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Demonstrating the Synergy of Synthetic, Mechanistic, and Computational Studies in a Regioselective Aniline Synthesis

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Tri- and tetrasubstituted anilines are formed in good to excellent yields by the addition of ketones to vinamidinium salts (up to 98%). The reaction proceeds via the formation of dienone intermediates, which react to form an enamine with the liberated amine. In the case of a nitro, or dimethylaminomethylene substituent, the enamines undergo a facile electrocyclic ring closure to form a cyclohexadiene, which goes on to form anilines with a high degree of selectivity (up to 50:1) with a minor competing pathway proceeding via the enol providing phenols. Competition experiments using isotopic substitution reveal that the rate determining step en route to dienone is enol/enolate addition to the vinamidinium salt, which is characterized by an inverse secondary isotope effect ($k_{H/D}$ 0.7−0.9). Computational studies have been used to provide a framework for understanding the reaction pathway. The original proposal for a [1,5]-H shift was ruled out on the basis of the calculations, which did not locate a thermally accessible transition state. The minimum energy conformation of the enamine is such that a facile electrocyclic ring closure is ensured, which is corroborated by the experimental studies. A framework for understanding the reaction pathway is presented.

Introduction

The practice of synthetic organic chemistry is constantly evolving as new methodologies are crafted to tackle contemporary problems that present unique challenges for chemical synthesis. Catalytic transition-metal cross-coupling technologies are now well-established and allow for the rapid construction of complex molecules. Recently, the advent of powerful new ligand/catalyst systems for carbon−carbon and carbon−heteroatom bond formation has significantly increased the utility of these coupling methodologies[1] and has significantly broadened the scope of compounds that can be prepared that have established value in medicinal chemistry. The extension of cross-coupling partners by Denmark and MacMillan to include silicon[2] and nitrogen[3] derivatives, respectively, has further enhanced the synthetic utility of cross-coupling strategies. In the discovery phase of a pharmaceutical program these methods enable the synthesis of a large range of compounds in a serial, parallel, or even combinatorial fashion from common precursors. They allow for the display of a wide range of functionality possessing interesting steric and electronic architectures to probe and ultimately optimize for the desired pharmacological properties.

The selective Cox-2 inhibitor *etoricoxib* (Arcoxia) **1** was discovered in an extremely successful medicinal chemistry program that relied heavily on state of the art cross-coupling reactions.[4] Inevitably the synthesis of the trisubstitued pyridine such as *etoricoxib* using a conventional cross-coupling reaction requires a trisubstituted precursor as a reaction partner. Hence the level of complexity of the starting material is similar to that of the product, which is clearly unattractive with respect to atom economy and synthetic efficiency.[5] Reactions that lead to an increase in molecular complexity are important synthetic tools. Attractive alternatives to substitutive

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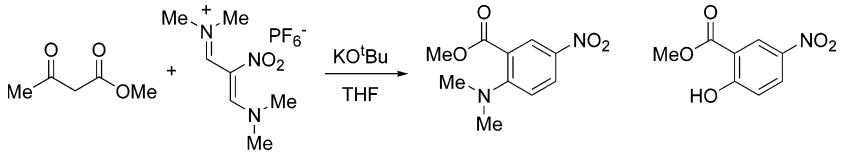
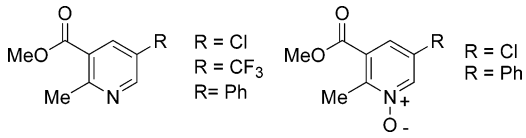
SCHEME 1

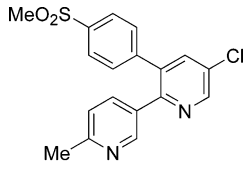


2 **3** **4** **5**

CHART 1



cross-coupling reactions that increase molecular complexity include C−H activation using transition metals, e.g., Ru,[6] Rh,[7] Ir,[8] and are currently attracting substantial efforts. These methods will undoubtedly mature to provide useful mainstream methodologies and may allow for the identification of new strategies for diversity synthesis.[9] However there is still a significant opportunity to establish new "classical" approaches involving multicomponent coupling reactions that construct aromatic and heteroaromatic compounds.

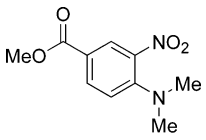


1 *etoricoxib*

We previously described how vinamidinium salts may be exploited as important synthetic intermediates in the synthesis of bipyridines such as *etoricoxib*. A variety of other di- and trisubstitued pyridines (Chart 1)[10] with substituents including trifluoromethyl, aryl, protio, and nitro groups have also been prepared by extension of this methodology to substituted and unsubstituted vinamidinium salts and aldehyde, ketone,[11] ester, or acid enolates.[12] Pyridine *N*-oxides are also readily accessible by using hydroxylamine as the third component in place of ammonia.[13] Gupton has also used vinamidinium salts very effectively for the synthesis of pyrroles,[14] pyrimidines,[15] and pyrazoles.[16]

With access to a wide range of vinamidinium salts in our laboratories, we have continued to explore their synthetic utility.[17,18] While examining the addition of methylacetoacetate **2** (MAA) to a β-nitrovinamidinium salt **3**, we discovered a novel reaction manifold where formation of aniline **4** and phenol **5** was observed rather than the expected pyridine in the presence or absence of ammonia (Scheme 1).

In a preliminary account of this work, we reported the formation of the regioisomeric aniline **6**, and the reaction



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was rationalized as proceeding through a facile [1,5]-hydrogen or hydride shift.[19] A combination of experimental studies using isotopically labeled substrates and DFT calculations were to further characterize the reaction pathway. The isotope studies provided kinetic isotope effects and product isotope effects that were difficult to understand within the context of a [1,5]-hydrogen shift. This would be a unique case and would require a hydrogen migration to be insensitive to isotopic substitution. An extensive series of calculations did not locate a thermally accessible transition state of <50 kcal/mol. On the basis of the compelling mechanistic and theoretical studies, the assignment of structure was revisited.[20] The regioisomeric aniline product **4** was demonstrated to be the unambiguous product in the reaction by authentic synthesis, NOE studies, and X-ray crystallographic analysis of an analogue. In this paper we provide full details of the synthetic, mechanistic and computational aspects of our program. We develop a conceptual framework for understanding the mechanistic features of the conversion

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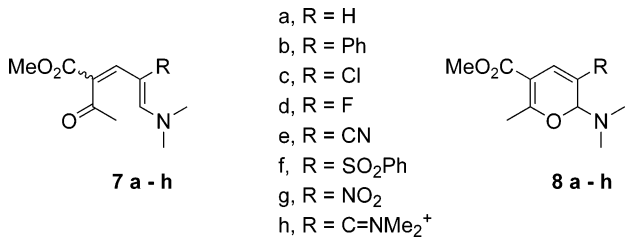
of ketones to substituted aromatic compounds in a highly convergent fashion.

