ORGANIC LETTERS

2002
Vol. 4, No. 3
439−441

An Unexpected [1,5]-H Shift in the Synthesis of Nitroanilines

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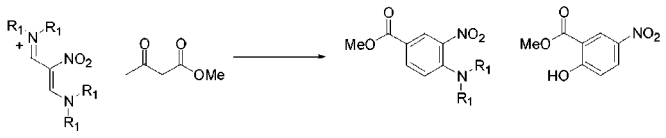
Received November 29, 2001

ABSTRACT



Addition of methyl acetoacetate to 2-nitrovinamidinium hexafluorophosphate salts leads to the formation of anilines or phenols in good to excellent yields depending on the alkylamine substituents. Small substituents, e.g., pyrrolidine, lead to the formation of anilines while large substituents, e.g., *N*,*N*-diisopropyl, exclusively give phenols. Labeling studies implicate a [1,5]-H shift proceeding with excellent isotopic fidelity.

The [1,5]-hydrogen shift is an example of a Woodward−Hoffmann pericyclic process which has been extensively studied by experimental and computational methods.[1] In degenerate systems, e.g., 1,3-pentadiene, the activation energy is 36.3 kcal/mol.[2] Substituent and steric effects are well understood.[3] As a general trend, decreasing the electron density of the π-system destabilizes the aromatic transition structure and increases the activation energy whereas electron-donating groups stabilize the transition structure.[4] In conformationally constrained systems, the activation energy is further reduced, e.g., cyclopentadiene 23.6 kcal/mol.[5] The [1,5]-H shift is also accelerated by appropriate oxy-anionic substitution, reducing the activation energy to 13.8 kcal/mol.[6]

Vinamidinium salts are important synthetic intermediates. They form the basis of the synthesis of the clinically significant Cox-2 inhibitor etoricoxib[7] as well as a variety of other heterocycles, e.g., pyrroles, pyrimidines, and pyrazoles.[8] As a result of the ease of access to these salts, we have continued to explore their synthetic utility.[9] In this Letter we disclose a simple tunable transformation that is able to deliver anilines or phenols in high yield together with mechanistic studies that confirm the involvement of a concerted [1,5]-H shift.

Addition of methyl acetoacetate (MAA) to the nitrovinamidinim hexafluorophosphate salt **1a** at room temperature led to the formation of a 9:1 mixture of aniline and phenol in high yield (Table 1). Similar results were obtained using a range of solvents and bases although potassium *tert*-butoxide gave the highest yield. There is no reaction in the absence of base; however, catalytic quantities (10−20 mol %) did give similar results with extended reaction times. Repeating the reaction at preparative scale using THF and KOtBu gave the aniline **2a** in 75% isolated yield.[10]

The formation of anilines in the reaction was somewhat surprising, but a mechanistic proposal was readily forthcoming (Scheme 1). Addition of MAA to the nitrovinamidinium

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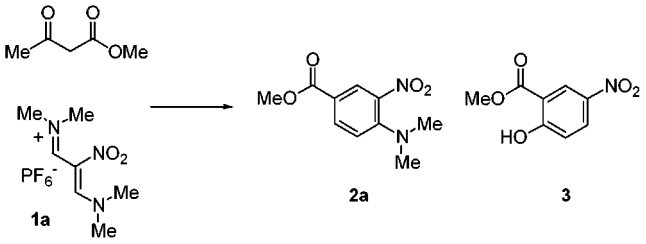
10.1021/ol017149f CCC: $22.00
Published on Web 01/05/2002

Table 1. Reaction of MAA and 2-Nitrovinamidinium Hexafluorophosphate **1a**[a]



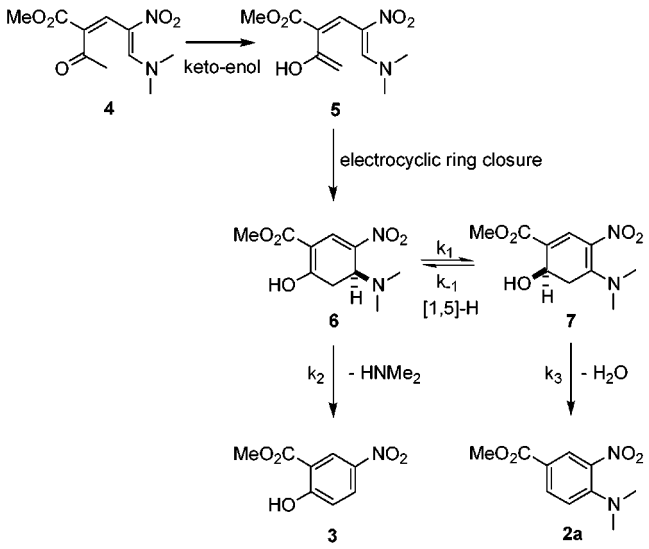
entry	solvent	base	% yield **2a**	% yield **3**	ratio **2a**:**3**
1	THF	KO^{t}Bu	78	9	9:1
2	DMF	KO^{t}Bu	65	14	5:1
3	CH_3CN	KO^{t}Bu	70	14	5:1
4	MeOH	KO^{t}Bu	70	9	8:1
5	MeOH	NaOMe	76	5	14:1
6	THF	KOH	70	8	9:1
7	THF	LiO^{t}Bu	70	5	14:1

