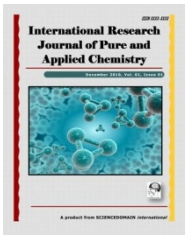

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Studies with Biologically Active Enaminones: an Easy Method for Structural Elucidation of Products Produced from Enaminone Starting Materials through Pathways Employing Microwave Irradiation

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ABSTRACT

Reactions of enaminones 3a-f with malononitrile under microwave irradiation conditions were found to afford cyano-substituted aminodienamides 8a-f, whose structures were elucidated using both X-Ray crystallographic analysis and NOE methods. In addition, cyclization of 8e to form pyridone 10 takes place upon treatment with a mixture of acetic acid and hydrochloric acid. Coupling enaminone 3e with benzenediazonium chloride affords hydrazone 12, which reacts with cyanoacetamide to produce pyridazinone 17. Finally, the biological activity of the prepared compounds against gram positive bacteria, gram negative bacteria and yeast were evaluated.

Keywords: Dienamides; X-ray crystal structure determination; microwave irradiation; pyridines; NOE difference experiment; pyridazines.

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1. INTRODUCTION

β-Enaminones are polydentate reagents that have wide utility in synthetic organic chemistry (Al-Etaibi et al., 2012a, 2012b, 2011; Bezensek et al., 2010; Al-Mousawi et al., 2010; Loghmani-Khouzani et al., 2008; Rosa et al., 2008; Riyadh et al., 2008; Al-Saleh et al., 2005; Al-Omran et al., 1997). Enaminones have been employed in the preparation of various biologically active compounds (Shawali, 2010; Kantevari et al., 2007), as well as dye intermediates (Simunek and Machacek, 2010; Shams et al., 2011; Simunek et al., 2007; Kascheres et al., 2003). Studies have shown that microwave irradiation is a beneficial method to promote diverse organic transformations that occur in remarkably reduced reaction times and improved yields. In previous work, we have described the utility of *β*-enaminones as precursors to polyfunctional aromatic compounds (Al-Awadi et al., 2008, 2001). In one effort, we observed that condensation reaction of enaminone 3 with malononitrile affords the dicyanoaminoketone 5 that undergoes ready cyclization to generate a substance originally thought to be pyran 6. A systematic study including X-Ray crystallographic analysis of the product led to the unambiguous conclusion that the product actually produced in the reaction of 3 with 5 is the aminodienamide 8 (Scheme 1). Subsequently Abdelrazek (Abdelrazek et al., 2009) and Gorobets (Gorobets et al., 2009) have confirmed this conclusion. A mechanism for this transformation, including an unexpected and unprecedented rearrangement was proposed for this reaction (Abdel Khalik et al., 2009; Al-Matar et al., 2010). In the course of more recent studies, it occurred to us that the structures of products arising from reactions of derivatives of 3 (for example 3a-f) with malononitrile would need to be confirmed by using X-Ray crystallographic methods. In the effort described below, we have explored reactions of a variety of enaminones 3a-f with malononitrile, which generate products whose structures have been established using both this analytical method along with NOE difference experiment as an easy method for structural elucidation. In addition, we have probed the utility of the enaminones in the synthesis of pyridones, arylhydrazonals and pyridazinones.

2. MATERIALS AND METHODS

Melting points were recorded on a Gallenkamp apparatus. IR spectra were recorded using KBr pellets on a JASCO FTIR-6300 FT-IR spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were recorded on Bruker DPX 400 MHz or AvanceII 600 MHz super-conducting NMR spectrometers with proton spectra measured at 400, 600 MHz and carbon spectra at 100 and 150 MHz, respectively. Mass spectra were measured on a high resolution GC/MS DFS-Thermo. Microanalyses were performed on Elementar-Vario Micro cube Analyzer. X-Ray analyses were performed using a Rigaku Rapid II diffractometer. All reactions were conducted under microwave irradiation conditions in heavy-walled Pyrex tubes (capacity 10mL). Microwave heating was carried out with a single mode cavity Explorer Microwave Synthesizer (CEM Corporation, NC, USA), producing continuous irradiation and equipped with simultaneous external air-cooling system at maximum power, temperature and pressure 300W, 300ºC and 300 bsi, respectively. Compounds 3a-e, 8a and 8f were prepared according to the published procedures (El-Apasery et al., 2011).

Agar-well diffusion techniques (Isaacson and Kirschbaum, 1986) were used to investigate the antimicrobial activities of the prepared compounds against six different microbial cultures. Pure cultures of *Bacillus subtilus* and *Staphylococcus auerus* (Gram positive bacteria), *Escherichia coli* and *Serratia sp.* (Gram negative bacteria) and *Candida albicans* and *Saccharomyces cerevisiae* (Yeast) were used. An aliquot of 0.1 ml of each bacterial

strain was inoculated and spread on nutrient agar (NA) while 0.1 ml of the yeast was spread on potato dextrose agar (PDA). The inoculated plates were supplied with 100 µl of each of the tested compounds with a total final concentration of 1mg ml^{-1}. In addition negative control was added which included 100 µl DMSO. Also positive references for chemicals with antimicrobial activities against prokaryotes and eukaryotes were used. 100 mg of Penicillin (Sigma, USA) and cycloheximide (Sigma, USA) were used as positive references in the work. The compounds were included in 4 mm wells produced by sterile cork borer. The NA plates were incubated at 37ºC for 24 hours while PDA plates were incubated at 25ºC for 48 hours. The zones of inhibition around the wells were determined and the averages based on triplicate measurements were recorded.