Results and Discussion

Reaction of enolates and vinamidinium salts leads to the formation of dienones **7a**−**h**.[21] These dienones are merocyanines based on resonance theory[22] and are typically formed as a ∼3:1 mixture of 3-*E*:*Z* isomers.[23] They possess interesting solvato-, thermo-, and photochromic properties due to the potential of valence isomerization to 2*H*-pyrans **8a**−**h**.[24]



Using MAA as a prototypical stabilized enolate we have prepared a range of pyridines and pyridine *N*-oxides, including 5-chloro, 5-aryl, and 5-trifluoromethyl substitution, which arise via the intermediacy of the dienone **7a**−**h**. During our studies to further expand the scope of this methodology we investigated the reaction of MAA and the nitrovinamidinium salt **3**[25] at 45 °C in THF. To our surprise, none of the expected pyridine was observed, and two aromatic compounds, aniline **4**[26] and phenol **5**,[27] were isolated in 65% and 10% yield, respectively, prior to the addition of ammonia (∼4:1 in the crude reaction mixture). The identity of the aniline **4** was confirmed by comparison with an authentic sample prepared from dimethylamine and 2-chloro-5-nitro-benzoate[28] and was further supported by X-ray crystallographic analysis of analogue **21d**. The observation of phenol **5** was precedented since β-fluorovinamidinium tetrafluoroborate salts reacts with 3-oxo-pentanedionate to give the 5-fluoro-2-hydroxyisophthalate in 31% yield.[29]

After trivial optimization of the reaction temperature, the selectivity could be increased to 7:1 at 20 °C and 9:1 at 0 °C. The reaction does not proceed in the absence of base but does proceed with reduced rate using catalytic quantities of *tert*-butoxide (10 mol %). The leveling pK_a due to the generation of phenol **5** in the reaction mixture is 6.1.[30] Because the reaction may be performed using catalytic amounts of potassium *tert*-butoxide, the reaction should therefore proceed with a much weaker base as long as the pK_a of the conjugate acid is ∼6. In fact potassium phenoxide works effectively in THF to give aniline **4** in 80% assay yield (1 equiv, 6:1 selectivity, 20 °C, 12 h). The reaction is also promoted by sodium acetate albeit at a much lower rate (6:1 selectivity, 48 h, 65% assay). Phenol or acetic acid do not catalyze the reaction. Reaction of nitrovinamidinium **3** in acetonitrile (ϵ 35.9) at −10 °C led to a 39:1 mixture of aniline **4** (81% assay) and phenol **5** vs 9.5:1 selectivity in THF (ϵ 7.58), indicating the reaction is sensitive to solvent polarity.

TABLE 1. pK_a Values

entry	R-CH_3	pK_a[a]
1	**9a**, R = H	56
2	**9b**, R = Ph	43
3	**9c**, R = Cl	41
4	**9d**, R = F	41
5	**9e**, R = CN	31
6	**9f**, R = SO_2Ph	29
7	**9g**, R = NO_2	17.2 (11)[b]
8	**9h**, R = C=NMe_2^+	(11)[b]

[a] In DMSO [b] In methanol/water

We verified that the protio-,[31] phenyl-,[32] chloro-,[33] fluoro-,[34] and dienones **7a**−**d** did not undergo cyclization in refluxing THF. The cyano-substituted dienone **7e** is also reported to be stable,[35] and we reasoned that the unexpected reactivity of nitro-substituted dienone **7g** was due to the ability of the nitro group to stabilize a developing negative charge in the transition state in the formation of a cyclohexadiene intermediate. A simple measure of this charge-stabilizing ability is available from the pK_a value of the corresponding methyl derivatives **9a**−**h** (Table 1). However, the reaction may be more accurately viewed as a *disrotatory* electrocyclization[36] (the orbital interactions that favor Michael-type addition also enhance electrocyclization), which would also be promoted by electron-withdrawing groups in the 6π-transition state.[37]

If the cyclization event is driven by charge stabilization in a transition state, the sulfonyl dienone **7f**, derived from the β-sulfonyl vinamidinium salt **10** (previously described by Gupton[38]), should be more reactive than the nitrile. In the event, reaction of **10** in THF at 20 °C (12

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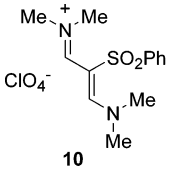
h) led to isolation of phenol **11** in 7% yield with the remainder of the mass balance accounted for by starting vinamidinium and dieneone. Performing the reaction in THF at reflux led to the formation of the phenol **11** in 69% isolated yield together with aniline **12** in 3% yield. The use of DMAP (0.4 equiv) in acetonitrile at 75 °C gave a 5:1 mixture **11**/**12**.[39]



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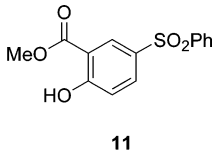

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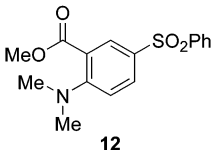

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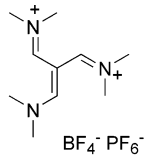
Substitution by a dimethylaminomethylene group at the γ-position should further increase the reactivity of the dienone since the pK_a of the corresponding methano-derivative is 11.[40] We have prepared the mixed tetrafluoroborate/hexafluorophosphate salt **13**,[41] which had excellent solubility in organic solvents (>15 wt % in acetonitrile).[42]

Reaction of **13** with MAA at 20 °C in acetonitrile led to an extremely facile reaction and gave an 8:1 mixture of the aniline **14** and phenol **15**[43] after 4 h. The formyl aniline **14** was isolated as a yellow oil in 56% yield following chromatography on silica gel. The reaction was complicated by overaddition of MAA to give crotonate **16** as a 1.5:1 mixture of (*Z*:*E*) olefin isomers in up to 6% yield. Performing the reaction at −10 °C using the vinamidinium salt in slight excess (1.25 equiv) increased the aniline/phenol **14/15** selectivity to 11:1 and reduced the crotonate **16** to <4%. Under these reaction conditions, the assay yield of aniline **14** was 68% (65% isolated), and when a large excess of the vinamidinium salt was used, the yield increased to 71% with the crotonate observed at 1%. DMAP (0.4 equiv) was also quite effective in place of potassium *tert*-butoxide and gave a 73% assay yield of aniline **14** (11:1 selectivity, 20 h, −10 °C) with the crotonate at <0.5%.



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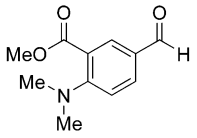

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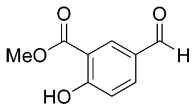

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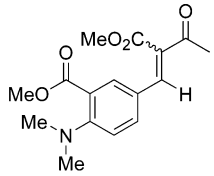

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Scope

We have surveyed the scope of the ketone enolates that undergo addition to the nitrovinamidinium **3** in acetonitrile (Table 2). Reaction of homologue **17a** at 70 °C led to the formation of aniline **18a** in 81% assay yield (75% isolated) and phenol **19a**[44] in 4%. Pentan-2,4-dione gave the aniline **18b**[45] in 80% (15:1) and traces of phenol (4%) **19b**[46] in acetonitrile at −10 °C. Acetone was reacted using a range of bases to give the aniline **18c**.[47] The best results in terms of yield were obtained using sodium acetate since competing aldol reactions were minimized. These results contrast nicely with the reaction of activated and unactivated ketones and the sodium salt of nitromalonaldehyde, which led to the formation of the nitrophenols in good yields.[48] This reactivity of substituted malonates to give phenolic products is general,[49] and pyrimidines behave as masked 1,3-dicarbonyls in a similar manner.[50] The current work reinforces the complimentary reactivity of the masked 1,3-dicarbonyl embedded in the vinamidinium salts.

