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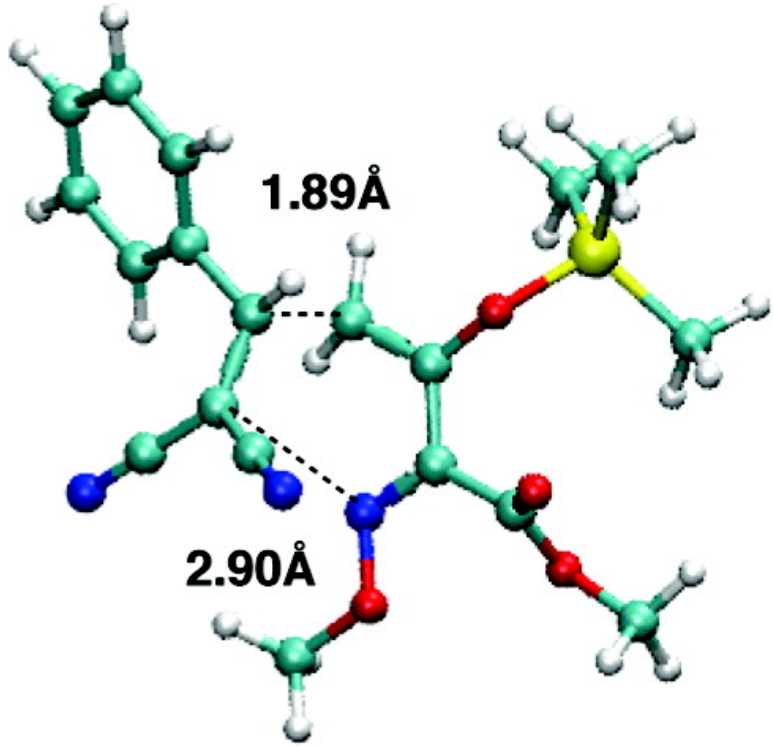

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Regioselective De Novo Synthesis of Cyanohydroxypyridines with a Concerted Cycloaddition Mechanism

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The broad activity profile of pyridines and their derivatives fuels constant progress in the development of pyridine syntheses.[1,2] For focused compound collections in drug discovery, target oriented synthesis, and the development of new materials, novel and selective de novo syntheses[3] are in demand which facilitate versatile access to pyridine scaffolds. Hetero-Diels−Alder (HDA) reactions of azadienes open useful routes to six-membered ring aza-heterocycles in this regard.[4,5] It was recently shown that 3-hydroxypyridines can be conveniently synthesized from alkynes and suitably functionalized 1-aza-dienes.[6,7] Aryl or electron withdrawing groups (EWG) were found preferable substituents, but variable regioselectivity was observed.[7]

To expand the scope of 1-azadiene cycloadditions, we explored alkenes that regenerate double-bonds by 1,2-elimination as alkyne surrogates (Scheme 1).[8] Initially the easily available[7] azadiene **1a** was investigated in thermal cycloadditions with alkenes **2**−**5** and **6a**.[9] Interestingly, the alkenes **2**−**5** remained unproductive, but a clean transformation to the pyridine **10a** (R = Ph) occurred for *bis*-cyano alkene **6a** without apparent formation of the intermediary *bis*-nitrile **7** or dihydropyridines (e.g., **8**).[10] This suggested rapid elimination of HCN and TMSOH by putative 1,4- and 1,2-elimination processes[10b] followed by loss of the phenolic TMS during workup (**9** → **10**).[7] Our initial analysis indicated the presence of a single regioisomer only.

The importance of the activating substituent on the nitrogen atom for cycloaddition efficiency was then studied using different *Z*-configured[11] azadienes **1** (Table 1). Screening reactions with **1a**−**h** were conducted at 150 °C without solvent.[7] It was found, that O-alkylated oximes were superior to O-silyl groups, with OMe giving best results (**1d**). The hydrazone derivative[4] **1b** did not lead to appreciable formation of pyridine products. The importance of steric factors was evident as an increase in substituent size (**1d** vs **1f**, **1d** vs **1e**) always attenuated reactivity. EWGs on the oxygen atom compromised the productivity of the dienes (**1g**, **1h**), probably as a result of thermal instability.