[a] Reactions were conducted at room temperature with 1.05 equiv of base and 1.1 equiv of **1a** for 4 h. Assay yield was determined by HPLC analysis using analytically pure standards.

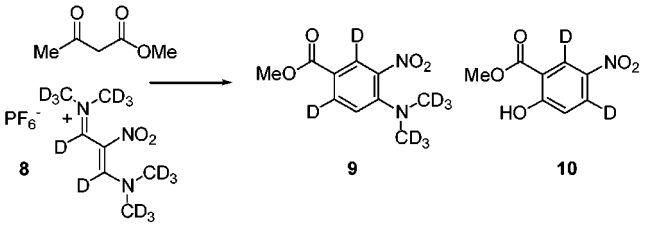
leads to the dienone **4**.[11] A simple keto−enol tautomerism to **5** sets the stage for an electrocyclic ring closure of the hexatriene to generate enol **6**.[12] At this point aromaticity can be achieved by the elimination of dimethylamine. However a [1,5]-H shift leads to enamine **7** with aromaticity being achieved by the elimination of water.

To confirm the involvement of a [1,5]-H shift, the per-deuterio nitrovinamidinium hexafluorophosphate **8** was prepared starting with d^7-dimethylformamide and chloroacetic acid.[13] Reaction of **8** and MAA in the presence of potassium *tert*-butoxide cleanly gave the aniline **9** and phenol **10** with no trace of the protio analogues (Scheme 2).[14]

Scheme 1



Scheme 2



The isotope labeling experiment implicates a [1,5] transposition of deuterium. However this result needs to be interpreted with caution since it does not rigorously exclude the intermediacy of a carbanion or ion-pair association. Further studies to unambiguously determine the nature of the [1,5]-H shift were guided by the classic Cram experiments on an inter- and intramolecularity in base-catalyzed proton transfers.[15] Conducting the reaction of **8** using potassium *tert*-butoxide in *tert*-butyl alcohol and sodium methoxide in methanol provides a very large isotopic reservoir of protons. In both cases only the deuterio aniline **9** and phenol **10** were observed. Reaction of protionitrovinamidinium **1a** using potassium *tert*-butoxide in *tert*-butyl alcohol-OD and sodium methoxide in CH_3OD only led to the protio aniline **2a** and phenol **3**.[16]

A range of nitrovinamidinium salts, **1b**−**d**, were also examined in the reaction with MAA and potassium *tert*-butoxide (Table 2).[17]

A clear trend emerges from this panel of experiments. The smaller the groups on nitrogen, the higher the preference

(10) **Typical procedure:** To a stirred solution of methyl acetoacetate (580 mg, 5 mmol) in THF (10 mL) at room temperature was added potassium *tert*-butoxide (5.25 mL, 1.0 M in THF) over 5 min. The solution was aged for 5 min, and nitrovinamidinium hexafluorophosphate **1a** (1.74 g, 5.5 mmol) was added in one portion. The mixture was stirred at room temperature for 8 h. The reaction mixture was diluted with ethyl acetate and washed with water. Concentration of the organic extracts and chromatography on silica gel eluting with ethyl acetate/heptane gave the aniline **2a** (842 mg, 75%) as a light yellow solid. DSC peak 88.4 °C (lit. mp 71.5 °C, Reverdin, F. *Chem. Ber.* **1907**, *40*, 2442). Found: C, 53.66; H, 5.39; N, 12.30. $C_{10}H_{12}N_2O_4$ requires C, 53.57; H, 5.39; N, 12.49. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (^{1}H, d, J = 3 Hz), 8.15 (1H, dd, J = 9, 3 Hz), 6.85 (1H, d, J = 9 Hz), 3.93 (3H, s), 3.03 (6H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 155.0, 137.1, 128.9, 127.4, 116.6, 114.6, 52.5, 42.9. HRMS, [M + H]$^+$ 225.0864.

(11) Nair, V.; Cooper, C. S. *J. Org. Chem.* **1981**, *46*, 6, 4759.

(12) For a simple model to predict the effect of substituents on the rates of thermal pericyclic reactions, see: Carpenter, B. *Tetrahedron* **1978**, *34*, 1877.

