheu, C. M.; Houk, K. N. *J. Org. Chem.* **1996**, *61*, 2517. (b) Musch, P. W.; Remenyi, C.; Helten, H.; Engels, B. *J. Am. Chem. Soc.* **2002**, *124*, 1823. (c) Mohamed, M.; Gonçalves, T. P.; Whitby, R. J.; Sneddon, H. F.; Harrowven, D. C. *Chem. Eur. J.* **2011**, *17*, 13698.

(14) (a) Takahashi, O.; Kobayashi, K.; Oda, A. *Chem. Biodivers.* **2010**, *7*, 1349. (b) Tadic, J. M.; Xu, L. *J. Org. Chem.* **2012**, *77*, 8621.

(15) When the thermolysis of **6a** was repeated using dioxane dried over molecular sieves, it gave dihydrofuropyridinone **7a** in 38% yield together with recovered starting material (28%). A similar outcome was seen when dioxane distilled from sodium was used. Computationally, we have yet to identify another pathway with a similar energy requirement.

(16) We additionally sought to demonstrate the reaction with a terminally unsubstituted alkyne, (*e.g.* **14f**, Ar = R = H), but found its thermolysis in dioxane at 150 °C for 1 h gave a complex product mixture.

(17) Usanov, D. L.; Yamamoto, H. *Org. Lett.* **2012**, *14*, 414.

(18) Smith, J. G.; Wikman, R.T. *Tetrahedron*, **1974**, *30*, 2603.