Diverse α,α-dicyanoalkenes **6a**−**h** were then accessed by base-mediated condensation of malono dinitrile with the respective aldehydes.[9] In the cycloadditions a broad spectrum of aromatic substituents were nicely tolerated (Table 2, entry **10a**−**d**), but also heterocyclic and alkyl groups reacted productively (**10e**−**h**). Interestingly, the alkynyl−phenyl-substituted dicyanoalkene **10i** gave only the alkene cycloaddition product, leaving the alkyne function untouched.[10b] The 6-cyano isomer was obtained exclusively (>98:2) in all cases, as shown by 2D-NMR and X-ray crystallography (Supporting Information). Evidence for the 5-cyano regioisomer was not found, neither in the crude mixtures (GC−MS, HPLC−MS) nor after purification.

Scheme 1. HDA Addition Screening with Alkyne Surrogates **2**−**6**

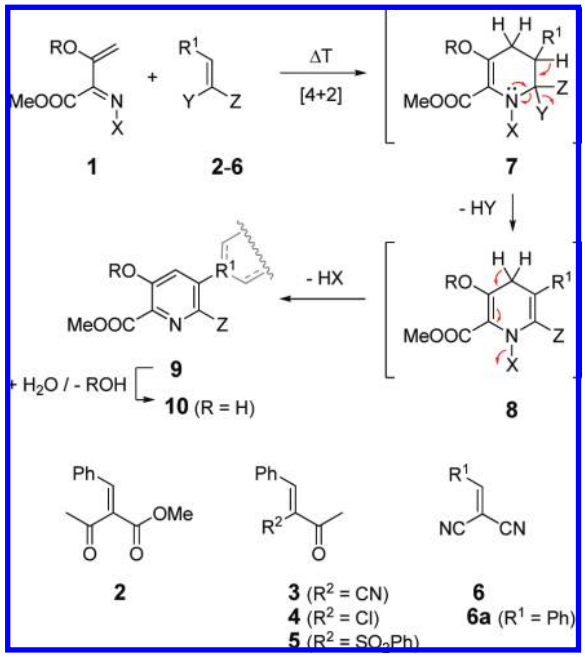

Table 1. Variations of 1-*aza*-Diene **1**

1-*aza*-diene	X	R	yield[a] of **10**
1a	OTMS	TMS	40%
1b	NMePh	TES	<5%
1c	OTES	TES	20%
1d	OMe	TMS	60%
1e	OMe	TES	30%
1f	OMOM	TMS	20%
1g	OAc	TES	4%
1h	OMs	TMS	2%

[a] Reactions run at 150 °C for 12 h; (**1c**) 120 °C, 60 h; (**1f**) 150 °C, 7 h.

A chemical microwave reactor allowed improving the transformation efficiency.[6b,7,12] Conversions were cleanest in DMF solvent and completed in 30−60 min at 130 °C core temperature, but considerable decomposition of diene **1d** was observed above 130 °C. In this way, high yields could be achieved (Table 2). Electron-poor aromatics (**6b**, **6c**, **6i**, 90−97%) transformed very well, and electron-rich aromatics (**6a**, **6d**, **6e**, 81−96%) performed almost equally well. The heterocycle- and the alkyl-substituted samples had a wider range in performance (**6e**−**g**, 66−87%), whereas an alkyl substituent showed reduced reactivity (**6h**, 60%).