2.1 2-(4-Dimethylamino-2-oxo-but-3-enyl) isoindole-1, 3-dione 3f

A mixtures of phthalimidoacetone 1f (0.01 mol) and DMFDMA (1.19 g, 0.01 mol) was irradiated by focused microwave at 180ºC for 20 min. Completion of the reactions was monitored by TLC. The build-up of pressure in the closed reaction vessel was carefully monitored. After the irradiation, the reaction tube was cooled with high-pressure air through an inbuilt system in the instrument until the temperature had fallen below 50ºC. The reaction mixture left to cool to room temperature and then treated with petroleum ether. The solid product, so formed, was collected by filtration and crystallized from a mixture of ethanol:dioxane (3:1) to afford compounds 3f as white crystals; yield: 42%; m.p. 162ºC (Lit. 159-162ºC[27]); Anal. Calcd. for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 65.18; H, 5.44; N, 10.76; IR, 1768, 1715, 1659 (CO). ^{1}H NMR (600 MHz, DMSO-d6): 2.71 (s, 3H, CH_3), 3.01 (s, 3H, CH_3), 4.31 (s, 2H, CH_2), 4.96 (d, 1H, J = 12.0, CH), 7.53 (d, 1H, J = 13.2, CH), 7.79 (d, 4H, J = 12.0 Hz, phthalimidyl-H); ^{13}C NMR (DMSO-d6): δ = 206.4 (CO), 186.3 (CO), 167.7, 134.5, 131.7, 123.1, 79.1, 54.8 (CH_2), 30.6 ($N(CH_3)_2$); MS: m/z (%) 258 (M^+, 24), 160 (25), 98 (100), 76 (12), 69 (22), 55 (29).

2.2 General Procedure for the Preparation of Compounds 8a-f

Mixtures of equimolecular amounts of each of the enaminones 3a-f (0.01 mol) and malononitrile (0.01 mol, 0.66 g) in ethanol (1 mL) and few drops of piperidine were irradiated by using a focused microwave at 150ºC for 5 min. The build-up of pressure in the closed reaction vessel was carefully monitored. After the irradiation, each reaction tube was cooled with high-pressure air through an inbuilt system in the instrument until the temperature had fallen to below 50ºC. The precipitated product was collected by filtration and crystallized from dioxane.

2.2.1 2-Cyano-5-dimethylamino-5-furan-2-yl-penta-2,4-dienoic acid amide 8b

This compound was obtained as brownish red crystals, yield (77%); mp 247ºC (Lit. mp 245-246ºC (Abdelkhalik et al., 2009)); IR: 3405 and 3330 (NH_2), 2189 (CN) and 1641 (CO); MS m/z $(M)^+$ = 231.1; ^{1}H NMR (DMSO-d_6): δ = 2.93 (s, 6H, $N(CH_3)_2$), 5.59 (d, 1H, J = 12.6 Hz, H-4), 6.71 (s, 1H, furyl H-3), 6.77 (d, 1H, J = 3.0 Hz, furyl H-5), 7.00 (s, 2H, NH_2), 7.53 (d, 1H, J = 12.6 Hz, H-3), 7.97 (s, 1H, furyl H-4); ^{13}C NMR (DMSO-d6): δ = 164.5 ($CONH_2$), 153.4 (C-5), 151.7, 145.3, 144.7, 118.4, 115.8, 111.5, 98.2, 90.4, 40.7 ($N(CH_3)_2$); Anal. calcd. for $C_{12}H_{13}N_3O_2$: (231.10): C, 62.33; H, 5.67; N, 18.17. Found: C, 61.20; H, 5.74; N, 18.02.

2.2.2 2-Cyano-5-dimethylamino-5-thiophen-2-yl-penta-2,4-dienoic acid amide 8c

This compound was obtained as yellow crystals, yield (72); mp 260ºC (Lit. mp 258-259ºC (Abdelkhalik et al., 2009)); IR: 3405 and 3329 (NH_2), 2195 (CN) and 1669 (CO); MS m/z $(M)^+$ = 247.1; ^{1}H NMR (DMSO-d6): δ = 3.00 (s, 6H, $N(CH_3)_2$), 5.66 (d, 1H, J = 13.2 Hz, H-4), 6.94 (s, 2H, NH_2), 7.18 (d, 1H, J = 3.6 Hz, thienyl H-3), 7.22 (t, 1H, J = 6.0 Hz, thienyl H-4), 7.37 (d, 1H, J = 12.6 Hz, H-3), 7.88 (d, 1H, J = 5.4 Hz, thienyl H-5); ^{13}C NMR (DMSO-d6): δ = 164.3 ($CONH_2$), 157.4 (C-5), 152.5 (C-3), 133.1, 130.7, 129.7, 127.6, 118.5 (CN), 98.7 (C-4), 89.4 (C-2), 40.0 ($N(CH_3)_2$).

