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AZA-DIELS-ALDER SYNTHESIS AND NMR CHARACTERIZATION OF AROMATIC SUBSTITUTED 1-METHYL-2-PHENYL 2,3-DIHYDRO-4(1H)-PYRIDINONES

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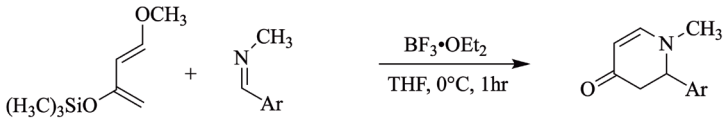
Abstract

A two-step reaction sequence was utilized to synthesize seven, 1-methyl-2-phenyl-2,3-dihydro-4(1H)-pyridinones with varying substituents on the phenyl ring. In the first step, the imine dienophile was generated from the corresponding aldehyde and N-methylamine over 4Å molecular sieves. In the second step, Danishefsky's diene was reacted with the respective imine in the presence of boron trifluoride as a catalyst to yield the 2,3-dihydropyridone. Products were purified by column chromatography and characterized by IR and NMR.



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Keywords: aza-Diels-Alder, 4+2 cycloaddition, N-(phenylmethylene)methanamine, Danishefsky's diene, 1-methyl-2-phenyl 2,3-dihydro-4(1H)-pyridinone, imines, 2,3-dihydropyridinones, COSY, HMQC4+2 cycloaddition, N-(phenylmethylene)methanamine
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Introduction

In 1928, Otto Diels and Kurt Alder published the synthesis of nitrogen containing heterocycles via [4+2] cycloaddition reactions involving a diene and an azo compound; now commonly referred to as aza-Diels-Alder reactions.[1] Of interest to us was the use of the aza-Diels-Alder reaction to synthesize 2,3-dihydropyridinones, which have important synthetic utility as precursors for natural products, pharmaceuticals, and amino acids.[2,3] In 1982, Danishefsky and Kerwin published an aza-Diels-Alder reaction involving Danishefsky's diene and various imines to make 2,3-dihydropyridinones (Figure 1a).[4,5] Their reactions were performed in the presence of zinc chloride as a Lewis acid catalyst and reaction times were listed between 36-48 hours with yields dependent on the stoichiometry of imine to diene. Later, in 1988, Midland and co-workers published a similar reaction that was carried out using Brassard's diene in the presence of diethylaluminum chloride as a catalyst, which cut the reaction time to 2-6 hours depending on the imine.[6]

We were interested in synthesizing the β-amino acid precursor, 1-methyl-2-phenyl-2,3-dihydro-4(1H)-pyridinone (Figure 1b). There have been several syntheses reported for this compound, all with very different methodologies.[7-10] Revuelta and co-workers utilized a palladium catalyzed transformation of spirocyclopropanes under pressurized oxygen.[7] Another interesting method by Ege and Wanner, incorporated a six-step synthesis involving reduction of a protected pyridine.[8] Related to the Danishefsky's original publication, Zheng and co-workers performed a one pot reductive cycloaddition utilizing Danishefsky's diene and multiple reagents in the presence of zinc chloride as a catalyst with an overall reaction time of over 11 hours.[9] In contrast, Takeda and co-workers performed a three-step synthesis of an iodobenzimidazolium salt, which was subsequentially used as a catalyst in the aza-Diels-Alder reaction and was complete after 1 hour at room temperature.[10] Our approach was to revisit Danishefsky's original work and utilize his two step reaction with an imine to diene at a ratio of 1:1 in the presence of boron trifluoride as a catalyst and a reaction time of 1 hour.

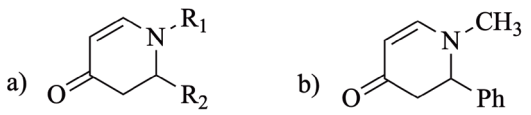

Figure 1: a) an example of a 2-3-dihydropyridinone where R1 and R2 can be H, alkyl or aryl, b) 1-methyl-2-phenyl-2,3-dihydro-4(1H)-pyridinone (**2b**).