Notably, alkenyl-alkyne **6i** delivered the 3-hydroxypyridine **10i** in excellent yield with very high chemoselectivity for the dicyanoalkene

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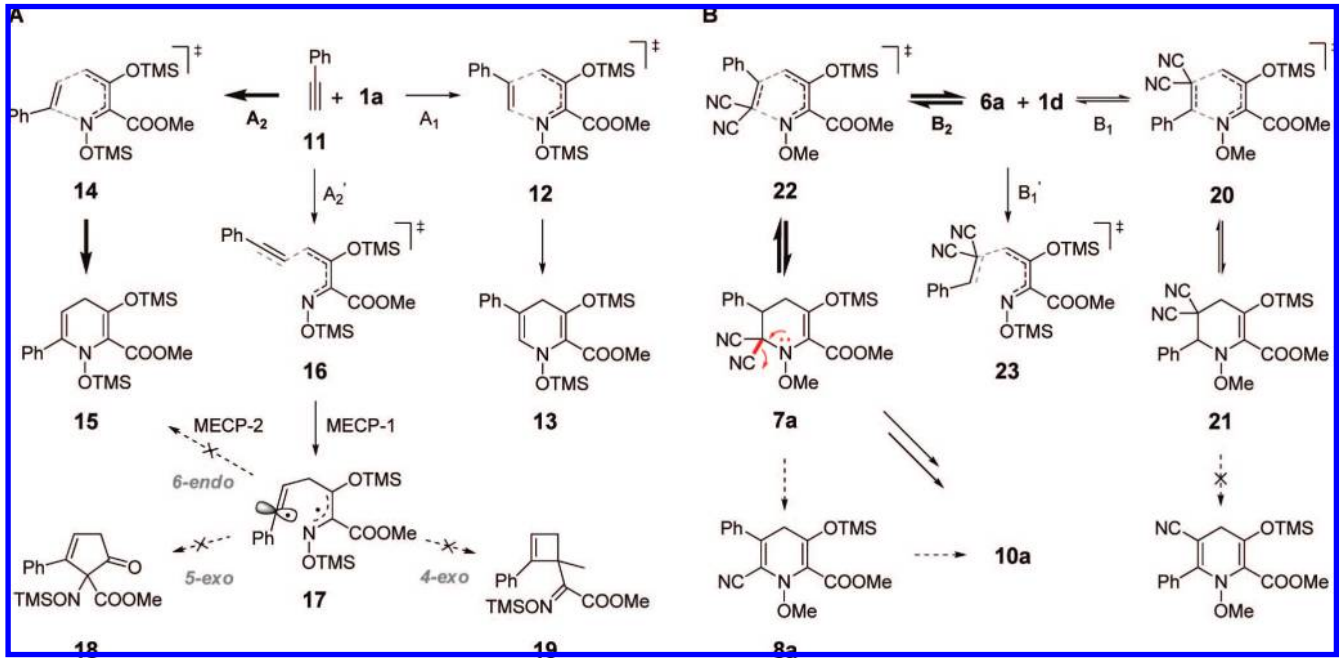

Figure 1. Reaction pathways as identified by DFT calculations, (A) for alkyne **11**, (B) for dicyanoalkene **6a**.

Table 2. Hydroxypyridines from Dicyanoalkenes **6a**−**i**

alkene	R^1	pyridine	method A[a]	B[a]
6a		**10a**	60% (12h)	96%
6b	CF_3	**10b**	75% (7h)	95%[b]
6c	CN	**10c**	74% (12h)	97%[b]
6d	OMe	**10d**	39% (24h)	81%
6e		**10e**	55% (5h)	87%
6f		**10f**	71% (5h)	72%
6g		**10g**	34% (5h)	66%[b]
6h		**10h**	47% (10h)	60%
6i		**10i**	59% (7h)	90%

[a] Isolated yields of **10**. All reactions were run either with 3 equiv of **1d** at 150 °C without solvent for the time indicated (method A) or in a microwave reactor at 130 °C for 60 min (method B) in DMF as solvent (0.7−0.9 M alkene). [b] Reaction run for 30 min.

function, even when an excess of 1-azadiene **1d** was employed (3 equiv). Nearly stoichiometric amounts of azadiene (1−1.5 equiv) still gave reasonable yields (−20%), underscoring the practical utility of this novel 3-hydroxypyridine synthesis.