2.2.3 2-Cyano-5-dimethylamino-5-phenylpenta-2,4-dienoic acid amide 8d

This compound was obtained as yellow crystals, yield (74%); mp 259ºC (Lit. mp 257-258ºC (Abdelkhalik et al., 2009)); IR: 3435 and 3334 (NH_2), 2195 (CN) and 1666 (CO); MS m/z $(M)^+$ = 241; ^{1}H NMR (DMSO-d6): δ = 2.77 (s, 3H, NCH_3), 3.15 (s, 3H, NCH_3), 5.63 (d, 1H, J = 12.6 Hz, H-4), 6.80 (s, 2H, NH_2), 7.12 (d, 1H, J = 12.6 Hz, H-3), 7.26 (s, 2H, phenyl-H), 7.53 (s, 3H, phenyl-H); ^{13}C NMR (DMSO-d6): δ = 165.0 ($CONH_2$), 164.6 (C-5), 153.2 (C-3), 133.8, 129.5, 128.8, 128.7, 118.8, 96.7, 87.5, 40.2 ($N(CH_3)_2$); Anal. calcd. for $C_{14}H_{15}N_3O$: (241.12): C, 69.69; H, 6.27; N, 17.41. Found: C, 69.59; H, 6.57; N, 17.26.

2.2.4 5-(4-Chlorophenyl)-2-cyano-5-dimethylamino-penta-2,4-dienoic acid amide 8e

This compound was obtained as orange crystals, yield (82%); mp 250ºC ; IR: 3475 and 3348 (NH_2), 2185 (CN) and 1653 (CO); MS m/z $(M)^+$ = 275.1; ^{1}H NMR (DMSO-d6): δ = 2.78 (s, 3H, NCH_3), 3.12 (s, 3H, NCH_3), 5.61 (d, 1H, J = 12.6 Hz, H-4), 6.85 (s, 2H, NH_2), 7.07 (d, 1H, J = 13.2 Hz, H-3), 7.29 (d, 2H, J = 8.4 Hz, arom-H), 7.59 (d, 2H, J = 8.4 Hz, arom-H); ^{13}C NMR (DMSO-d6): δ = 164.5 ($CONH_2$), 163.6 (C-5), 152.6 (C-3), 134.3, 132.6, 130.7, 128.9, 118.7, 96.8, 88.3, 39.9 ($N(CH_3)_2$); Anal. calcd. for $C_{14}H_{14}ClN_3O$: (275.73): C, 60.98; H, 5.12; N, 15.24. Found: C, 60.66; H, 5.39; N, 14.96.

2.3 6-(4-Chloro-phenyl)-2-oxo-1,2-dihydro-pyridine-3-carbonitrile 10

A mixture of compound 8e (10 mmol), AcOH (6 mL) and conc. HCl (2 mL) was irradiated by using a focused microwave at 120ºC for 5 min (progress of reaction was monitored by TLC). Upon cooling to room temperature a solid precipitate formed and was collected by filtration and crystallized from EtOH to give white crystals, yield (72%); mp 343-345ºC (Lit. mp 344ºC (Liebscher, and Hartmann, 1976)); Anal. calcd. for $C_{12}H_7ClN_2O$: (230.65): C, 62.49; H, 3.06; N, 12.15. Found: C, 62.05; H, 3.32; N, 12.06; IR, 3410 (NH), 2223 (CN) and 1665 (CO), 1H NMR: δ = 6.82 (s, 1H, pyridyl-H), 7.59 (d, 2H, J = 8.4 Hz, arom-H), 7.83 (d, 2H, J = 8.4 Hz, arom-H), 8.20 (d, 1H, J = 7.6 Hz, pyridyl H-4), 12.81 (s, 1H, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d6): δ = 161.4 (CO), 152.0, 148.3, 136.0, 131.4, 129.4, 129.0, 116.6, 105.3, 100.6. MS: m/z (%) 230 (M+, 100), 202 (27), 167 (5), 140 (17), 111 (5), 64 (7).

2.4 3-(4-Chlorophenyl)-3-oxo-2-(phenylhydrazono)-propionaldehyde 12

A cold solution of the diazonium salt (10 mmol) (prepared by adding a cold solution of sodium nitrite (0.7 g) in water (5 mL) to a solution of the aniline (10 mmol) in conc. HCl (5 mL) was added to a cold solution of enaminone 3e (10 mmol) in EtOH (10 mL) containing NaOH (1.6 g). The mixture was stirred at room temperature for 1 h, and the solid precipitate that formed was collected by filtration and crystallized from EtOH to give yellow crystals;

yield (74%); mp 136-137ºC (Lit. mp 135-137ºC (Al-Awadi et al., 2001)); Anal. Calcd For $C_{15}H_{11}ClN_2O_2$:(286.71), C, 62.84; H, 3.87; N, 9.77. Found: C, 62.74, H, 4.81, N, 9.76; IR: 3431, (NH), 1646, 1635 (CO); ^{1}H NMR (DMSO-d6): δ = 7.22 (t, 1H, J = 6.8 Hz, arom-H), 7.40-7.48 (m, 4H, arom-H), 7.61 (d, 2H, J = 8.4 Hz, arom-H), 7.89 (d, 2H, J = 8.0 Hz, arom-H), 10.00 (s, 1H, CHO, D_2O exchangeable), 14.24 (s, 1H, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d6): δ = 190.0 (CHO), 189.7 (CO), 188.0, 141.4, 136.9, 135.7, 131.8, 129.6, 128.1, 126.1, 116.7. MS: m/z (%) 286.1 (M^+, 89), 257 (10), 166 (92), 139 (97), 111 (95), 93 (100), 77 (84), 65 (82).

