The Behavior of 3-Anilinoenone and N-Phenyl Cinnamamide toward Carbon Nucleophiles: Spectroscopy and X-Ray Studies Reveal Interesting New Synthesis Routes to Nicotinonitriles and Tetrahydropyridine-3-Carbonitrile

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Abstract

The reactions of 3-anilinoenones with active methylene nitrile either in acid or base media were investigated. Reasonable mechanisms to account for the formation of the nicotinonitrile, ethyl nicotinate, nicotinic acid and dienamide derivatives were suggested. A one-pot multicomponent reactions (MCRs) of enaminone, aniline and either malononitrile or ethyl cyanoacetate in acid or base media afforded 1,3,5-triacycl benzene derivative. Treatment of N-phenyl cinnamamide with malononitrile in refluxing sodium ethoxide lead to tetrahydropyridine derivative. The structures of the synthesized compounds were elucidated by elemental analyses, X-ray and a variety of spectroscopic methods, including proton and carbon nuclear magnetic resonance spectroscopy (1H-NMR and 13C-NMR), correlation spectroscopy (COSY), heteronuclear single quantum coherence spectroscopy (HSQC), and mass spectrometry (MS).

Keywords: Enaminones; 3-Anilinoenones; 2-Anilinonicotinonitriles; Ethoxy nicotinate; N-Phenyl cinnamamides; Nicotinic acids; Tetrahydropyridines 1,3,5-Triacyl benzene

Introduction

The chemistry of enaminones is recognized as a significant field of study because enaminones serve as both starting materials for the synthesis of various heterocyclic compounds that have potential agrochemical use [1-10] and as intermediates in dye and pharmaceutical industries [11-15]. Due to their biological activities and pharmacological properties, pyridines and pyridones represent a significant class of compounds that have been developed using functionally substituted enaminones [16-22]. In continuation of our interest in the synthesis of functionally substituted heteroaromatic compounds such as pyridines and pyridones, utilizing enaminones as starting materials [22-33], we report here the behavior of 3-anilinoenone and N-phenyl cinnamamide toward malononitrile in the synthesis of pyridine derivatives. The 3-anilinoenone derivative 2a have been used previously, by Al-Saleh et al. [19]. They have reported that 3-anilinoenone 2a reacted with malononitrile in acetic acid afforded non isolated N-phenyl-1,2-dihydropyridine 3. In this article, it was assumed that malononitrile initially dimerizes and then condenses to a carbonyl group in 2a, followed by cyclization. The authors failed to isolate 3, until it was reacted with piperidine to afford 4 (Scheme 1). To the best of our knowledge, this was the only paper reported that discusses the reactions of 3-anilinoenone 2a with active methylene nitriles (Scheme 1).

On the other hand, Abdelrazek and Elsayed [20] have reported that the reaction of enaminones 1a-b with active methylene nitriles afforded pyridone 8 through the isolated intermediate 7. The authors proposed a synthetic pathway for the formation of 2-pyridone 8 includes 1,4-addition of active methylene in malononitrile to dimethylamino group of enaminone 1 rather than 1,2-addition to the carbonyl group (Scheme 2). These assumptions have attracted our attention and have raised doubts about whether enaminone 1 have the same behavior as 3-anilinoenone 2 toward carbon nucleophile or have different behavior. Also we would investigate whether anilino group is a good leaving group as N,N-dimethyl amino group. Therefore, we decided to investigate the reactions of a compound 2a-b with active methylene nitriles [such as i.e. malononitrile and ethyl cyanocacetate] in acetic acid and extend the studies in sodium ethoxide and ethanolic piperidine. We reported here new synthesis routes to nicotinonitriles, ethyl nicotinate, nicotinic acid, and dienamide with comprehensive spectroscopic analysis of these compounds and supplies with X-ray crystallography.

Scheme 1: Reported structures for the products of reactions of 3-anilinoenone derivative 2a with malononitrile or ethyl cyanocacetate [19].