To demonstrate the formation of biaryls, a series of 1-aryl-nitrovinamidiniums **20a**−**d** was prepared using procedures analogous to those described by Gupton[51] followed by the straightforward nitration using nitric acid/acetic anhydride.[52] These 1-aryl-vinamidiums also proved to be good partners in the coupling reaction giving rise to anilines in 80−98% yield using DMAP as base. An excess (>2 equiv) of MAA was required to drive the reactions to completion. The aniline/phenol ratio was excellent in all cases, and none of the regioisomeric anilines resulting from initial reaction at the 1-aryl

(38) Gupton, J. T.; Riesinger, S. W.; Shah, A. S.; Gall, J. E.; Bevirt, K. M. *J. Org. Chem.* **1991**, *56*, 976.

(39) Performing the reaction in a sealed tube at 80 °C led to 1:1 aniline/phenol selectivity.

(40) pK_a's (in methanol/water) and proton affinities are available by experimental and theoretical methods for a range of tertiary vinylamines. (a) Adams, R.; Mahan, J. E. *J. Am. Chem. Soc.* **1942**, *64*, 2588. (b) Cook, M. J.; Katritsky, A. R.; Linda, P.; Tack, R. D. *J. Chem. Soc., Perkin Trans. 2* **1972**, 1295. (c) Ellenberger, M. R.; Dixon, D. A.; Farneth, W. E. *J. Am. Chem. Soc.* **1981**, *103*, 5377.

(41) Davies, I. W.; Tellers, D. M.; Schultz, C. S.; Fleitz, F. J.; Cai, D.; Sun, Y.-K. *Org. Lett.* **2002**, *4*, 2969.

(42) The trimethinium bisperchlorate salt was first reported by Arnold and has been used successfully in the synthesis of pyrimidines. (a) Arnold, Z. *Collect. Czech. Chem. Commun.* **1961**, *26*, 3051. (b) Arnold, Z. *Collect. Czech. Chem. Commun.* **1965**, *30*, 2125. (c) Gupton, J. T.; Gall, J. E.; Riesinger, S. W.; Dahl, M. L.; Arnold, A. *J. Heterocycl. Chem.* **1991**, *28*, 1281. For the preparation of the bistetrafluoroborate see: Keshavarz, K. M.; Cox, S. D.; Angus, R. O., Jr.; Wudl, F. *Synthesis* **1988**, 641.

(43) Wayne; Cohen *J. Chem. Soc.* **1922**, *121*, 1022. For NMR data, see: Filler, R.; Lin, S.; Zhang, Z. *J. Fluorine Chem.* **1995**, *74*, 69.

(44) Pierre Fabre S. A., U.S. Patent 3,958,002; *Chem. Abs.* **1976**, *88*, 55070.

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(46) Joshi, S. *J. Am. Chem. Soc.* **1954**, *76*, 4993.

(47) Bamberger, T. *Chem. Ber.* **1899**, *32*, 1897. For preparation via S_NAr see: Gupton, J. T.; Idoux, J. P.; Baker, G.; Colon, C.; Crews, D. A. *J. Org. Chem.* **1983**, *48*, 2933.

(48) Jones, E. C. S.; Kenner, J. *J. Chem. Soc.* **1931**, 1842.

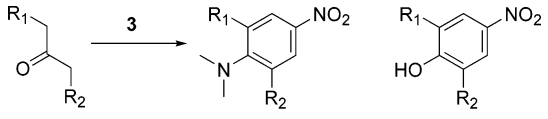
(49) (a) Prelog, V.; Wursch, J.; Konigsbacher, K. *Helv. Chim. Acta* **1951**, *34*, 358. (b) Hirota, K.; Kitade, Y.; Senda, S. *J. Org. Chem.* **1981**, *46*, 3949. (c) Nantz, M. H.; Fuchs, P. L. *Synth. Commun.* **1987**, *17*, 761.

(50) Remennikov, G. Y.; Kurilenko, L. K.; Boldyrev, I. V.; Cherkasov, V. *Chem. Heterocycl. Compd.* **1987**, *23*, 422 (English). Remennikov, G. Y.; Kurilenko, L. K.; Boldyrev, I. V.; Cherkasov, V. *Khim. Geterotsikl. Soedin.* **1987**, *4*, 508 (Russian).

(51) Gupton, J. T.; Moebus, M. A. M.; Buck, T. *Synth. Commun.* **1986**, *16*, 1561−74.

(52) Kucera, J.; Arnold, Z. *Collect. Czech. Chem. Commun.* **1967**, *32*, 1704.

TABLE 2. Reaction of Substituted Ketones with *N,N*-Dimethyl-2-nitro-trimethinium Hexafluorophosphate[a]

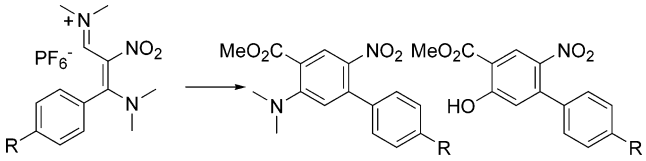


17 a - d 18 a - d 19 a - d

entry	R_1	R_2	assay yield (%)[b]	
1	CO_2Me	CH_3	**18a** (81)	**19a** (4)
2	C(O)Me	H	**18b** (79)	**19b** (5)
3	H	H	**18c** (30)[c]	**19d** (−)[d]
4	4-F-C_6H_4	H	**18d** (10)	**19d** (35)

[a] Unless otherwise noted, all reactions were conducted in acetonitrile using 1.05 equiv of *t*-BuOK and 1.1 equiv of **3g**. [b] Assay yield determined by HPLC analysis using analytically pure standard. [c] Sodium acetate (3 equiv) was used in place of *t*-BuOK at 45 °C. [d] Not detected in the crude reaction mixture by NMR or LCMS of the crude reaction mixture.

TABLE 3. Reaction of MAA and 1-Aryl-2-nitro-trimethinium Hexafluorophosphates[a]



20 a-d 21a-d 22a-d

entry	R	assay yield (%)[b]	
1	Cl	**21a** (98)	**22a** (1)
2	H	**21b** (95)	**22b** (5)
3	CH_3	**21c** (88)	**22c** (7)
4	OMe	**21d** (75)	**22d** (8)

[a] Unless otherwise noted, all reactions were conducted in acetonitrile at 20 °C using 2 equiv of DMAP, 1 equiv of vinamidinium salt, and 2−4 equiv of MAA. [b] Assay yield determined by HPLC analysis using an analytically pure standard.

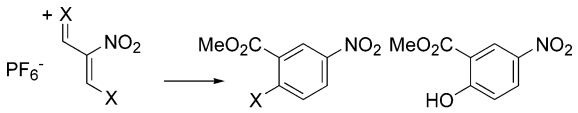
position were detected.[53] The identity of the aniline **21d** was unambiguously assigned by X-ray crystallography (see Supporting Information), and the other isomers **21a**−**c** were assigned by analogy and supporting NOE data between OMe and NMe_2.