Experimental Methods:

Materials and Methods.

P-Tolualdehyde (Acros), benzaldehyde (Fisher), 3-chlorobenzaldehyde (Sigma-Aldrich), 4-trifluoromethylbenzaldehyde (Sigma-Aldrich), 4-nitrobenzaldehyde (Sigma-Aldrich), 3,5-dichlorobenzaldehyde (Sigma-Aldrich), 3,5-bistrifluoromethylbenzaldehyde (Sigma-Aldrich), 30% methylamine in anhydrous ethanol (Sigma-Aldrich), anhydrous ethyl ether (Fisher), 4Å molecular sieves (8-12 mesh) (Sigma-Aldrich), anhydrous tetrahydrofuran (VWR), *trans*-1-Methoxy-3-trimethylsiloxy-1,3-butadiene (Danishefsky's diene) (Sigma-Aldrich) boron trifluoride etherate (Sigma-Aldrich), acetone (VWR), ethyl acetate (VWR), silica gel (Acros), and plastic backed silica gel TLC plates (J.T. Baker) chloroform-d1 ($CDCl_3$) (Alfa Aesar) and acetonitrile-d3 (CD_3CN) (Alfa Aesar) were purchased from their respective suppliers. It should be noted that Danishefsky's diene was purchased in sealed ampoules and the purity was checked via ^1H NMR prior to use. All chemicals were handled with nitrile gloves and all reactions and purifications were performed in a laboratory hood. All NMR spectra were recorded at room temperature on a JEOL ECX-400 NMR (JEOL, Inc., Peabody, MA, USA) equipped with a NM40-TH5/AT/FG-B probe. Proton and carbon spectra were operated at 399.78MHz and 100.52MHz, respectively, with a field strength of 9.39T. All spectra were collected using JEOL's Delta NMR Software v. 4.3.6. with default pulse programs and processing methods. The 1H and 13C chemical shifts were reported in ppm(δ) and referenced to the either $CDCl_3$ for the N-(phenylmethylene) methanamines **(1a-g)** or CD_3CN for the 1-methyl-2-phenyl-2,3-dihydro-4(1H)-pyridinones **(2a-g)**. In addition, the 1-methyl-2-phe-

nyl-2,3-dihydro-4(1H)-pyridinones **(2a-g)** were characterized by IR spectroscopy using a Nicolet iS5 infrared spectrometer outfitted with a diamond crystal ATR accessory and Omnic software.

*General procedure for the synthesis of imines **(1a-g)**.*

All imines were synthesized using the method described by Tsuchimoto et. al.[11] The desired substituted benzaldehyde (~2 g, 1 eq), 30% methylamine in anhydrous ethanol (~3.5 mL, 2 eq), 35 mL of anhydrous ethyl ether, and 15 g of 4Å molecular sieves (8-12 mesh) were added to a bottle with a Teflon lined cap. The mixture was stirred, capped, and left to react in a refrigerator for at least 1 day. The reaction was monitored by 1H NMR spectroscopy for the disappearance of the aldehyde hydrogen. Upon complete conversion to the imine, the solution was gravity filtered to remove the sieves and rotary evaporated. All imines were clear liquids with a slight yellow tint.

N-[(4-Methylphenyl)methylene]methanamine (**1a**) (55.6%). ^{1}H-NMR ($CDCl_3$): δ 2.32 (s, 3 H), 3.46 (d, *J*=1.37 Hz, 3H), 7.17 (d, *J*=7.79 Hz, 2H), 7.57 (d, *J*=7.79 Hz, 2H), 8.17 (d, *J*=1.37 Hz, 1H).*

N-(Phenylmethylene)methanamine (**1b**) (38.1%). ^{1}H-NMR ($CDCl_3$): δ 3.52 (d, J=1.37 Hz, 3H), 7.41 (m, 3H), 7.70 (m, 2H), 8.28 (d, J=1.37 Hz, 1H)*.