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Experimental Section

Reagents and apparatus

All m.p values are reported uncorrected and were determined on a Gallenkamp apparatus. The Fourier Transform-Infrared (FT-IR) spectra were recorded on a FT-IR (Jasco FT/IR-6300) using a KBr disc. The 1H and 13C-NMR spectra were recorded on a Bruker DPX 400 MHz spectrometer, with DMSO-d6 or CDCl3 as solvent and tetramethylsilane (TMS) as internal standard. Chemical shifts are reported as δ unit (ppm). Mass spectra were measured on GC/MS DFS, THERMO instrument. Microanalyses were performed on a CHNS-Vario Micro Cube Analyzer (Germany), a single-crystal X-ray crystallography instrument (Rigaku, Rapid II, Japan), and a Bruker Xs Prospector (Bruker, Germany) in the Chemistry Department of Kuwait University. Compound 2 was prepared by a method reported in the literature [19].

Synthesis

6-Aryl-2-anilino-3-nicotinonitrile derivatives (9a-b): Method A:
A mixture of 2b (2.29 gm, 10.0 mmol) and aniline (0.92 gm, 10.0 mmol) in acetic acid (20 mL) was refluxed for 6 hours. The reaction mixture was allowed to cool to room temperature for 24 hours. The solid product so formed was collected by filtration and crystallized from ethanol.

Method B: A mixture of 1a-b (10.0 mmol) and aniline (0.92 gm, 10.0 mmol) in ethanol (20 mL) was refluxed 6 hours. To a stirred reaction solution, malononitrile (1.13 gm, 10.0 mmol) in acetic acid (10 mL) was added and refluxed for 6 hours. The solid product, so formed, was collected by filtration and crystallized from ethanol.

2-(phenylamino)-6-phenyl-2-yl-3-nicotinonitrile (9a): Yellow crystals: Yield: 2.03 (75%), m.p 252-253°C. FTIR: νmax/cm−1 3454(NH) and 2189(CN). 1H-NMR (DMSO-d6): δH 1.37 (t, 3H, J=8Hz, CH3), 4.44 (q, 2H, J=8Hz, OCH2), 7.18 (q, 2H, J=8Hz, CH2), 7.54 (d, 1H, J=4Hz, H-4'), 7.57 (d, 1H, J=4Hz, H-5'), 7.92 (d, 1H, J=4Hz, H-6'), 8.01 (d, 1H, J=4Hz, H-5), and 9.13 ppm (s, 1H, NH, D2O exchangeable). 13C-NMR (DMSO-d6): δC 161.6 and 153.1(C-2 and C-6), 144.0, 142.5 (C-2', C-3'), 136.4, 132.2, 129.1, 128.9, 127.8, 125.4, 121.2 (phenyl carbons), 115.6 (CN), 111.3 (C-5), and 92.7 (C-3), 62.4 ppm. MS m/z (%): [M+, 100%].

6-Aryl-2-Ethoxy-3-nicotinonitrile (15a-b): A mixture of 1b-c (10.0 mmol) and malononitrile (0.66 gm, 10.0 mmol) in sodium ethoxide (30 mL) was refluxed for 5 hours. The reaction mixture was allowed to cool to room temperature, poured into ice-cold water, and neutralized with HCl (10%). The solid product so formed was collected by filtration and crystallized from the ethanol.