Nitrovinamidinium salts derived from a range of secondary amines were examined as partners in the reaction using 1.05 equiv of *t*-BuOK and 1.1 equiv of vinamidinium salt in THF (Table 4). The piperidinyl vinamidinium salt **23a** gave aniline **24**[54] with good selectivity at room temperature (9:1). The *N*,*N*-diisopropylvinamidinium salt **23b** gave the phenol **5** in 60% isolated yield with none of the aniline **24c** detected by ^{1}H NMR analysis of the crude reaction mixture.

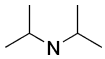
Mechanistic Studies

The formation of phenols as the minor product in the reaction was not altogether unexpected on the basis of a report that the fluorovinamidinium and salt led to the

TABLE 4. Reaction of MAA and *N,N*-Substituted 2-Nitro-trimethinium Hexafluorophosphate[a]



23 a - c 24 a - c 5

entry	X =	aniline (%)[b]	phenol **5** (%)[b]
1	 **23a**	**24a** (93)	(5)
2	 **23b**	**24b** (89)	(11)
3	 **23c**	**24c** (−)	(63)

[a] Unless otherwise noted, all reactions were conducted in THF at 20 °C using 1.05 equiv of *t*-BuOK and 1.1 equiv of vinamidinium salt. [b] Assay yield determined by HPLC analysis using analytically pure standard. [c] Not detected by ^{1}H NMR or LCMS of the crude reaction mixture.

formation of a phenol in 31% yield.[29] The observation of an aniline in the reaction was somewhat surprising.[55] A road map was generated to account for the products of the reaction based on the known reactivity profile of vinamidinium salts (Scheme 2). Addition of MAA to the nitrovinamidinium salt leads to the adduct **25**, which undergoes elimination of dimethylamine to give dienone **7g**. A simple keto−enol tautomerism to **26** sets the stage for an electrocyclic ring closure to generate enol **27**. Aromaticity can be achieved by the elimination of dimethylamine to give phenol **5**. To explain the formation of aniline **6**, a [1,5]-H shift of enol **27** to enamine **30** was invoked followed by a facile elimination of water.[56] This [1,5]-H shift would have a low activation barrier since the reactions were routinely conducted at or below room temperature. Such a small activation energy would be unprecedented, so we aggressively set out to understand the reaction using experimental and computational studies. The experimental studies and the computational aspects of the program are presented below.

As a probe of the mechanistic features of the reaction we decided to investigate the effect of isotopic substitution on the reaction.[57] Without a good basis for speculation on the rate-determining step, a competition method was employed.[58] Initially for the sake of expediency, *perdeuterio* nitrovinamidinium hexafluorophosphate **31**

(53) Gupton, J. T.; Krumpe, K. E.; Burnham, B. S.; Dwornik, K. A.; Petrich, S. A.; Du, K. X.; Bruce, M. A.; Vu, P.; Vargas, M.; Keertikar, K. M.; Hosein, K. N.; Jones, C. R.; Sikorski, J. A. *Tetrahedron* **1998**, *54*, 5075.

(54) Arnone, C.; Consiglio, G.; Frenna, V.; Spinelli, D. *J. Org. Chem.* **1997**, *62*, 3093.

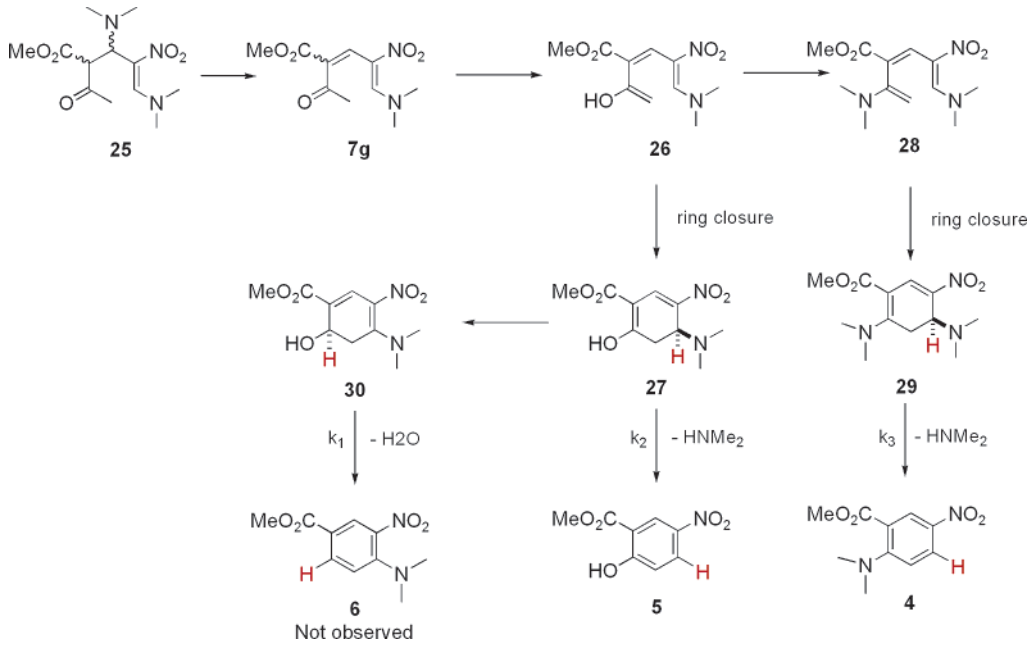
(55) For preparation of anilines via Diels−Alder reaction of dimethylacetylene dicaraboxylate and 1,3-(dialkylamino)butadiene, which was prepared insitu from a 1-methylvinamidinium perchlorate salt, see: Gompper, R.; Heinemann, U. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 216.

(56) Jia, Z. S.; Brandt, P.; Thibblin, A. *J. Am. Chem. Soc.* **2001**, *123*, 10147. The elimination of water from benzene hydrate in glycerol/water at pH 5.57 is exothermic by −39 kcal/mol with a rate constant of 58 M^{-1} s^{-1}. A value of 190 M^{-1} s^{-1} has been reported for the acetic acid catalyzed dehydration of benzene hydrate in water: Rao, S. N.; More O'Ferrall, R. A.; Kelly, S. C.; Boyd, D. R.; Agarwal, R. *J. Am. Chem. Soc.* **1993**, *115*, 5458.

(57) For discussions see: Melander, L.; Saunders, W. H., Jr. *Reaction Rates of Isotopic Molecules*; John Wiley and Sons: New York, 1980. Westheimer, F. H. *Chem. Rev.* **1961**, *61*, 265.

(58) Cohen, T.; McMullen, C. H.; Smith, K. *J. Am. Chem. Soc.* **1968**, *90*, 6866.