N-[(3-Chlorophenyl)methylene]methanamine (**1c**) (50.4%). ^{1}H-NMR ($CDCl_3$): δ 3.52 (d, J=1.37 Hz, 3H), 7.34 (m, 2H), 7.55 (d, J=7.33 Hz, 1H), 7.71 (m, 1H), 8.22 (d, J=1.37 Hz, 1H).*

N-[(4-Trifluoroethylphenyl)methylene]methanamine (**1d**) (55.4%). ^{1}H-NMR ($CDCl_3$): δ 3.53 (d, J=1.37 Hz, 3H), 7.64 (d, J=7.79 Hz, 2H), 7.79 (d, J=7.79 Hz, 2H), 8.28 (d, J=1.37 Hz, 1H).*

N-[(4-Nitrophenyl)methylene]methanamine (**1e**) (47.8%). ^{1}H-NMR ($CDCl_3$): δ 3.58 (d, J=1.37 Hz, 3H), 7.86 (d, J=8.70 Hz, 2H), 8.25 (d, J=8.70 Hz, 2H), 8.36 (d, J=1.37 Hz, 1H).*

N-[(3,5-Dichlorophenyl)methylene]methanamine (**1f**) (90.4%). ^{1}H-NMR ($CDCl_3$): δ 3.52 (d, J=1.37 Hz, 3H), 7.38 (t, J=1.83 Hz, 1H), 7.57 (d, J=1.83 Hz, 2H), 8.16 (d, J=1.37 Hz, 1H).*

N-[(3,5-Bistrifluoromethylphenyl)methylene]methanamine (**1g**) (82.3%). ^{1}H-NMR ($CDCl_3$): δ 3.59 (d, J=1.83 Hz, 3H), 7.91 (s, 1H), 8.17 (s, 2H), 8.37 (d, J=1.83 Hz, 1H).*

*The imine hydrogen is an apparent doublet.

*General procedure for the synthesis of 2,3-dihydropyridinones **(2a-g)**.*

Anhydrous tetrahydrofuran (30 mL) and the imine **(1a-g)** (~0.3 g, 1 eq) were added to a 50mL round bottom flask equipped with a stir bar. The flask was stoppered and placed in an ice bath. Addition of Boron trifluoride etherate (~0.2 mL, 1 eq) was quickly followed by the addition of Danishefsky's diene (~0.5 mL, 1.5 eq) and the reaction was stirred for 1 hour at 0°C. As the reaction progressed, the solution turned from clear yellow to a clear dark orange-red. After 1 hour, 15 mL of deionized water and 20 mL of ethyl acetate were added to the reaction mixture and the resulting solution was transferred to a 125 mL separatory funnel. After gentle rocking, the mixture separated into two layers and the bottom aqueous layer was removed. The organic layer was washed a second time with 15 mL of deionized water. The remaining organic layer was then dried over sodium sulfate. Following filtration, the solvent was removed by rotary evaporation. Flash column chromatography using silica gel and a 50:50 acetone:ethyl acetate eluent was used to purify the crude product. Fractions were monitored by silica gel TLC (all compounds eluted with an Rf of ~0.65). Fractions containing the product were combined, the solvent was removed by rotary evaporation, and the resulting oil was placed under vacuum to remove residual solvent. All compounds were then characterized by IR and NMR.

2,3-Dihydro-1-methyl-2-(4-methylphenyl)-4(1*H*)-pyridinone (**2a**) (17.2%). ^{1}H-NMR (CD_3CN): δ 2.32 (s, 3 H), 2.46 (dd, J=16.26, J=7.79 Hz, 1 H), 2.78 (dd, J=16.26, J=6.87 Hz, 1 H), 2.84 (s, 3 H), 4.53 (t, J=7.33 Hz, 1 H),† 4.78 (d, J=7.79 Hz, 1 H), 7.20 (s, 4 H), 7.22 (d, J=7.79 Hz, 1H). ^{13}C-NMR (CD_3CN): δ 21.1, 41.8, 44.4, 63.3, 97.8, 127.8, 130.4, 137.0, 138.7, 156.2, 190.3. IR($\tilde{\nu}$): 1564, 1586, 1633.