2-Ethylo-6-(thiophen-2-yl)-3-nicotinonitrile (15a): Yellow crystals: Yield: 1.74 (76%), m.p 81–83°C. Lit [24] m.p 80–82°C. FTIR: νmax/cm−1 2212 cm−1 (CN). 1H-NMR (DMSO-d6): δH 1.37 (t, 3H, J=8Hz, CH3), 4.44 (q, 2H, J=8Hz, OCH2), 7.18 (q, 2H, J=4Hz, H-4), 7.54 (d, 1H, J=4Hz, H-5), 7.75 (d, 1H, J=4Hz, H-6), 8.01 ppm (d, 1H, J=4Hz, H-5), and 9.13 ppm (s, 1H, NH, D2O exchangeable). 13C-NMR (DMSO-d6): δC 162.6 (C-2), 153.4 (C-4), 144.0 (C-4'), 142.5 (C-2'), 130.9 (C-3'), 128.8 (C-4'), 128.1 (C-5'), 115.6 (CN), 111.3 (C-5), and 92.7 (C-3), 62.4 (CH3) and 14.1 (CH3) ppm. MS m/z (%) 230%M+, 100%. Anal. Calcd. for C18H13N3S: C, 66.64, H, 4.97, N, 8.63%. Found: C, 66.52, H, 4.88, N, 8.52%.

2-Ethoxy-6-(furyl)-3-nicotinonitrile (15b): Dark brown crystals: Yield: 1.56 (73%), m.p 159–160°C. Lit [24] m.p 160°C. FTIR: νmax/cm−1 2216 cm−1 (CN). 1H-NMR (DMSO-d6): δH 7.32 (t, 3H, J=4Hz, H-4'), 7.89 (d, 1H, J=4Hz, H-5'), 8.12 ppm (d, 1H, J=4Hz, H-5'), and 8.40 ppm (s, 3H, phenyl-H). 13C-NMR (DMSO-d6): δC 185.8 (3CO), 142.1 (C-2) 136.4, 132.2, 129.1 (phenyl and thiophene carbons). MS m/z (%) 408%M+, 15%. Anal. Calcd. for C16H11N3S: 408.51: C, 67.04, H, 2.96%. Found: C, 67.12, H, 3.01%.
A mixture of 1a (1.75 gm, 10.0 mmol) and aniline (0.92 gm, 10.0 mmol) in ethanol (20 ml) was refluxed for 6 hours. To a stirred reaction solution, malononitrile (0.66 gm, 10.0 mmol) in sodium ethoxide (20 ml) was added and refluxed for 6 hours. The reaction mixture was allowed to cool to room temperature, poured into ice-water and neutralized with HCl (10%). The solid product so formed was collected by filtration and crystallized from the ethanol as yellow crystals. Yield: 2.22 (77%), m.p 264-266°C. FTIR: νmax 3467, 3362 (NH and NH), 1642(CO), 2819 cm⁻¹(CN). 1H-NMR (DMSO-d6): δH 2.93 (S, 6H, 2CH₃), 5.66 (d, 1H, J=4.8 Hz, thiophene-H). 13C-NMR (DMSO-d6): δC 164.4 (CO), 157.4, 152.6, 133.2, 130.7, 129.7, 127.7 (thiophene carbons, C-3 and C-5), 118.6 (CN), 98.2(C-2), 89.3(C-4), 41.0 ppm (2CH₂). MS m/z (%): 247 [M+ 100%]. Anal. Calcd. for C₁₇H₁₄N₃O: (247.32): C, 58.28, H, 5.30, N, 14.99%. Found: C, 58.32, H, 5.41, N, 16.88%.