SCHEME 2



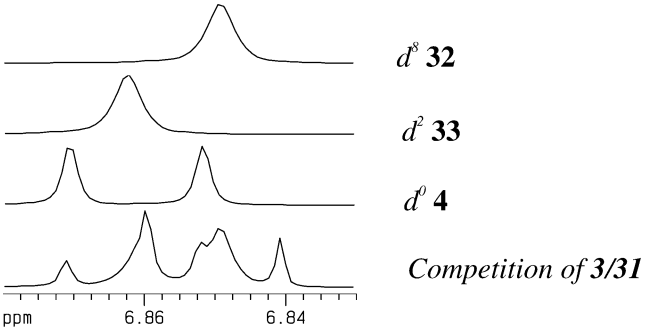
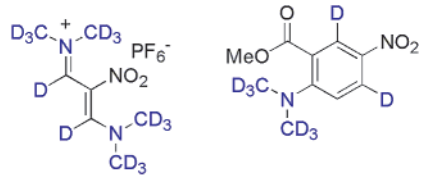
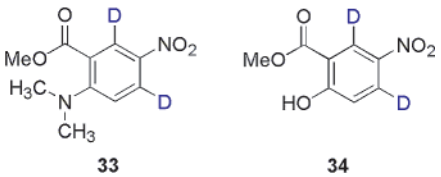


FIGURE 1. Stack plot analysis of ^{1}H NMR (500 MHz) in $CDCl_3$.

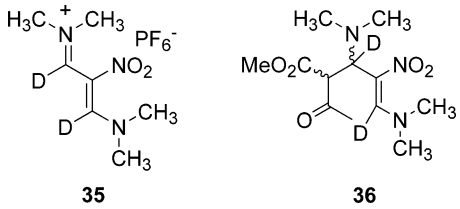
was prepared starting with d^7-dimethylformamide and chloroacetic acid.[59] Initial competition experiments using 10 equiv of a 1:1 mole ratio of **3/31** vs **MAA** were performed at 20 °C in THF using *tert*-butoxide as base.





Analysis of the crude reaction mixture by ^{1}H NMR at 500 MHz revealed the presence of up to 40 mol % of the aniline **33**, which indicates attack of the liberated dimethylamine on an intermediate (Figure 1). The stack plot confirms the initial interpretation after the purified isotopic analogues were available for unambiguous assignment.

For a more rigorous study of the effect of isotopic substitution, the nitrovinamidinium d^2-**35** was prepared from d^1-DMF.



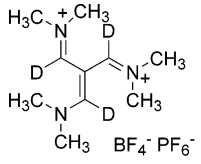
Competition experiments using 0.1−0.15 equiv of MAA and a 1:1 mole ratio of **3/35** were performed at 25 °C in THF using *tert*-butoxide as base. At the end of reaction the yield was determined by HPLC analysis to ensure consistency with the experiments performed with a synthesis objective. Following concentration, the ratio of all four possible compounds was determined by ^{1}H NMR at 500 MHz. The total amount of deuterium observed in the product distribution is fixed downstream after the first irreversible step en route to the products. Since the elimination of dimethylamine from **25**/**36** is essentially irreversible,[60] the total amount of deuterium observed in the products is controlled by the addition of the enol/enolate to the vinamidinium salt. Once the irreversible step has been traversed the relative partitioning pathways are no longer in isotopic competition. It follows that (sum of hydrogen products)/(sum of deuterium products), i.e., (**4** + **5**)/(**32** + **34**) represents a secondary kinetic isotope effect.[61] From the competition experiments of

(59) Whilst a deuterium label is only required at the sp^2 methine bond, the availability of d^7-DMF initially dictated our choice of labeling strategy.

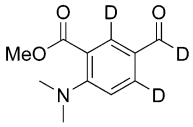
(60) Attack of a nucleophile by microscopic reversibility can be envisioned at C-4, attack of nucleophiles occurs in these systems is at the distal carbon (C-6) by analogy with organometallic reagents and heteroatoms (e.g., ammonia, see ref 16).

3/**35**, the experimentally determined inverse isotope effect $k_{H/D}$ was 0.7 at 25 °C in THF for the nitrovinamidinium using *tert*-butoxide. It also follows that (**4**/**5**)/(**32**/**34**) represents a product isotope effect, and a value of 1.15 was observed.

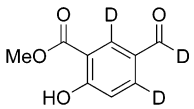
Competition experiments using 0.1−0.15 equiv of MAA and a 1:1 mole ratio of **13**/**37** were performed at −10 °C in acetonitrile using *tert*-butoxide or DMAP as base. Trimethinium salt d^3-**37** was prepared from d^1-DMF. As in the nitro series, the (sum of hydrogen products)/(sum of deuterium products), i.e., (**14** + **15**)/(**38** + **39**) represents a secondary kinetic isotope effect. The experimentally determined value $k_{H/D}$ was 0.93. A small product isotope effect of 1.25 was also observed (**14**/**15**)/(**38**/**39**). The small observed isotope effects are inconsistent with the intermediacy of a [1,5]-H shift since the migration would have to be almost insensitive to isotopic substitution.[62] Taken together, these experimental data and the calculations provide overwhelming data that precludes the involvement of a [1,5]-H shift or oxyanionic variants en route to **6**. This prediction turned out to be extremely gratifying since the calculations served as a predictive tool that led us to question and eventually reassign the identity of the major product to aniline **4**.



37

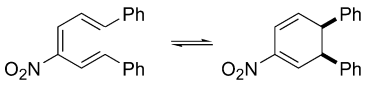


38



39

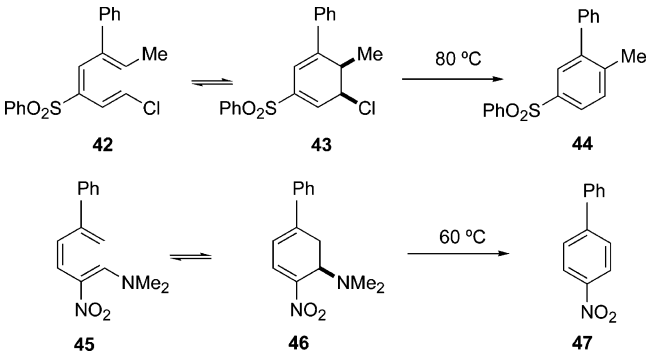
With the correct structural assignment in hand, a more conventional mechanistic proposal was developed focusing on a key electrocylization of the intermediate triene (as the enol or enamine).



40 **41**

The 1,6-diphenyl-3-nitro-1,3,5-hexatriene **40**, which has the 1*E*,3*E*,5*E* configuration as determined by X-ray crystallography,[63] undergoes electrocyclization at 60 °C to the corresponding cyclohexadiene **41**. Alkyl and vinyl substituents at the 3-position of hexatriene decrease the electrocyclization activation energy by 3−5 kcal/mol.[64] Aromatic compounds **44** and **47** are obtained from hexatrienes when a latent leaving group, e.g., chloro[65] **42** or dimethylamino[66] **45** is located at the triene terminus (Scheme 3). These reactions involving a reversible disrotatory electrocylization are very close analogues for the electrocylization of **26** and **28**, and elimination occurs at slightly higher temperatures to the reactions of vinamidium salts described in this article.