The remarkable selectivity of the cycloadditions with the *bis*-nitriles **6** compared to alkynes[7] prompted us to investigate the mechanism of this transformation from first principle quantum mechanics. Earlier

Table 3. Overall Energetics ($\triangle E$, kcal/mol) for Reactions **A** and **B**

	path A_1(→**13**)		path A_2(→**15**)	
compound	vacuum	solvated	vacuum	solvated
1a + **11**	0	0	0	0
12/14	32.5	35.2	26.9	30.4
16	not identified		23.0	25.3
MECP-1	not calculated		23.5	26.6
17 (singlet)	29.7	32.8	15.8	18.1
17 (triplet)	29.7	32.8	17.2	19.5
MECP-2	not calculated		38.0	39.3
13/15	−36.3	−33.3	−34.5	−31.5

	path B_1(→**21**)		path B_2(→**7a**)	
compound	vacuum	solvated	vacuum	solvated
1d + **6a**	0	0	0	0
stepwise TS	41.8	44.5	relaxed to **22**	
concerted TS (**20/22**)	32.1	33.9	23.9	21.7
21/7a	−2.7	1.0	−3.3	−1.2

computational work in the field concentrated on *E*-1-aza-1,3-butadiene and ethylene as a dienophile in the gas-phase,[13] and on "inverse-electron-demand"-type cycloadditions of electron-poor 1-azadienes to vinyl ethers[14] or enamines.[15] We evaluated the "normal-electron-demand" type reactions of **1a** with phenylacetylene **11**[7] (Figure 1, reaction **A**) and of **1d** with **6a** (reaction **B**) with density functional theory (DFT).[16]

Concerted/asynchronous, singlet and triplet stepwise radicaloid,[17] and stepwise polar mechanisms were considered for the cycloadditions (Figure 1, Table 3). An advanced method was used to determine minimum energy crossing points (MECPs) between singlet and triplet states. This method uses a hybrid gradient of singlet and triplet states to pinpoint the transition state (TS) intersection of the respective surfaces.[18] This algorithm was run in tandem with DFT and provided more dynamical correlation than CAS wave function methods. Furthermore, it reported the identities of multideterminental species that would otherwise not be obtained by standard DFT techniques.[18]

For reaction **A**, a concerted pathway through TS **12** leads to **13**. Step-wise processes leading to **13** were not identified. For reactions

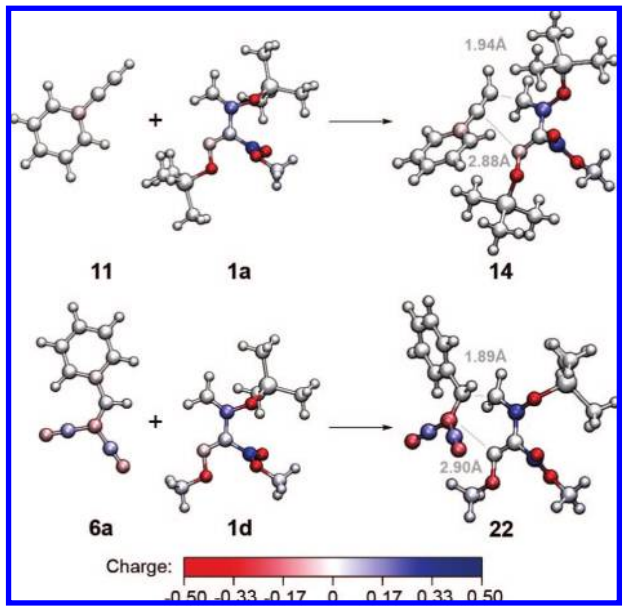

Figure 2. Structures of reactants and transition states **14** and **22** with annotated distances and NBO charges (red, −0.50 → blue, +0.50).

leading to **15**, the stepwise process for C−C bond formation (**16**) was lower than the concerted barrier (**14**). The MECP linking the closed-shell singlet surface to the open-shell singlet surface (**MECP-1**) was essentially isoenergetic to TS **16**. Diradical intermediates **17** were found metastable, but the MECP linking the open-shell surface of **17** to the closed shell-surface of **15** (**MECP-2**) was prohibitively high in energy (Table 3).