N-Phenyl cinnamamide (26): A mixture of aniline (0.92 gm, 10.0 mmol) and cinnamyl chloride (1.66 gm, 10.0mmol) in ethanol (20 ml) was stirred at room temperature for 2 hours. The solid product, so formed was collected by filtration and crystallized from the ethanol as white crystals. Yield: 1.73 (78%), m.p 134-136°C. FTIR: νmax 3270 (2NH) and 1661 cm⁻¹(CO). 1H-NMR (DMSO-d6): δH 6.54 (1H, d, J=16 Hz, H-3), 6.86 (1H, d, J=12 Hz, H-2), 7.06-7.73 (5H, 10H, Ar-H), 10.23 ppm (1H, NH, D₂O exchangeable). 13C-NMR (DMSO-d6): δC 167.5, 143.9, 141.0, 139.3, 134.7, 129.8, 129.0, 128.8, 128.3, 123.3, 119.2 (phenyl and alkenes carbons). MS m/z (%): 223 [M+ 100%]. Anal. Calcd. for C₁₇H₁₃NO (223.27): C, 80.69, H, 5.86, N,6.27%. Found: C, 80.55, H, 5.82, N, 6.16%.
the addition of deuterium oxide. Moreover, the chemical shifts of carbon of compound 9b were assigned using heteronuclear single quantum coherence (HSQC) (Figure 2). The $^{13}$C-NMR spectrum for 9b is characterized by two signals at d 155.0 and 153.4 ppm assigned to the C-2 and C-6, respectively. The assignments of $^1$H and $^{13}$C chemical shifts of 9b are presented in Figure 3 (cf. Experimental Section). The X-ray crystallography pictures [The CCDC files 972454 and 934259 contain the supplementary crystallographic data for compounds 9a-b in this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk] afforded an unambiguous evidence of structures 9a-b (Figures 4 and 5). It shows that the anilino group is attached to the 2- position of the pyridine ring that affords a conclusive evidence to 2-anilinopyridine structures 9. The formation of nicotinonitriles 9 from the reactions of 3-anilinoenone 2a-b with malononitrile is assumed to occur via the sequence depicted in Scheme 4. The nicotinonitrile 9 formed most likely via initial 1,4- addition of malononitrile to the activated double bond in 2, followed by the elimination of the aniline molecule under acidic conditions to give the intermediate malononitrile derivative 12. The latter then undergoes ring closure via its enolized form to yield the imidoester 13. The aniline molecules that is still present in the reaction medium is attacked to C-2 of imidoester 13 to yield the intermediate 14, which then undergoes cyclization via elimination of water to give the final nicotinonitrile derivative 9. To the best of our knowledge a rearrangement reaction of aniline group has not been reported. Elnagdi and co-workers [19] claim that enamino 1 and 3-anilinoenone 2 have the same behaviour with regard to their reaction with active methylene reagent. If this conclusion is true, we would expect the formation of the 2-$H$-pyridone derived 8 from the reaction of 1 with malononitrile, as
reported recently by Abdelrazek et al. [20]. The alternative pathway is assumed for the formation of nicotinonitrile 9 take place via the attack of aniline molecule to one of the nitrile groups in 11 to give intermediate 14, which then undergoes cyclization via elimination of water under the reaction condition to afford the final nicotinonitrile derivative 9. On the other hand, a different route has been also observed such as a one-pot two step reactions of the enaminones 1a-b with aniline in refluxing ethanol followed by treating the reaction mixture with malononitrile or with ethyl cyanoacetate in acetic acid to give 9a-b and 9c respectively in good yield (Scheme 3). The analytical and spectral data of the latter reaction products are all consistent with the proposed structure. The X-ray crystallography afforded an unambiguous evidence of structure 9c (Figures 6). [The CCDC file 972453 contains the supplementary crystallographic data for compounds 9c in this report. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk]. The X-ray of the compound 9c (Scheme 3) shows that anilino group attached to carbon-2 of pyridine. This result is in contrast to what Elmagdi et al. [19] has been reported for the formation of 6 (Scheme 1).

The 2-anilinonicotinate 9c has represented further evidence for the suggested mechanism aforementioned. It is apparent that ethyl cyanoacetate followed the same sequence of reaction mechanism as reaction 3-anilinoenone with malononitrile in acetic acid to afford 2-anilinonicotinate through non isolated intermediates 11-14 (Scheme 4).

On the other hand, one-pot method involving multicomponent reactions (MCRS) of enaminone 1b, aniline with either malononitrile or ethyl cyanoacetate in refluxing acetic acid or ethanolic piperidine, gave the 1,3,5-triacyl benzene derivatives 19 [36] in good yield (Scheme 3). The mass spectrum revealed a molecular ion peak [M+], with m/z=408, which corresponds to a molecular weight consistent with a formula of C21H12O4S3. The structure of tri-thiophen-2-y benzene derivative 10 was unambiguously confirmed by X-ray crystallography as 1,3,5,-tri-[(thiophen-2-yl)methanoyl]benzene 10 (Figure 7). The CCDC file 959796 contains the supplementary crystallographic data for compound 10 in this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk.