SCHEME 3



42 **43** **44**

45 **46** **47**

The downstream elimination of dimethylamine from **27** or **29** is expected to be extremely facile on the basis of the literature precedent for **46**. The generation of the aromatic systems is expected to be extremely favorable and provide a thermodynamic driving force, and as such the aminocyclohexadienes may not be long-lived discrete intermediates.[67]

The inverse secondary kinetic isotope effect found experimentally is fully consistent with rate-limiting addition of the enol/enolate to the vinamidinium salt.[68] The smaller inverse isotope effect (0.93 vs 0.75) in the case of the dimethylaminomethylene vinamidinium **13** is consistent with an earlier transition state during the addition reaction.[69]

The observation of aniline products and the intermolecular scrambling of isotopically distinct dimethylamine species provided strong evidence for the intermediacy of an enamine that is ultimately derived by the dimethylamine liberated in the initial addition/elimination. To provide further support for the intermediacy of an enamine, we have investigated the direct reaction of crystalline **48** derived from methyl acetoacetate and pyrrolidine (Scheme 3).[70] Reaction of the enamine **48** with nitrovinamidinium **3** (3 equiv) led to the aniline **24a** in 75% yield in acetonitrile at 60 °C in the absence of base (Scheme 4). Under these conditions aniline **4** was observed in 3% and phenol **5** was present at 1% by HPLC analysis.[71]

To provide confirmation that entering the reaction with a preformed enamine **48** was not a significant perturba-

(61) See Supporting Information for a road map of isotopic distribution and formulae for the calucluation of kinetic and product isotope effects (Scheme S-1).

(62) Wiberg, K. *Chem. Rev.* **1955**, *55*, 713. Wiberg, K.; Motell, E. L. *Tetrahedron* **1963**, *19*, 2009.

(63) Dell' Erba, C.; Gabellini, A.; Mugnoli, A.; Novi, N.; Petrillo, G.; Tavani, C. *Tetrahedron* **2001**, *57*, 9025.

(64) Substituent effects on electrocyclization reactions. (a) Spangler, C. W.; Ibrahim, S.; Bookbinder, D. C.; Ahmad, S. *J. Chem. Soc., Perkin Trans. 2* **1979**, *6*, 717. (b) Spangler, C. W. *Tetrahedron* **1976**, *32*, 2681. (c) Schiess, P.; Dinkel, R. *Tetrahedron Lett.* **1973**, *29*, 2503. (d) Marvell, E. N.; Caple, G.; Delphey, C.; Platt, J.; Polston, N.; Tashiro, J. *Tetrahedron* **1973**, *29*, 3797.

(65) Ogura, K.; Takeda, M.; Xie, J. R.; Akazome, M.; Matsumoto, S. *Tetrahedron Lett.* **2001**, *42*, 1923.

(66) Jutz, C.; Wagner, R. M. *Angew. Chem.* **1972**, *11*, 315.

(67) For the rate of elimination of water from benzene hydrate, see ref 55. A kinetic study of the rate of elimination of dimethylamine has not been reported. Related cyclohexadienes have been prepared via photochemically initiated addition of amines to chlorobenzene, although not in pure form. Gilbert, A.; Krestonosich, S.; Westover, D. L. *J. Chem. Soc., Perkin Trans. 1* **1981**, 295.

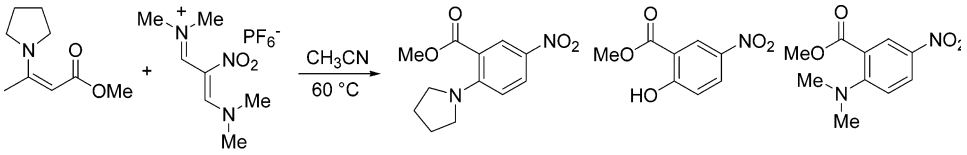
(68) This value is in agreement with enol ether addition to benzaldehyde and may suggest a later transition state for the addition to **3g** than for **11d**: Myers, A. G.; Widdowson, K. L.; Kukkola, P. J. *J. Am. Chem. Soc.* **1992**, *114*, 2765.

(69) For a discussion of secondary isotope effects in carbonyl addition see: (a) Gajewski, J. J.; Bocian, W.; Harris, N. J.; Olson, L. P. *J. Am. Chem. Soc.* **1999**, *121*, 326. (b) Gajewski, J. J.; Bocian, W.; Brichford, N. L.; Henderson J. L. *J. Org. Chem.* **2002**, *67*, 4236.

(70) Bieräugel, H.; Akkerman, J. M.; Armande, J. C. L.; Pandit, U. K. *Recl. J. R. Neth. Chem. Soc.* **1976**, *95*, 268.

(71) For the preparation of phenols from enamines, see: Kang, G. J.; Chan, T. H. *J. Org. Chem.* **1985**, *50*, 452.

SCHEME 4



48 **3** **24a** **5** **4**

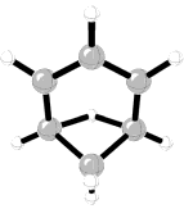
tion of reaction upstream of the electrocylization, we again investigated the effect of isotopic substitution. From the competition experiments of enamine **48** and **3**/**35**, the experimentally determined secondary kinetic isotope effect $k_{H/D}$ was 0.75 at 60 °C. The yield of aniline **24a** under these competition conditions with a large excess of vinamidinium (total 10 equiv vs enamine) was 85% and phenol **5** was again present at <1%.

Computational Studies

General Considerations. All calculations were performed with GAUSSIAN 98.[72] All structures, reactants, transition structures, and products were optimized with the B3LYP functional[73] and the 6-31G*[74] and 6-31++G** basis sets.[75] The effect of solvent was explored with the Cosmo Polarized Continuum Model (CPCM)[76] for THF solvent. All minima and transition states were characterized by their vibrational frequencies. All energy changes reported in this paper include zero-point energies that are scaled by 0.9804. The initial conformational searches were performed with Monte Carlo calculations employing the Macromodel program (MM2 force field).[77]

1,5-Hydrogen Shift. The preliminary assignment of aniline **6** as the product from reaction of MAA and the nitrovinamidnium **3** invoked the intermediacy of a [1,5]-H shift in our road map. However, the [1,5]-H shift would have to occur at or below room temperature, which would be unprecedented based on previous experimental studies.

The [1,5]-H migration in 1,3-cyclohexadiene **49**, unlike that in 1,3-cyclopentadiene[78] requires a high activation energy.[79] The kinetic study of 1,3-cyclohexadiene was performed at temperatures from 303 to 330 °C, and the activation energy was 40 kcal/mol.[80]



50

FIGURE 2. Transition structure for the degenerate [1,5]-hydrogen shift in 1,3-cyclohexadiene.

49

In a related observation 5-methyl-1,3-cyclohexadiene isomerizes to 4-methyl- and 2-methyl-1,3-cyclohexadienes at temperatures between 350 and 420 °C.[81] As a starting point for the computational studies and to serve as a calibration, the degenerate [1,5]-H shift in 1,3-cyclohexadiene **49** was used. The calculated transition structure is shown Figure 2.

Transition structure **50** for the degenerate 1,5-H shift in 1,3-cyclohexadiene has C_1 symmetry with C1−H6 and C5−H6 distances of 1.49 Å. The C1−H6−C5 bond angle is 97.9°. The calculated activation enthalpy is 41.9 kcal/mol, in close agreement with the experimental value and in accord with the recent calculations of 41.7 kcal/mol reported by Alabugin.[82] Calculations were then carried out for the reactions studied experimentally. Geometries for **27** and **30** and the transition structure **51** interconverting these species are shown in Figure 3.