2,3-Dihydro-1-methyl-2-phenyl-4(1*H*)-pyridinone (**2b**) (29.2%). ^{1}H-NMR (CD_3CN): δ 2.48 (dd, J=16.49, J=7.33 Hz, 1 H) 2.81 (dd, J=16.49, J=6.87 Hz, 1 H), 2.86 (s, 3 H), 4.58 (t, J=7.33 Hz, 1 H),† 4.79 (d, J=7.79 Hz, 1 H), 7.24 (d, J=7.79 Hz, 1 H), 7.31-7.41 (m, 5 H). ^{13}C-NMR (CD_3CN): δ 41.8, 44.3, 63.5, 97.8, 127.8, 128.9, 129.8, 140.1, 156.2, 190.1. IR($\tilde{\nu}$): 1588, 1604, 1623.

2,3-Dihydro-1-methyl-2-(3-chlorophenyl)-4(1*H*)-pyridinone (**2c**) (36.6%). ^{1}H-NMR (CD_3CN): δ 2.45 (dd, J=16.49, J=6.87 Hz, 1 H), 2.83 (dd, J=7.33 Hz, 1 H),* 2.87 (s, 3 H), 4.59 (t, J=6.87 Hz, 1 H),† 4.80 (d, J=7.79 Hz, 1 H), 7.24 (d, J=7.33 Hz, 1 H), 7.26-7.40 (m, 4 H). ^{13}C-NMR (CD_3CN): δ 41.9, 44.0, 62.9, 98.0, 126.3, 127.7, 128.9, 131.5, 135.0, 142.5, 156.1, 189.7. IR($\tilde{\nu}$): 1573, 1589, 1636.

2,3-Dihydro-1-methyl-2-(4-trifluoromethylphenyl)-4(1*H*)-pyridinone (**2d**) (31.0%). ^{1}H-NMR (CD_3CN): δ 2.46 (dd, J=16.49, J=6.41 Hz, 1 H), 2.89 (s, 3 H), 2.90 (dd, J=7.33 Hz, 1 H),* 4.70 (t, J=6.87 Hz, 1 H),† 4.82 (d, J=7.79 Hz, 1 H), 7.28 (d, J=7.79 Hz, 1 H), 7.51 (d, J=8.24 Hz, 2 H), 7.70 (d, J=8.24 Hz, 2 H). ^{13}C-NMR (CD_3CN): δ 41.9, 43.9, 62.9, 98.1, 125.3 (q, J=271.2 Hz), 126.7 (q, J=3.8 Hz), 128.5, 130.2 (q, J=32.6 Hz), 144.7, 156.1, 189.6.IR($\tilde{\nu}$): 1575, 1620, 1633.

2,3-Dihydro-1-methyl-2-(4-nitrophenyl)-4(1*H*)-pyridinone (**2e**) (33.0%). ^{1}H-NMR (CD_3CN): δ 2.45 (dd, J=16.49, J=5.95 Hz, 1 H), 2.91 (s, 3 H), 2.93 (dd, J=7.33 Hz, 1 H),* 4.75 (t, J=6.87 Hz, 1 H),† 4.82 (d, J=7.79 Hz, 1 H), 7.28 (d, J=7.79 Hz, 1 H), 7.54 (d, J=8.70 Hz, 2 H), 8.21 (d, J=8.70 Hz, 2 H). ^{13}C-NMR (CD_3CN): δ 42.0, 43.6, 62.7, 98.2, 124.9, 128.9, 147.6, 148.6, 156.0, 189.2. IR($\tilde{\nu}$): 1586, 1610, 1629.