When enaminones 1b-c was allowed to react with malononitrile in refluxing sodium ethoxide for 6 hours, 2-ethoxy nicotinonitrile derivatives 15 a-b was afforded (Scheme 5). The mass spectra of these compounds revealed a molecular ion peak (M+) with a m/z value of 230 and 214 respectively. These masses are compatible with the molecular ion peak (M+) for C12H10N2SO and C12H10N2O2 respectively as described previously [24]. The complete assignment of 1H and 13C chemical shift for 15a are presented in Figure 8. The 1H-NMR spectrum of 15a revealed two doublets at δH 8.12 and 7.54, respectively, with a J value of 8 Hz that could be attributed to the pyridine protons H-4 and H-5, respectively. In addition, thiophene protons and a signal for ethoxy protons at d 1.37
and 4.44 ppm ($\delta = 8$ Hz) were characterized as a triplet and a quartet for methyl and methylene protons, respectively. The $^{13}$C-NMR chemical shift assignments for 15a were assigned using HSQC measurement (Figure 10). The $^{13}$C-NMR spectrum for 15a showed two downfield signals at $\delta_c 162.6$ and 153.4 ppm assignable to C-2 and C-6 respectively. The structure of compound 15a was unambiguously confirmed by X-ray crystallography as 2-ethoxy-6-(thiophen-2-yl) nicotinonitrile 15a (Figure 11). (The CCDC file 934259 contains the supplementary crystallographic data for compound 15 in this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk). The structure of the isolated product 15 from the reaction of enaminone 1b with malononitrile in basic medium is assumed to take place via the sequence described in Scheme 6. The active methylene group of malononitrile undergoes addition to the double bond of 1b to generate the intermediate 19, under this condition we expected that ethoxide ion will attack one of the nitrile groups in 20 to give the imidoester 21, which then undergoes cyclization via elimination of water under acidic media to afford the final nicotinonitrile derivative 15.

Furthermore, a one-pot, three-step synthesis of 2,4-dienamide derivative 16 has been achieved by allowing enaminones 1a-b to

Figure 8: Complete assignment of $^1$H and $^{13}$C chemical shifts of 2-ethoxy nicotinonitrile derivative 6 based on COSY and HSQC experiments.
reacted with aniline in refluxing ethanol, followed by treatment the reaction mixture with malononitrile in sodium ethoxide and then neutralized with HCl at room temperature. However, the mass spectra of obtained product revealed a molecular ion peak (M⁺) with m/z 289 and was compatible with the molecular formula C₁₈H₁₅N₃O. The X-rays crystallographic picture (the CCDC file 972452 contains the supplementary crystallographic data for compound 16 in this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk) afforded an unambiguous evidence of structure 16. It shows that anilino group attached to the same carbon atom (C-5) which carrying the phenol group and the terminus carrying the cyano and the amide group on (C-2) as shown in Figure 12 and Scheme 5.

The formation of 2,4-dienamide derivative 16 from the reaction of 2a with malononitrile in sodium ethoxide as catalyst is assumed to occur via the sequence depicted in Scheme 6. The active methylene group of malononitrile undergoes via initial 1,4- addition activated double bond in 2b to give intermediate 22. The base removes a proton from α-carbon followed by the elimination of the aniline molecule to afford the intermediate malononitrile derivative 22. The latter then undergoes ring closure via its enolized form to yield the imidoester 23. The aniline molecule that is still present in the reaction medium is attacked to C-6 of iminopyran 24 and undergoes ring opening to afford the isolated 2,4-dienamide derivative 16. Conversions of 16 into nicotinic acid derivatives 17 were achieved by boiling in EtOH/ HCl 17, via elimination of anilino group.