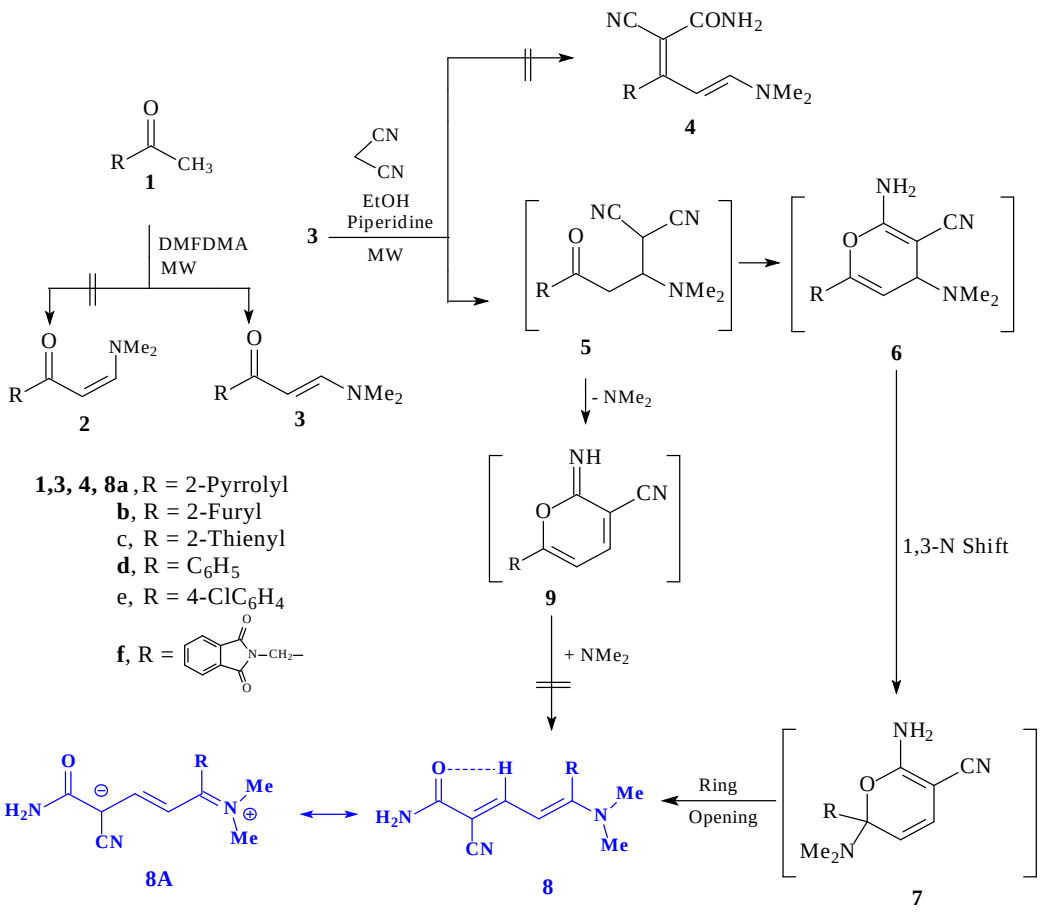
2.5 6-(4-Chlorobenzoyl)-3-oxo-2-phenyl-2,3-dihydropyridazine-4-carboxylic acid amide 17

A mixture of 12 (0.01 mol), cyanoacetamide (0.01 mol) and ammonium acetate (1 g) in acetic acid (1 mL) was irradiated by using a focused microwave at 120ºC for 5 min (reaction progress was monitored by using TLC using 1:1 ethyl acetate: petroleum ether). The mixture was cooled and then poured onto ice-water. The sold that formed was collected by filtration and crystallized from EtOH to give buff crystals, yield (70%); mp 211-213ºC; Anal. calcd. for $C_{18}H_{12}ClN_3O_3$:(353.76), C, 61.11; H, 3.42; N, 11.88. Found: C, 61.52; H, 3.42; N, 11.80; IR: 3347, 3164 (NH_2), 1701, 1667(CO); ^{1}H NMR (DMSO-d6): δ = 7.47-7.56 (m, 3H, arom-H), 7.60-7.65 (m, 4H, arom-H), 7.61 (d, 2H, J = 8.4 Hz, arom-H), 8.22 (brs, 1H, NH, D_2O exchangeable), 8.54 (brs, 1H, NH, D_2O exchangeable), 8.57 (s, 1H, pyridazinyl-H); ^{13}C NMR (DMSO-d6): δ = 187.8 (CO), 162.0, 159.5, 142.2, 141.0, 138.4, 133.7, 132.3, 130.9, 129.1, 129.0, 128.8, 126.0, 117.4. MS: m/z (%) 353 (M^+, 100), 318 (7), 248 (5), 214 (23), 167 (6), 139 (75), 111 (36), 91 (5), 77 (37).