We investigated pathways leading to five- and four-membered rings (**18**, **19**); however, preliminary results on nonfully optimized structures suggest that these processes are prohibitive. Thus, **12** (+35.2 kcal/mol) and **14** (+30.4 kcal/mol) are deemed the most likely processes to reach products **13** and **15**, respectively. Considering the inherent uncertainty of barrier heights and the omission of thermal corrections (≈5 kcal/mol), our results agree well with the observed moderate selectivity for **A**.[7]

For reaction **B** (**1d** + **6a**), concerted **20** (+33.9 kcal/mol) and concerted-asynchronous **22** (+21.7 kcal/mol) were the lowest energy pathways. TS calculations leading to the corresponding diradicals either relaxed into Diels−Alder type TS **22** or were ≈10 kcal/mol higher (**23**) than concerted process barriers. In contrast to the study on reaction **A**, the activation barriers **20** and **22** were distinctly different ($\Delta\Delta E^{\ddagger}$ ≈ 10 kcal/mol), fully consistent with the experiment. On the other hand the net energy gain along the reaction coordinate was found to be small (0 to −3 kcal/mol). Microscopic reversibility thus suggests that the initial cycloadducts **21** and **7a** should be in equilibrium with the starting materials. In a scenario where CN-elimination precedes aromatization, **7a** is hence expected to easily convert to **8a** and drive the equilibrium assisted by the adjacent α-N lone pair (Figure 1B). This agrees well with the observed regiospecificity.

Computational evidence for stepwise polar mechanisms was never secured for reactions **A** and **B**, in line with the neutral reaction conditions and negligible solvent effects.[7] In fact we note that solvation does not appear to play much of a role since vacuum energies lead to the same conclusions (Table 3). When comparing the preferred TSs, both **14** and **22** are clearly asynchronous with substantially longer C−N than C−C distances (Figure 2). Mulliken charges and natural bond order (NBO) analysis of **22** both show matching azadiene and dienophile polarity. Although the forward barriers out of **20** were found prohibitive, a partial opening of the diradical pathway would agree with the beneficial effect of aryl substitutents.[7] Stronger preference for the concerted mechanisms can be expected for more electron-withdrawing substituents on the alkyne.

In summary we have shown that highly functionalized 3-hydroxypyridines can be directly obtained from α,α-dicyanoalkenes **6** with excellent yield, chemoselectivity, and complete regiocontrol. DFT calculations clearly report concerted Diels−Alder-type mechanisms being operative for alkynes and dicyanoalkenes **6** in this novel 1-azadiene cycloaddition. These findings are expected to facilitate the exploration of 3-hydroxypyridines in materials, synthesis, and medicinal chemistry.