(13) The per-deuterio nitrovinamidinim salt was prepared analogously to the protio compound in two steps via pTSA/PPh_3 reduction of the chlorovinamidinium salt followed by nitration, see: Davies, I. W.; Marcoux, J.-F.; Wu, J.; Corley, E. G.; Robbins, M. A.; Palucki, M.; Tsou, N.; Ball, R. G.; Dormer, P.; Larsen, R. D.; Reider, P. J. *J. Org. Chem.* **2000**, *65*, 4571. Davies, I. W.; Taylor, M.; Hughes, D.; Reider, P. J. *Org. Lett.* **2000**, *2*, 3385.

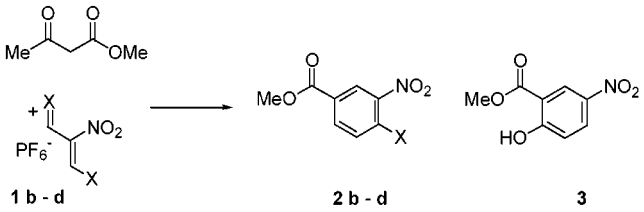
(14) The products were characterized by proton and deuterium NMR spectroscopy, elemental analysis, and high-resolution mass spectrometry. The limit of detection for the proton signal is < 0.3 mol %.

(15) Almy, J.; Uyeda, R. T.; Cram, D. J. *J. Am. Chem. Soc.* **1967**, *89*, 6768.

(16) In these cases, deuterium was incorporated in up to 47% at the site derived from the enolizable methyl ketone without incorporation at any other site.

(17) The vinamidinium salts were prepared via amine exchange, see: Davies, I. W.; Taylor, M.; Marcoux, J.-F.; Wu, J.; Dormer, P. G.; Hughes, D.; Reider, P. J. *J. Org. Chem.* **2001**, *66*, 251.

Table 2. Reaction of MAA and 2-Nitrovinamidinium Hexafluorophosphates **1b**−**d**[a]



1 b - d **2 b - d** **3**

entry	X =		% yield **2**	% yield **3**	ratio **2**:**3**
1	**1 b**	pyrrolidine	91	7	13:1
2	**1 c**	piperidine	89	11	8:1
3	**1 d**	N,N-diisopropyl	ND	63	1:20

[a] Reactions were conducted at room temperature with 1.05 equiv of base and 1.1 equiv of **1b**−**d** for 12 h. Assay yield was determined by HPLC analysis using analytically pure standards.

for the aniline. In fact, *N*,*N*-diisopropylamine led exclusively to the formation of phenol **3**. This trend does not reflect leaving group ability. However, the *o*-nitro group and the aniline alkyl substituents will face significant steric interactions in the transition state leading to the diisopropyl intermediate.[18] The reaction is tunable for either anilines or phenols by the choice of nitrogen substituent.

In summary, we have described a simple synthesis of nitroanilines from nitrovinamidinium salts. The reaction leads to the formation of anilines or phenols depending on the choice of vinamidinium salt and should lend itself to synthetic application.[19] This transformation may be rationalized as proceeding via two sequential pericyclic processes: an electrocyclic ring closure and a facile [1,5]-H shift, a transfer which proceeds with excellent isotopic fidelity. We are continuing to explore the scope of this novel transformation and to study the mechanistic features of the [1,5]-H shift including kinetic and computational studies.[20]

Supporting Information Available: Characterization and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Replacement of dimethylamine with diisopropylamine presumably affects the k_1/k_{-1} equilibrium more than the k_2 and k_3 elimination rates. The elimination of dimethylamine from **6** or water from **7** is not expected to be rate-limiting, see: Jia, Z. S.; Brandt, P.; Thibblin, A. *J. Am. Chem. Soc.* **2001**, *123*, 10147. The rate of dehydration of benzene hydrate in glycerol/water at pH 5.57 is 58 M^{-1} s^{-1} at 25 °C and is exothermic by −39 kcal/mol.

(19) The 3-nitro-4-aminobenzoate motif is a feature of combinatorial libraries directed at G protein-coupled receptors. Pan, P.-C.; Sun, C.-M. *Tetrahedron Lett.* **1998**, *39*, 9505. For intermediates in the synthesis of influenza neuraminidase inhibitors, see: Brouillette, J. W.; Atigadda, V. R.; Luo, M.; Air, G. M.; Babu, Y. S.; Bantia, S. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1901. For the use of 3-nitro-4-aminobenzoates in the solid-phase synthesis of benzopiperazinones, see: Morales, G.; Corbett, J. W.; DeGrabo, W. F. *J. Org. Chem.* **1998**, *63*, 1172.

(20) Preliminary results indicate that the reaction is not limited to MAA and 2,4-pentanedione works effectively with **1a** to give a 30:1 mixture of aniline and phenol in 80% yield.