2,3-Dihydro-1-methyl-2-(3,5-dichlorophenyl)-4(1*H*)-pyridinone (**2f**) (67.0%). ^{1}H-NMR (CD_3CN): δ 2.43 (dd, J=16.49, J=6.41 Hz, 1 H), 2.87 (dd, J=16.49, J=7.33 Hz, 1 H), 2.89 (s, 3 H), 4.59 (t, J=6.87 Hz, 1 H),† 4.80 (d, J=7.79 Hz, 1 H), 7.24 (d, J=7.79 Hz, 1 H), 7.29 (d, J= 1.83 Hz, 2 H), 7.42 (t, J=1.83 Hz, 1 H). ^{13}C-NMR (CD_3CN): δ 41.9, 43.6, 62.4, 98.2, 126.5, 128.7, 136.0, 144.2, 156.1, 189.4. IR($\tilde{\nu}$): 1561, 1582, 1626.

2,3-Dihydro-1-methyl-2-(3,5-bistrifluoromethylphenyl)-4(1*H*)-pyridinone (**2g**) (88.4%). ^{1}H-NMR (CD_3CN): δ 2.49 (dd, J=16.49, J=6.87 Hz, 1 H), 2.90 (s, 3 H), 2.92 (dd, J=7.33 Hz, 1H),* 4.78 (t, J=6.87 Hz, 1 H),† 4.84 (d, J=7.79 Hz, 1 H), 7.29 (d, J=7.33 Hz, 1 H), 7.90 (s, 2 H), 7.97 (s, 1 H). ^{13}C-NMR (CD_3CN): δ 41.9, 43.8, 62.9, 98.1, 125.3 (q, J=271.2 Hz), 126.7 (q, J=3.8 Hz), 128.5, 130.3 (q, J=32.6 Hz), 144.6, 156.1, 189.6. IR($\tilde{\nu}$): 1586, 1640.

*The N-methyl group overlaps one doublet (of the doublet of doublets) and therefore, only one vicinal J value could be estimated.

†Stereotopic hydrogen is an apparent triplet with the same J value on both sides of the triplet.

Results and Discussion:

The synthesis of seven 1-methyl-2phenyl-2,3-dihydro-4(1H) -pyridinones was carried out using a two-step reaction involving the synthesis of the aromatic substituted N-(phenylmethylene) methanamines (Figure 2: **1a-g**) followed by an aza-Diels-Alder reaction with Danishefsky's diene (Figure 3: **2a-g**). Synthesis of the methanamines incorporated a previously published synthesis of the imines by reacting N-methylamine with the respective aldehyde in the presence of 4Å molecular sieves (Figure 2).[11]

The resulting N-(phenylmethylene)methanamines were then reacted, without purification, with Danishefsky's diene in the presence of boron trifluoride etherate in anhydrous THF for a period of 1 hour at 0°C (Figure 3). After aqueous workup, extraction, and rotary evaporation, the aza-Diels-Alder products were purified by column chromatography. Products were then characterized by IR, ^{1}H, ^{13}C, DEPT-135, HMQC, and COSY NMR spectroscopy. While the products are arranged in Figure 3 by increasing electron-withdrawing ability, we were not able to ascertain whether induction influenced percent yield. During our investigation we found that the imine will decompose over time in the presence of boron trifluoride in THF. It was therefore important to add Danshefsky's diene directly after the boron trifluoride was added to the imine.

We selected 1-methyl-2-(4-nitrophenyl)-2,3-dihydro-4(1H) -pyridinone (**2e**) as an example for discussion of the NMR spectra, but it should be noted that all 1-methyl-2-phenyl-2,3-dihydro-4(1H)-pyridinones (**2a-g**) displayed similar results for splitting, integration, and coupling; with only the shifts being varied (see experimental). In addition, characterization of the unsubstituted 1-methyl-2-phenyl-2,3-dihydro-4(1H)-pyridinone (**2b**) was consistent with previously reported spectra[7-10]. For clarity purposes, the C and CHx groups in compound **2e** have been labelled with letters A-J (Table 1, Figure 4).