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Supporting Information Available: Experimental procedures, characterization data, X-ray structure determination of a derivative of compound **10b**, computational methodology, and computed energies and coordinates for all reactant and TS structures. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Recent examples: (a) Dediu, O. G.; Yehia, N. A. M.; Oeser, T.; Polborn, K.; Müller, T. J. J. *Eur. J. Org. Chem.* **2005**, 1834. (b) Craig, D.; Henry, G. D. *Tetrahedron Lett.* **2005**, *46*, 2559. (c) McCormick, M. M.; Duong, H. A.; Zuo, G.; Louie, J. *J. Am. Chem. Soc.* **2005**, *127*, 5030. (d) Senaiar, R. S.; Young, D. D.; Deiters, A. *Chem. Commun.* **2006**, 1313. (e) Movassaghi, M.; Hill, M. D.; Ahmad, O. K. *J. Am. Chem. Soc.* **2007**, *129*, 10096. (f) Dash, J.; Lechel, T.; Reissig, H.-U. *Org. Lett.* **2007**, *9*, 5541.
(2) (a) Jones, G. In Comprehensive Heterocyclic Chemistry II; Mc Killop, A. Ed.; Pergamon: Oxford, U.K., 1996, Vol. 5, pp 167. (b)Spitzner, D. In Science of Synthesis; Thieme: Stuttgart, Germany, 2004; p 11.
(3) Henry, G. D. *Tetrahedron* **2004**, *60*, 6043.
(4) (a) Serckx-Poncin, B.; Hesbain-Frisque, A. M.; Ghosez, L. *Tetrahedron Lett.* **1982**, *23*, 3261. (b) Pautet, F.; Nebois, P.; Bouaziz, Z.; Filion, H. *Heterocycles* **2001**, *54*, 1095.
(5) Reviews: (a) Tietze, L. F.; Kettschau, G. *Top. Curr. Chem.* **1997**, *189*, 1. (b) Behforouz, M.; Ahmadian, M. *Tetrahedron* **2000**, *56*, 5259. (c) Jayakumar, S.; Ishar, M. P. S.; Mahajan, M. P. *Tetrahedron* **2002**, *58*, 379.
(6) (a) Igarashi, J.-e.; Kawakami, Y.; Kinoshita, T.; Furukawa, S. *Chem. Pharm. Bull.* **1990**, *38*, 1832. (b) Fletcher, M. D.; Hurst, T. E.; Miles, T. J.; Moody, C. J. *Tetrahedron* **2006**, *62*, 5454.
(7) Lu, J.-Y.; Arndt, H.-D. *J. Org. Chem.* **2007**, *72*, 4205.
(8) de Lucchi, O.; Modena, G. *Tetrahedron* **1984**, *40*, 2585.
(9) Zhang, B.; Zhu, X.-Q.; Lu, J.-Y.; He, J.; Wang, P. G.; Cheng, J.-P. *J. Org. Chem.* **2003**, *68*, 3295.
(10) (a) Sain, B.; Sandhu, J. S. *J. Org. Chem.* **1990**, *55*, 2545. (b) Hopf, H.; Kreutzer, M. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 393. (c) Tietze, L. F.; Henrich, M.; Niklaus, A.; Buback, M. *Chem.—Eur. J.* **1999**, *5*, 297.
(11) Lu, J.-Y.; Shen, W.-Z.; Preut, H.; Arndt, H.-D. *Acta Cryst., E* **2008**, *64*, o602.
(12) Review: Kappe, O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250.
(13) (a) Trân Huu Dâu, M. E.; Flament, J.-P.; Lefour, J.-M.; Riche, C.; Grierson, D. S. *Tetrahedron Lett.* **1992**, *33*, 2343. (b) Bachrach, S. M.; Liu, M. *J. Org. Chem.* **1992**, *57*, 6736. (c) Tietze, L. F.; Fennen, J.; Geißler, H.; Schulz, G.; Anders, E. *Liebigs Ann.* **1995**, 1681. (d) Park, Y. S.; Lee, B.-S.; Lee, I. *New. J. Chem.* **1999**, *23*, 707.
(14) Boger, D. L.; Corbett, W. L.; Curran, T. T.; Kaspar, A. M. *J. Am. Chem. Soc.* **1991**, *113*, 1713.
(15) Domingo, L. R. *Tetrahedron* **2002**, *58*, 3765.
(16) Calculations utilized unrestricted and restricted DFT (B3LYP hybrid functional. *Jaguar,* version 7.0; Schrödinger LLC: New York, 2007). Initial geometry and vibrational frequencies were computed with mixed 6−31G**/midi! basis sets to confirm intermediates. Geometries were then optimized with the full 6−31G** basis set. Single point energies on these geometries were calculated with the 6−311G**+ basis set. DMF solvent was treated implicitly by Jaguar's Poisson-Boltzmann continuum solver ($\epsilon = 36.7$ and $r = 2.49$ Å) with the 6−311G** basis set. Colored graphics were created with VMD, see: Humphrey, W.; Dalke, A.; Schulten, K. *J. Mol. Graphics* **1996**, *14*, 33.
(17) For a discussion and historical perspective on cycloaddition mechanisms see: Houk, K. N.; Gonzáles, J.; Li, Y. *Acc. Chem. Res.* **1995**, *28*, 81.
(18) Harvey, J. N.; Aschi, M.; Schwarz, H.; Koch, W. *Theor. Chem. Acc.* **1998**, *99*, 95.

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