3. RESULTS AND DISCUSSION

Enaminones 3a-e were synthesized in moderate yields by condensation reactions of methylketones 1a-e with dimethylformamide dimethyl acetal (DMFDMA) in xylene (Tseng et al., 1987). It is noteworthy that enaminone 3f was reported earlier to be formed as the cis-isomer, characterized by analysis of olefinic proton coupling constants (Al-Omran et al., 2005). In an independent investigation, Al-Mousawi (Al-Mousawi et al., 2011; 2010; 2008) suggested the trans form is actually produced a proposal that is confirmed unambiguously by the X-ray crystallographic data provided below (Figs. 1 and 2) (CCDC, 2011).

Conditions for the efficient synthesis of enaminones from methylketones and DMFDMA involving microwave irradiation have been reported earlier by us and more recently by Bezensek (Bezensek et al., 2010). In addition, the results of a recent investigation have shown that heating the neat reactants in ionic liquids affords enaminones 3a,d (Martins et al., 2008) (cf. Scheme 1). Based on these earlier findings, an improved approach to the preparation of enaminones 3a-e was found to involve the use of condensation reactions of the methylketones with DMFDMA in absence of solvent in a focused microwave oven at 120-180ºC for 5-20 min. In these “green” processes, 3a-f was produced in much shorter time frames and higher yields.



Scheme 1. Synthesis of enaminones and dienoic acid amides

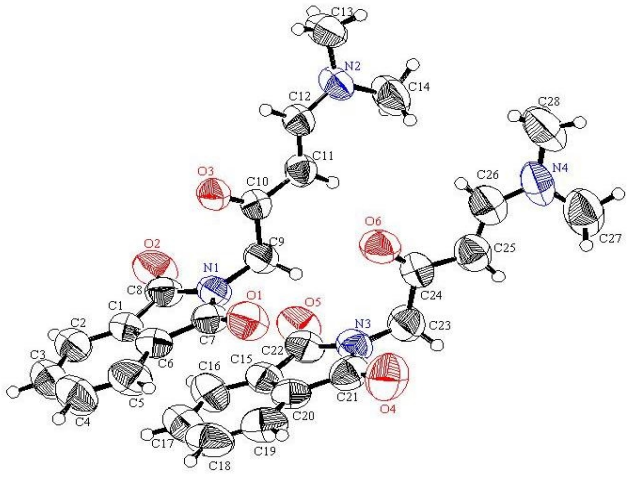


Fig. 1. ORTEP drawing of 3f

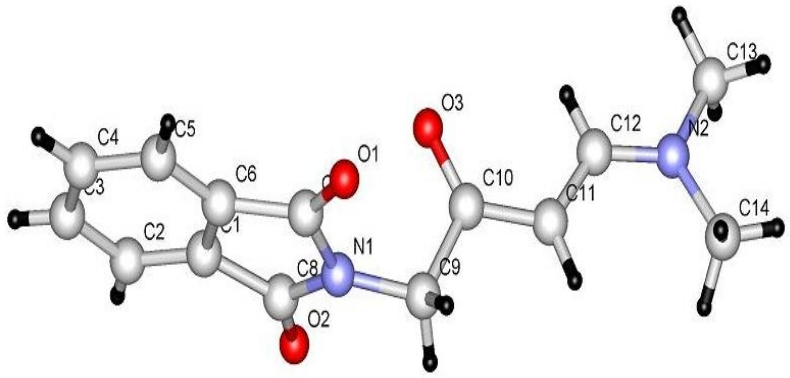


Fig. 2. Ball and stick drawing of 3f

Reactions of enaminones 3a-f with malononitrile using a focused microwave oven gave products whose analytical and spectroscopic properties are consistent with dienamides 8a-f as well as their isomeric counter parts 4a-f. NOE difference experiments were carried out in order could to demonstrate that the products actually have the structures and stereochemistry represented by 8a-f. Thus irradiation dimethylamino-protons in 8a-f, which resonate respectively at 3.00, 3.00, 3.02, 3.15, 3.13 and 3.00 ppm led to enhancements of the H-4 olefinic proton signals at 5.55, 5.61, 5.66, 5.65, 5.61 and 5.44 ppm, respectively. Furthermore, irradiating olefinic protons H-4 5.55, 5.61, 5.66, 5.65, 5.63 and 5.44 ppm leads to enhancement of the dimethylamino proton signals at 3.00, 2.96, 3.00, 3.15, 3.13 and 3.01 ppm, respectively.

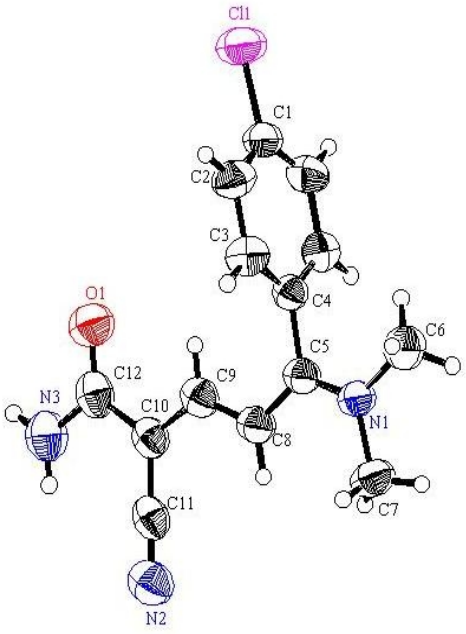
Further support for assignment of the products as dienamides 8 rather than 4 came from the finding that irradiation of the NH and CH_2 protons at 11.38 and 4.79 ppm cause enhancements in the signals for the H-3 olefinic protons H-3 at 7.04 and 8.22 ppm.