Enol **27** is 4.9 kcal/mol more stable than the enamine **30**, which would not provide a thermodynamic driving force for isomerization. Significantly, the calculated activation enthalpy for conversion of **27** to **30** is 51.2 kcal/mol, even higher than the activation energy of the parent [1,5]-H shift in cyclohexadiene. The reactions are performed in fairly polar solvents (THF or acetonitrile); the

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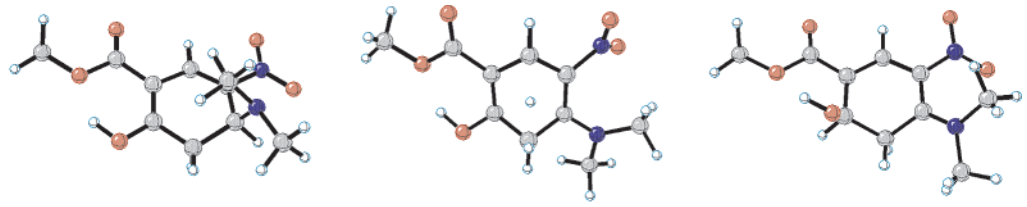


	27	51	30
gas phase	0.0	51.2	4.9
CPCM (THF)	0.0	55.3	3.0

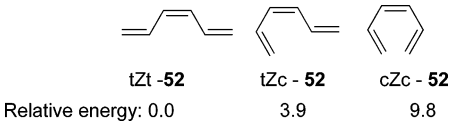
FIGURE 3. Optimized structures for **27** and **30** and [1,5]-shift transition structure **51**.

estimation of solvent effects using CPCM for THF predicts that the [1,5]-H shift activation energy will be increased by 4.1 kcal/mol.

Cope rearrangements of 3-hydroxy-1,5-hexadienes are accelerated by deprotonation of the hydroxyl-substituent: anionic oxy-Cope rearrangements are very rapid.[83] The computed activation energy for the parent anionic oxy-Cope rearrangement is 8.3 kcal/mol, which is 26.4 kcal/mol lower than the oxy-Cope rearrangement.[84] The effect of oxyanionic substitution in the [1,5]-H shift has been observed experimentally. In the case of 5-hydroxy-1,3-cycloheptadiene, activation energies measured for the alcohol and its potassium alkoxide are 24.6 and 13.8 kcal/mol, respectively.[85] The analogous anionic oxy-[1,5]-H shift involving **27** was studied using the larger B3LYP/6-31++G** basis set. The calculated activation energy was found to be 15.5 kcal/mol higher than that of the neutral system, since in this case the ground state is stabilized more than the transition state by deprotonation.

Taken together, these calculations provide overwhelming data that precludes the involvement of a [1,5]-H shift or oxyanionic variants en route to **6**. This prediction turned out to be extremely gratifying since the calculations served as a predictive tool that led us to question and eventually reassign the identity of the major product to aniline **4**. With the correct structural assignment in hand, a more conventional mechanistic proposal was developed involving a key electrocylization of the intermediate triene.

We first studied computationally the ring closure of 1,3,5-hexatriene **52** to form 1,3-cyclohexadiene, which is probably the simplest disrotatory electrocyclization initially described by Woodward and Hoffmann.[86] Kinetic studies in the gas phase at 117−190 °C were performed by Lewis and Steiner.[87] The activation energy for this reaction is 29.9 ± 0.5 kcal/mol. The reaction has also been studied extensively computationally.[88] The hexatriene **52** has three conformers, a planar tZt conformer and nonplanar conformers tZc and cZc. B3LYP/6-31G** predicts that the tZt isomer is the most stable and cZc the least.[89]



tZt -**52**	tZc - **52**	cZc - **52**
Relative energy: 0.0	3.9	9.8

The conformations accessible to enol **26** and enamine **28** were also calculated. The rotational barriers about C=C double bonds are quite low in push−pull ethylenes containing electron-donor groups (typically amino groups) at one terminus and an acceptor group (NO_2, CN, etc.) at the other end of the double bond.[90] The C=C rotational barrier ranges from 10 to 25 kcal/mol for a variety of substituted compounds. The low barriers are explained in terms of the capacity of the donor and acceptor groups to stabilize the developing dipolar transition states.[91] The experimentally determined rotational barrier for 1,1-diamino-2,2-dicyanoethylene is 11.2 kcal/mol.[92] The initial addition/elimination step of ketone to the vinamidinium leads to a ~3:1 mixture of 3(*E*,*Z*)-isomers of the dienone.[93] Energy differences between the most and the least stable conformations are 9.7 and 7.7 kcal/mol for enol **26** and enamine **28**, respectively.[94] Significantly, the minimum energy conformations for **26** and **28** are essentially aligned for electrocyclization (Figure 4).

The structural features of transition structures and energies for electrocyclic ring closing process are given in Table 5. Since anionic substitution has important consequences in some pericyclic processes such as the anionic oxy-Cope rearrangement, we studied the neutral and anionic closures of hexatriene **53** to cyclohexadiene **54**. The activation energies for these processes were calculated to be 29.9 and 29.6 kcal/mol, respectively. That is, there is essentially no effect of the deprotonation of the

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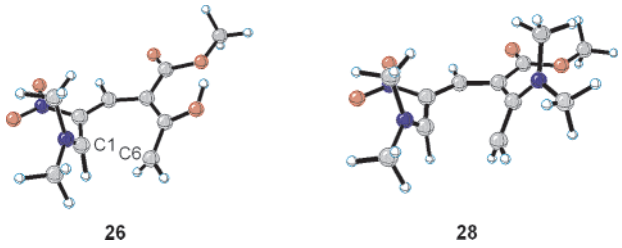
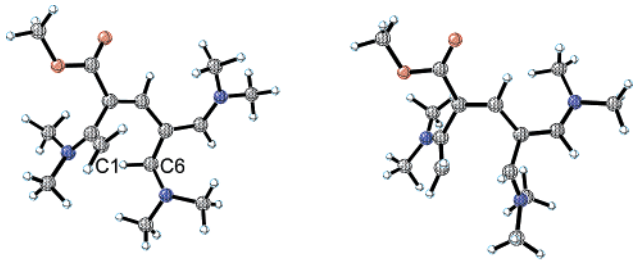
TABLE 5. Calculated Activation Energies and Geometry Parameters for the Transition State of Electrocyclic Closure of Substituted Hexatrienes

			dihedral angle (deg)			
triene	$\Delta H^{\ddagger}$ (kcal/mol)	distance C1−C6 (Å)	C1C2C3C4	C6C5C4C3	C2C3C4C5	C2C1C6C5
26	12.5	2.495	11.8	33.6	12.5	43.5
58	11.1	2.315	19.7	44.8	7.0	38.3
28	10.0	2.281	18.8	46.8	4.4	39.3
55	4.3	2.493	36.1	59.3	1.5	24.9



26 28

FIGURE 4. Minimum energy conformers for enol **26** and enamine **28**.



55 56

FIGURE 5. Minimum energy conformer for enamine **55** and transition structure for elctrocylization **56**.

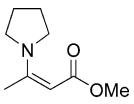
alcohol in this case. Therefore the corresponding anionic reactions of **27** were not considered as alternatives.