Interesting, when the enaminoles 1a-b allowed to react with aniline in refluxing ethanol, followed by treatment the reaction mixture with malononitrile in ethanolic piperidine instead of sodium ethoxide, in one pot reactions, unexpected product with formula of C₁₄H₁₅N₃O and C₁₂H₁₃N₃OS was produced (Scheme 5). The X-ray crystallographic

![Figure 9: COSY spectrum of 2-ethoxy nicotinonitrile derivative 6.](image)

![Figure 10: HSQC spectrum of 2-ethoxy nicotinonitrile derivative 6.](image)

![Figure 11: Perspective view and atom labeling of X-ray structure of 2-ethoxy nicotinonitrile derivative 6.](image)

![Figure 12: Perspective view and atom labeling of X-ray structure of compound 16.](image)
protons confirmation of methylene protons at position 5 will not in the same environment. These germinal pairs, H-5a, H-5b, and H-4 are resonating at 2.68, 3.10, and 3.94 ppm. Each signal appears as a doublet of doublets with coupling constant $\gamma_{5a,5b}=16\text{Hz}, \gamma_{5b,4}=6.8\text{Hz}$, $\gamma_{5a,4}=5.2\text{Hz}$, the germinal protons have largest coupling constant. Moreover, the chemicals of the carbons for compound 32 were assigned using HSQC measurement. The $^{13}$C NMR spectrum for 32 is revealed a low field signal at δC 170.1 ppm corresponding to carbonyl carbon. While the high field signals at 6.39 and 37.6 ppm corresponding to methylene and methine carbons respectively. The X-rays crystallographic picture (the CCDC file 9724451 contains the supplementary crystallographic data for compound 32 in this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk).

It is believed that 18 is produced via mechanistic route displayed in Scheme 6, involving intermediates 22-23, by changing the solvent in the second step from sodium ethoxide to ethanolic piperidine solvent change encourage the N,N-dimethyl amine molecule to be much faster than an aniline molecule (which they are still present in the reaction medium) to attack to C-2 of imidoester 24 and undergoes ring opening to afford the isolable compound 18.

On the other hand, treatment at room temperature of cinnamoyl chloride with aniline in ethanol afforded the corresponding the N-phenyl cinnamide 26. The structure of the product 26 was confirmed on the basis of elemental analysis and spectral data. The compound 26 reacts with malononitrile in refluxing ethanolic sodium ethoxide afforded the tetrahydropyrididine-3-carbonitrile derivative 32 in good yield (Scheme 7). The mass spectrum of the reaction product revealed a molecular ion peak [M$^+$], with m/z 289 which corresponds to a molecular weight consistent with a formula of $\text{C}_{36}\text{H}_{35}\text{N}_3\text{O}$. The IR spectrum of 32 shows the two NH, nitrile and carbonyl amide absorption bands in the region of $\nu_{\text{max}}$ 3214, 2189 and 1642 cm$^{-1}$ respectively. The chemical shift of protons for 32 were assigned using the COSY (correlation spectroscopy) measurement which provided the

**Scheme 6:** Proposed pathways for formation of each 2-ethoxy nicotinonitrile, 2,4-dienamides and 2-nicotinic acid derivatives in sodium ethoxide solution.

**Scheme 7:** Proposed pathway for formation of tetrahydropyridine 32.
5. spectral and analytical data (Project GS01/01, GS03/08, GS01/03). Also we have suggested a reasonable mechanism that explains the behavior structures. The structures of the synthesized compounds were either acetic acid, or ethanolic piperidine solution for 2-5 hours failed. An attempt to react compound 26 with malononitrile in refluxing either acetic acid, or ethanolic piperidine solution for 2-5 hours failed.

An attempt to react compound 26 with malononitrile in refluxing either acetic acid, or ethanolic piperidine solution for 2-5 hours failed.

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**References**