Finally, the X-ray crystallographic structure of 8e was obtained, which together with the X-ray structures of 8a and 8b determined earlier (El-Apasery et al., 2011; Al-Mousawi et al., 2009), provided unambiguous support for these assignments (Fig. 3 and 4) (CCDC, 2012).

In the processes leading to 8, it appears that malononitrile undergoes initial 1,4-addition to the unsaturated ketone function in 3 to yield adduct 5 that cyclizes to form aminopyran 6. Rearrangement of 6 then takes place via a 1,3-shift of the dimethylamino-moiety to form intermediate 7 followed by electrocyclic ring opening to generate 8 (cf. Scheme 1). Although seemingly less likely, the possibility that elimination of dimethylamino-moiety in 5 occurs to produce the pyran-imine 9 which then re-adds dimethylamine cannot be ruled out as the pathway responsible for formation of 8 (Abdelrazek and Elsayed, 2009).

The selected bond lengths and angles, given in Table 1, reveal existence hydrogen bond between proton H-9 and amid carbonyl carbon as they are at 2.428 Å apart. Moreover evidence for existence of π-π overlap interaction between C10-C9, C9-C8, and C8-C5 as these bonds are of almost the same length 1.39 Å, suggesting existence of extensive resonance delocalization. Moreover N-1 showed bond angles 121.4 typical for SP^2 nitrogen as would be the case for imine ion. Perhaps resonance delocalization of electrons is deriving

force for formation of the end product as it is thermodynamically more stable than any intermediates on its way of formation.



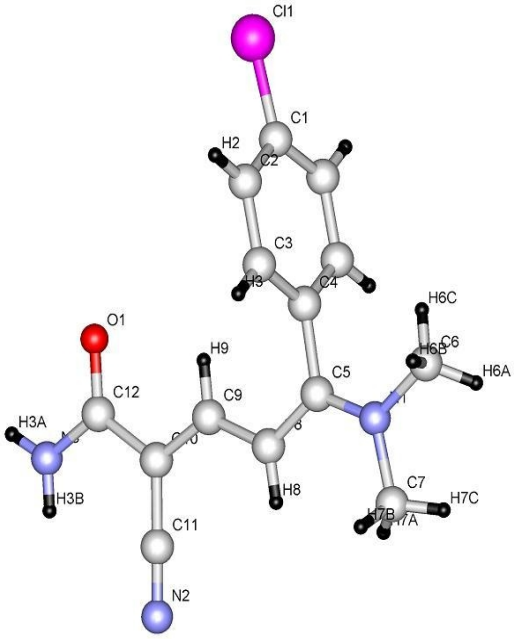


Fig. 3. ORTEP drawing of 8e.

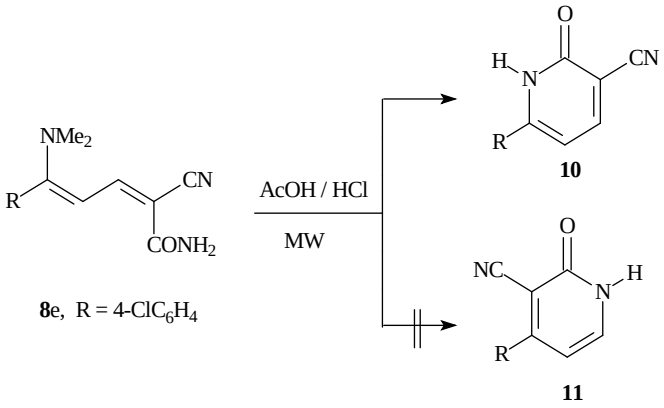
Fig. 4. Ball and stick drawing of 8e

Table 1. Selected bond lengths and angles data for 8e

Bond	Bond lengths (Å)	Bond	Bond angles (°)
O1-H9	2.428	C5-N1-C7	121.4(4)
O1-H3A	2.428	N1-C5-C8	124.2(4)
O1-C12	1.229(6)	C4-C5-C8	118.9(3)
N1-C5	1.330(5)	C8-C9-C10	128.6(4)
N1-C7	1.448(5)	C5-C8-C9	121.6(4)
N1-C6	1.454(5)	C9-C10-C12	117.9(4)
C5-C8	1.391(5)	C11-C10-C12	120.4(4)
C8-C9	1.392(6)	O1-C12-C10	123.4(5)
C9-C10	1.369(6)		
C10-C12	1.476(7)		

Our studies next turned to an exploration of the chemistry of dienamides 8a-f, prepared in the manner described above. We observed that amino-dienamide 8e can be converted to the previously prepared pyridone 10 (Liebscher and Hartmann, 1976) by heating in a focused microwave oven at 120ºC for 5 min in the presence of a 3:1 mixture of acetic acid and hydrochloric acid (cf. Scheme 2). This is a straightforward and simple procedure for the preparation of 2-oxo-1,2-dihydro-pyridine-3-carbonitrile which is useful as start material for many biologically active compounds such as nonpeptidic inhibitors of human leukocyte elastase (HLE) (Damewood et al., 1994; Bernstein et al., 1992) and as azo disperse dyes for synthetic fibers (Okada et al., 2009a, 2009b, 2008; Gadre et al., 2006).