53 **54**

The activation energy for electrocylization is strongly linked to substitution on the triene. Introduction of oxygen or nitrogen substituents at C-1 and C-5 has a marginal impact versus the parent 1,3,5-hexatriene **52**. Introduction of a conjugating, electron-withdrawing group at C-4 reduces the activation energy by 4−5 kcal/mol, whereas introduction of electron-withdrawing groups at C-2 has a profound effect of 12−16 kcal/mol. In the nitro-substituted cases the reactants **26** and **28** have the conformation required for the ring closure. The lowest activation energy calculated for any of the electrocylizations (4.3 kcal/mol) was observed for enamine **55** (Figure 5) with transition structure **56**. These calculations provide a credible account of the facility with which the observed products − anilines and phenols are produced in the reaction from vinamidiniums that possess strongly electron withdrawing groups at the β-carbon.

Mechanistic Implications

The initial computational objectives were to characterize the electrocylization and the proposed [1,5]-sigmatropic hydrogen shift. These objectives were met, with the calculations supporting facile electrocylization reactions with systems possessing electron-withdrawing groups (sulfonyl, nitro, iminium). These studies also ruled out the intermediacy of the [1,5]-H shift and allowed for a reassignment of the major product. With the data in hand from these studies, we have attempted to provide a detailed mechanistic road map. The schematic representation of the energetics that appear to control these reactions are highlighted for the iminium series and are shown in Figure 6. The interconversion of **55** and **58** is expected to be very facile and to involve the dienone intermediate.[95] The products, aniline **14** and phenol **15**, are determined by the ease of electrocyclization, which has a remarkably low activation barrier for the enamine electrocylization (4.3 kcal/mol). A complicating feature in this scheme is the interconvertibility of the downstream intermediates **57** and **59**. This process should be almost as easy as the conversion of **55** and **58**.[96] However, the downstream eliminations of dimethylamine from **57** or **59** are expected to be extremely facile, most likely much faster than the interconversion of **57** and **59**.[97] This interpretation is supported experimentally by the reactions of preformed pyrrolidine enamine **48** with the nitrovinamidinium salt and the observation of small but consequential dialkylaniline product **4**. Using a similar rationale, for the nitro-substituted analogues, the lower activation energy for enamine over enol electrocylization (10.0 vs 12.5 kcal/mol) predicts a higher amount of aniline **4** over phenol **5**. In the case of the sulfone analogue **7g** the calculations predict the phenol **11** as the major product rather than aniline **12**, (7.5 vs 10.0 kcal/mol), which again is the case experimentally.



48

A satisfactory explanation for the product isotope effect in these reactions remains elusive. Experimental studies by Baldwin, Hess, and Schaad[98] have established that the diastereotopically distinct hydrogens in the electro-

(95) The activation energy is presumably <10 kcal/mol. Herrera, F. G. *An. Real Soc. Espan. Fis. Quim.* **1961**, *57B*, 601.

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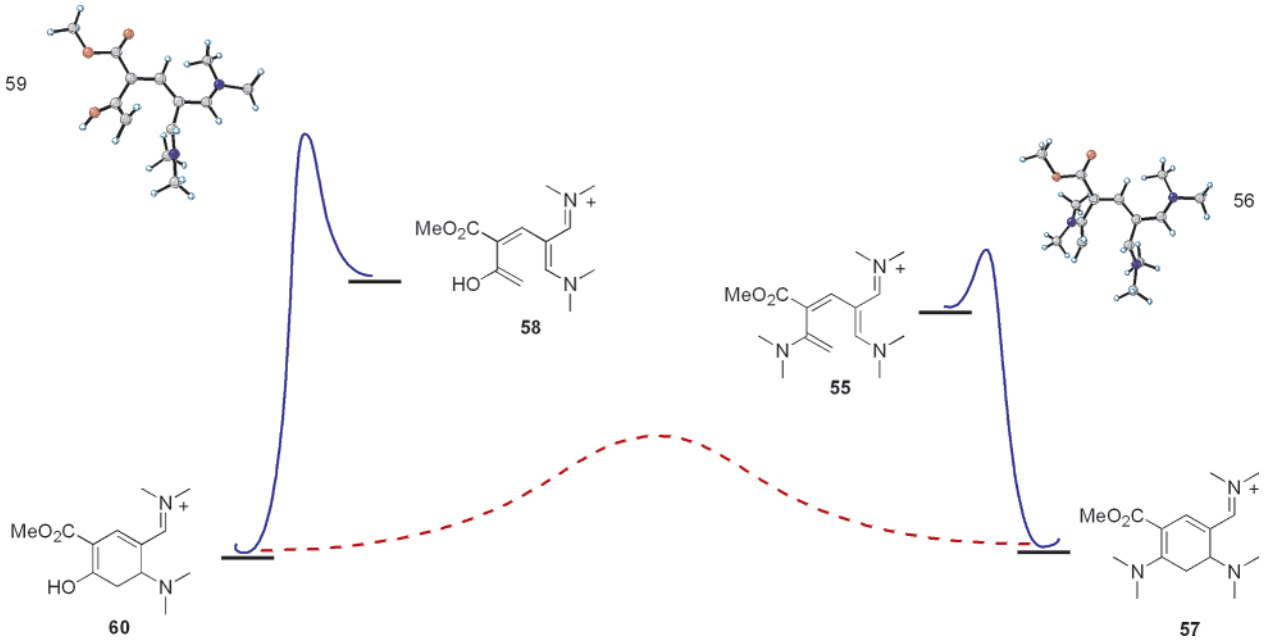

FIGURE 6. Schematic representation of the energies responsible for controlling aniline/phenol product ratio.

cylization of 1,3,5-hexatriene **52** exhibit a SKIE of 0.88 for the IN and 1.05 for the OUT atom, which manifest themselves in the rate of electrocylization. This system has also been studied computationally by Houk.[99] The difference between IN and OUT isotope effects in the degenerate 1,3,5-hexatriene system has proved to be a very sensitive probe for reaction mechanism The minimum energy conformations for the nitro and iminium enol and enamines all have the hydrogen in the IN position and isotopic substitution is expected to manifest itself by a change in activation energy but would be qualitatively quite similar in all systems.

Conclusion

We have described a synthesis of nitro anilines and formyl anilines from simple acyclic precursors in a reaction that should lend itself to synthetic application. Highly functionalized substituted benzenes including biaryls are accessible using this methodology. The reaction emphasizes that substituted aromatics are easily accessible via de novo synthesis rather than the use of conventional electrophilic substitution. The level of complexity introduced in a single step is formidable. The mechanistic features of the reaction were probed by isotopic substitution and computational studies and precluded the proposed [1,5]-hydrogen shift. Taken together the two approaches provide a complete road map for the mechanistic pathway from ketone (rate-determining addition to vinamidinium, $k_{H/D}$ 0.7−0.93) through a remarkably facile electrocylization with an activation energy ($\Delta H^{\ddagger}$ 4.3−12 kcal/mol) that is strongly dependent upon substitution of hexatriene. Facile elimination of dimethylamine leads to aromatic products.

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Supporting Information Available: Spectroscopic and characterization data for all new compounds; refined data and coordinates for X-ray analysis of **21b**; B3LYP/6-31G* optimized Cartesian coordinates for reactants and transition structures of neutral 1,5-hydrogen migrations in cyclohexadienes, the most stable conformers of hexatrienes and their transition structures for electrocyclic ring closure. This material is available free of charge via the Internet at http://pubs.acs.org.

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