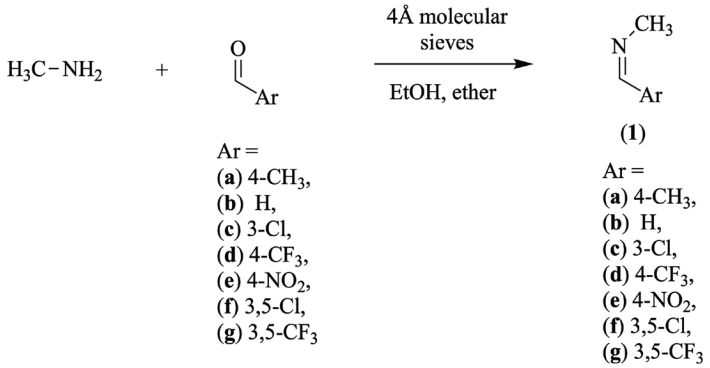

Figure 2: Synthesis of aromatic substituted N-(phenylmethylene)methanamines (**1a-g**).

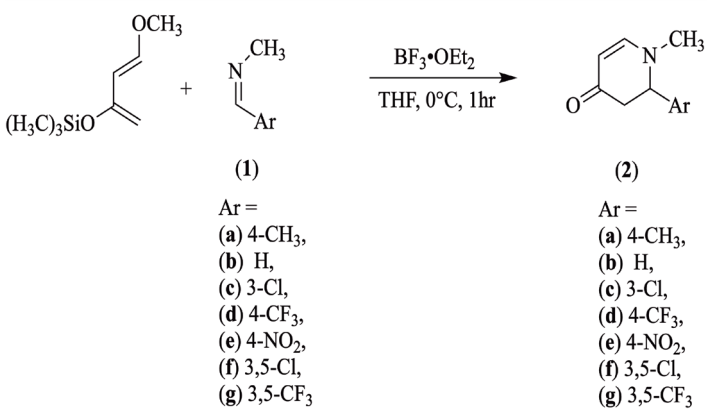

Figure 3: Synthesis of aromatic substituted 1-methyl-2-phenyl-2,3-dihydro-4(1H)-pyridinones (**2a-g**)

Beginning with the ^{1}H NMR assignments of the pyridinone ring (Table 1, Figure 5), the hydrogens of B (4.82 ppm) and C (7.28 ppm) each integrated to 1H and appeared as coupled doublets (J=7.79 Hz), both in J value and by COSY NMR (Figure 6). The locations of hydrogens B and C were confirmed by comparison to reported proton spectra of 4-amino-3-buten-2-one[12] and 1-methyl-3,3-diethyl-2,4-dioxotetrahydropyridine.[13] The methyl group, D (2.91 ppm) on the nitrogen, appeared as a singlet which integrated to 3H and was not coupled in the COSY spectrum.

Table 1: Proton and carbon assignments of 2,3-dihydro-1-methyl-2-(4-nitrophenyl)-4(1H)-pyridinone (2e).*One of the doublets of one of the protons of E (2.93 ppm) overlaps with the N-methyl peak, D (2.91 ppm), and therefore only one vicinal J value could be estimated.