Based on the reactivity profile of the enaminones with malononitrile, we next investigated the coupling reaction of enaminone 3e with benzenediazonium chloride. This process afforded hydrazone 12, which is analogous to substances that have been previously shown to exist in the solid state in both *syn* and *anti*-forms (Al-Awadi et al., 2001). X-ray crystallographic analysis demonstrated that the product of this process has the structure represented by 12 and confirmed that in the solid state it exists in the *anti* rather than *syn*-form (Figs. 5 and 6) (CCDC, 2011). Evidence for hydrogen bond between proton H-2A and aldehyde carbonyl group O-2 can be seen from (Fig. 4) as they are at length 2.017 Å apart.



Scheme 2. Synthesis of pyridones 10

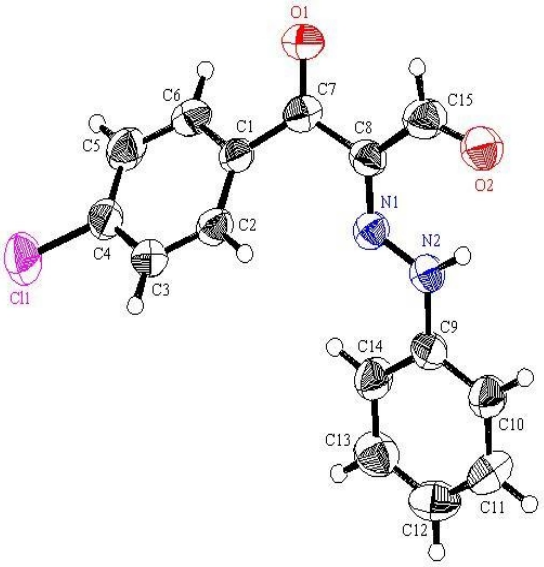


Fig. 5. ORTEP drawing of 12

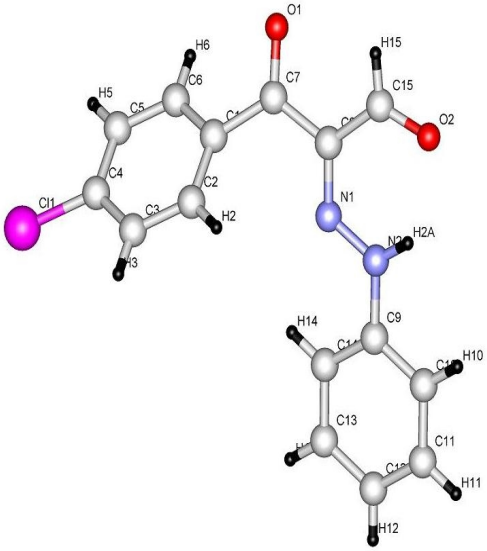
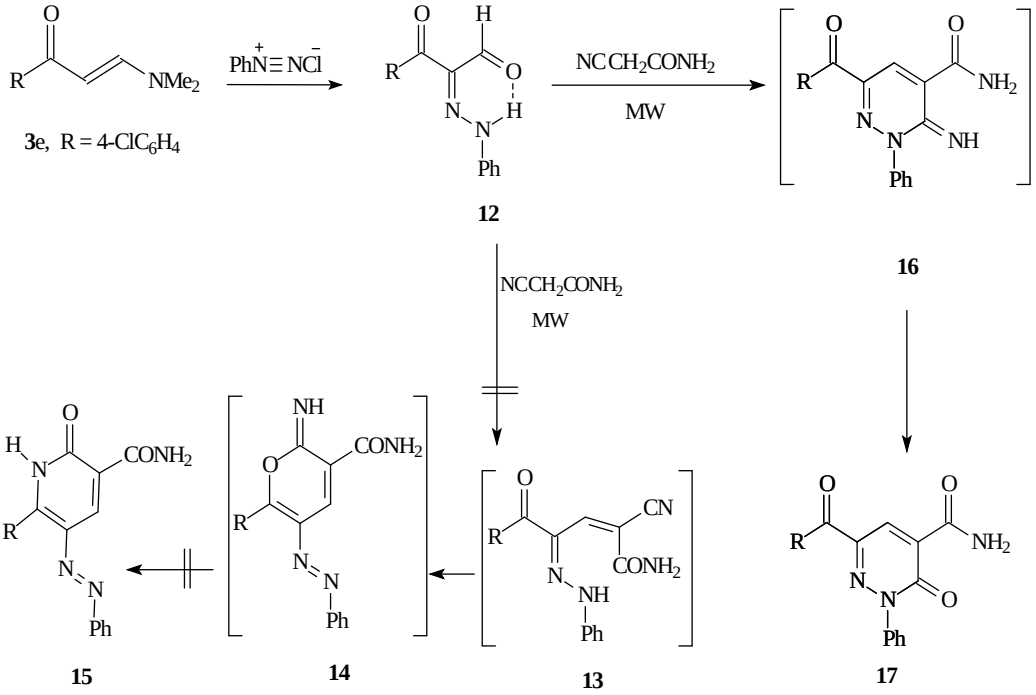


Fig. 6. Ball and stick drawing of 12

In addition, we observed that condensation of the hydrazonoketone 12 with cyanoacetamide afforded pyridazinone 17 by heating in a focused microwave oven at 120ºC for 5 min in the presence of ammonium acetate and a few drops of acetic acid. The possibility that the 2-pyridone 15 was the product generated in this reaction via intermediates 13 and 14 was

ruled out based on ^{13}C-NMR spectroscopic data, which revealed that the product contained a carbonyl carbon (187 ppm) (cf. Scheme 3).



Scheme 3. Synthesis of 3-(4-chlorophenyl)-3-oxo-2-(phenylhydrazono)-propionaldehyde and 6-(4-chlorobenzoyl)-3-oxo-2-phenyl-2,3-dihydropyridazine-4-carboxylic acid amide.

The antimicrobial activities of compounds prepared in this effort were evaluated. The results in terms of inhibition zone diameters, given in Table 2, reveal that enaminones 3b-e and dienamide 8e exhibit strong activities against the (Gram positive) bacteria *Bacillus subtilus* and *Staphylococcus auerus*, the (Gram negative) bacteria *Escherichia coli* and *Serratia sp*., and the (Yeasts) *Candida albicans* and *Saccharomyces cerevisiae*.

In addition, an evaluation of the results displayed in Table 2 indicates pyridazinones 17 have moderate growth inhibitory activities against the tested organisms. In addition, pyridones 10 and 2-phenylhydrazonoketone 12 were found to exhibit weak antimicrobial activities in comparison to the most of the tested compounds. However, their effect is equal or stronger than penicillin, while dienamides 8b and 8d showed activity only towards Gram negative bacteria and *Saccharomyces cerevisiae*. In general, the results show that enaminones are more biologically active than the pyridines and pyridazinones and that five of the heterocycles probed in this investigation exhibit strong antimicrobial activity against at least five of the tested organisms.

Table 2. Diameter of the zones of inhibition of the tested compounds against microorganisms

Compound number	Inhibition zone diameter (Nearest mm)					
	Prokaryotic organisms				Eukaryotic organisms	
	B. subtilus Mean ±SD	***S. aureus*** Mean ±SD	***E. coli*** Mean ±SD	***Serratia sp.*** Mean ±SD	***C. albicans*** Mean ±SD	***S. cerevisiae*** Mean ±SD
3b	9.6 (1.1)	7.6 (1.1)	8.3 (1.1)	5.6 (1.1)	18 (2)	27.6 (2.3)
3c	11 (0)	19 (3.4)	15 (0)	13 (3.4)	23.3 (3)	34.3 (6.4)
3d	11.6(1.1)	9 (0)	7.6 (1.1)	13.6 (3)	20.6 (5)	33.6 (1.1)
3e	18.3(1.1)	19.6(2.3)	15 (0)	5 (2)	28 (4)	43 (5.2)
8b	NI	NI	3 (2)	6.3 (1.1)	NI	1.6 (1.1)
8d	NI	NI	5 (0)	5.6 (3)	NI	1 (0)
8e	12.3(1.1)	9 (2)	5 (0)	5 (2)	6 (2)	8.3 (2.3)
10	3.6 (1.1)	1 (0)	3 (0)	4.3 (1.1)	6 (2)	5.6 (2.3)
12	6.3 (2.3)	4.3 (1.1)	1 (0)	1 (0)	4 (2)	2.3 (1.1)
17	8.3 (1.1)	6.3 (2.3)	3.6 (1.1)	1 (0)	0.6 (1.1)	1.3 (1.5)
DMSO	NI	NI	NI	NI	NI	NI
Penicillin**	13 (1.2)	46(0)	14.6(1.1)	36(0)		
Cyloheximide***					NI	46(0)

n = 1 only, (-) not determined, (NI) no inhibition, ** Penicillin: Antibacterial (100 mg ml^{-1}), * Cycloheximide: Antifungi (100 mg ml^{-1})*

It worth noting that the compounds 3b-e showed inhibition zone for *Candida albicans* stronger than what was recorded for cycloheximide despite the fact that 100 mg ml^{-1} of Cycloheximide was used in the experimental. This means the compounds 3b-e are important eukaryote cell inhibitors and may have significance in medicine. Yet, more work need to be done to determine the effect of these compounds have another eukaryote cells such as mammals and mainly human cell. Currently, we are inspecting the utility of dienoic acid amides, pyridones, phenylhydrazonoketones, and pyridazinones as intermediates for synthesizing of azo disperse dyes and applying the later to polyester fibers by using high temperature dyeing method.

4. CONCLUSION

In conclusion, the results of the studies described above, we have prepared a variety of dienamides through reactions of enaminones with malononitrile. NMR spectroscopic and X-ray crystallographic methods have been employed to unambiguously establish the structures and stereochemistry of the dienamide products. In addition, the results of an exploratory effort probing the chemistry of the novel dienamides are described. Finally, the antimicrobial activities against Gram-positive and Gram-negative bacteria and yeast of the substances prepared in this work have been evaluated

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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