Position	1H NMR δ(ppm) (multiplicity, J(Hz), int)	COSY (H→H)	13C NMR δ (ppm) (DEPT-135)
A	-	-	189.2 (4°)
B	4.82 (d, J =7.79, 1H)	C	98.2 (+)
C	7.28 (d, J=7.79, 1H)	B	156.0 (+)
D	2.91 (3H, s)	-	43.6 (+)
E	2.45 (dd, J=16.49, J=5.95, 1H) and 2.93 (dd, J=7.33, 1H)*	E,F	42.0 (-)
F	4.75 (t, J= 6.87, 1H)	E	62.7 (+)
G	-	-	147.6 (4°)
H	7.54 (d, J=8.70, 2H)	I	128.9 (+)
I	8.21 (d, J=8.70, 2H)	H	124.9 (+)
J	-	-	148.6 (4°)

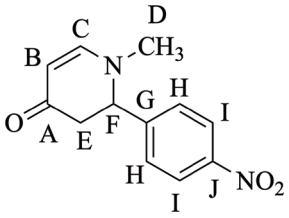

Figure 4: 2,3-Dihydro-1-methyl-2-(4-nitrophenyl)-4(1H)-pyridinone (**2e**)

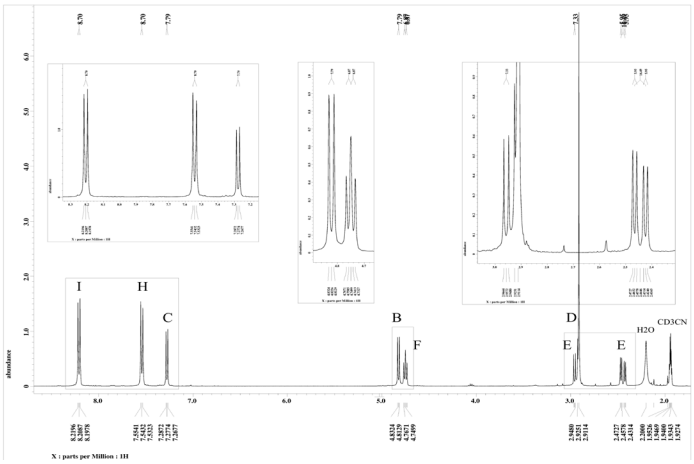

Figure 5: ^{1}H NMR spectrum of 2,3-dihydro-1-methyl-2-(4-nitrophenyl)-4(1H)-pyridinone (**2e**).

The hydrogens of E appeared in two separate locations, 2.45 ppm (J=16.49, J=5.95 Hz) and 2.93 ppm (J=7.33 Hz), each as a doublet of doublets integrating to 1H. The second doublet of doublets at 2.93 ppm overlapped with the N-methyl peak, D, at 2.91 ppm and therefore only one vicinal coupling from E→F for this hydrogen could be estimated. This overlap was also observed for compounds **2c**,**d**,**g**, however, there was no overlap for compounds **2a**,**b**,**f**, and all geminal and vicinal couplings were reported. It should be noted that this reaction is not stereoselective and the difference in location indicates that the hydrogens of E are diastereotopic because of their proximity to hydrogen F, which could have either R or S stereochemistry. As such, the hydrogens on E are split by each other (geminal), and hydrogen F (vicinal), which was confirmed by the COSY spectrum (Figure 6). Hydrogen F, 4.75 ppm, appeared as a triplet that integrated to 1H and was coupled to both hydrogens of E. Theoretically, the splitting should be a doublet of doublets with equivalent J-couplings to each of the hydrogens of E. The J values for both sides of the triplet happened to be equal (J=6.87 Hz) and were equal for all seven compounds. Interestingly, these J values only match one of the vicinal J values for compounds **2b**,**c**,**g**, and for none of compounds **2a**,**d**,**e**,**f**. This was attributed to the apparent triplet being an overlap of two doublets. In support of this, Zheng and co-workers reported a doublet of doublets for hydrogen F with J values matching their respective coupling to each hydrogen of E for the unsubstituted 1-methyl-2-phenyl-2,3-dihydro-4(1H)-pyridinone (**2b**).[9] They reported collecting spectra on both a 400MHz and 600MHz Bruker NMR which, presumably, the 600MHz NMR would allow for greater resolution of hydrogen F. Lastly, the aromatic ring consisted of hydrogens H and I, 7.54 ppm and 8.21 ppm respectively, which appeared as doublets that each integrated to 2H and were coupled to each other (J=8.70 Hz) in the COSY spectrum. Assignment of the aromatic hydrogens was based on previously published literature of para substituted nitro compounds[14] and upon comparison to predicted values.[15]

Carbon assignments were made based on coupling to the affiliated hydrogens by HMQC and DEPT-135 (Table 1, Figure 7). Carbon E was the only negative peak in the DEPT and carbons A, G and J were not observed due to being quaternary. Assignments of carbons G and J were made in comparison to predicted values.[15]

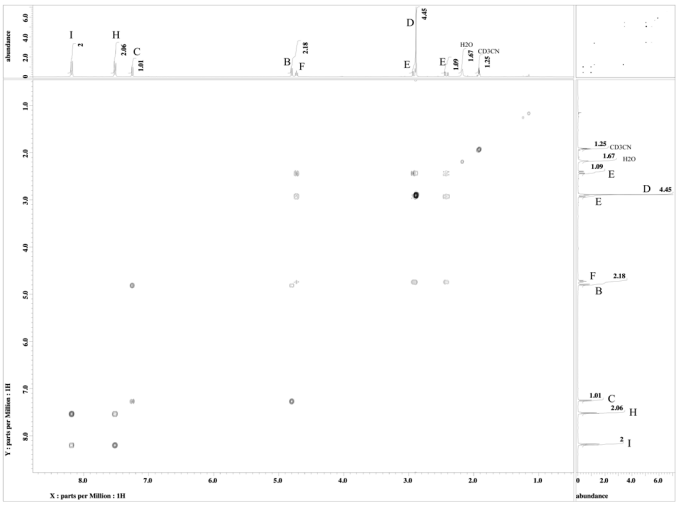

Figure 6: COSY spectrum of 2,3-dihydro-1-methyl-2-(4-nitrophenyl)-4(1H)-pyridinone (**2e**).

In conclusion, seven phenyl substituted 1-methyl-2-phenyl-2,3-dihydro-4(1H)-pyridinones were synthesized using a streamlined adaptation of Danishevsky's original procedure.[4,5] In comparison to their work utilizing zinc chloride and a reaction time of 36-48 hours, our reaction utilized boron trifluoride etherate as a Lewis acid catalyst, and a reaction time of 1 hour at 0°C for the cycloaddition.

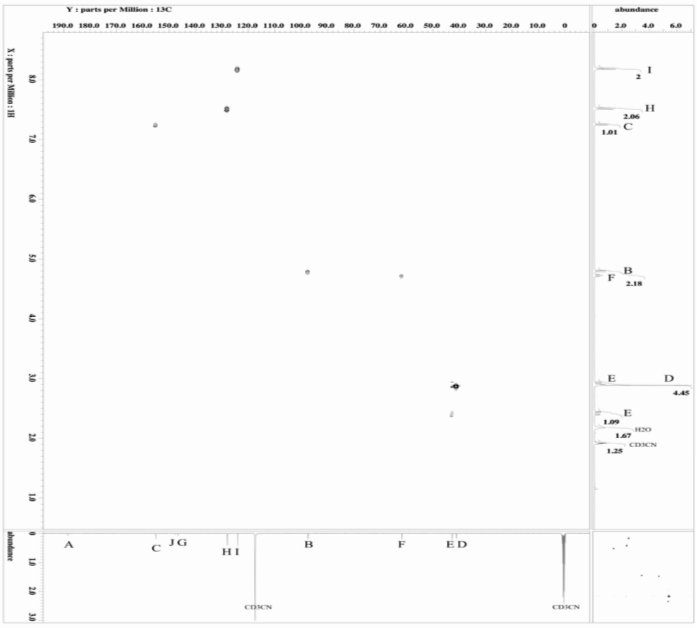

Figure 7: HMQC spectrum of 2,3-dihydro-1-methyl-2-(4-nitrophenyl)-4(1H)-pyridinone (**2e**).

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