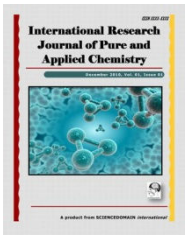

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Novel Routes to Biologically Active Enaminones, Dienoic Acid Amides, Arylazonicotinates and Dihydropyridazines under Microwave Irradiation

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Research Article

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ABSTRACT

Condensation of methylketones 1a,b with dimethylformamide dimethyl acetal (DMFDMA) without solvent in microwave oven afforded enaminones 2a,b, which reacted with malononitrile in ethanolic piperidine to yield dienoic acid amides 7a,b. In contrast, reactions of 2a,b with cyanoacetic acid resulted in the formation of pyranones 10. The pyranones were readily converted into 2-arylhydrazonoketones 13. Condensations of 13 with ethyl cyanoacetate afforded the 5-arylazonicotinates 17. Finally, 2-oxoarylhydrazonals 18 reacted with arylidenemalononitriles 19a,b in presence of chitosan to afford dihydropyridazines 21a,b. In addition the biological activity of the title compounds against Gram positive bacteria, Gram negative bacteria and Yeast were also evaluated.

Keywords: Enaminones; arylhydrazonals; arylazonicotinates; pyridazines; dihydropyridazines; microwave heating; chitosan;

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1. INTRODUCTION

Functionally substituted nitriles have been extensively utilized as starting materials in organic synthesis (Fabiani, 1999; Bradamante and Pagani, 1996; Ie Questel et al., 2000; Tekeuchi et al., 1997). Moreover, β -enaminone systems represent versatile synthetic intermediates that combine the ambient nucleophilicity of enamines with the ambient electrophilicity of conjugated enones. The presence of three nucleophilic and two electrophilic sites in β -enaminoketones makes them potential participants in a wide variety of chemical reactions. For this reason, nucleophilic (Singh et al., 1998) and electrophilic (Strah, and Stanovnik, 1997) substitutions, photochemical (Blache et al., 1994), reduction (Martin et al., 1994) and oxidation (Dominguez et al., 1996) reactions of these substances that lead to the formation of various biologically and medicinally active compounds (Singh et al., 2009) have found great utility in synthetic organic chemistry (Zhu et al., 2009; Loghmani-Khouzani et al., 2008; Riyadh et al., 2008; Stanovnik and Svete, 2004) and/or as dye intermediates (Sheikhshoaie and Walter, 2009; Macho et al., 2005; De Oliveira et al., 2003). Some cyclic enaminones have anticonvulsant activity that act due to synaptic and non-synaptic mechanisms (Edafiogho et al., 2009). Also, some studies proved their antitumor (Shawali et al., 2009) and antimicrobial activities (Riyadh, 2011). Finally, microwave irradiation has been used frequently to promote diverse organic transformations owing to the fact that it typically leads to remarkable reduction of reaction time, improvements in yields, and selectivities. For sometimes high-speed synthesis with microwaves has attracted a considerable amount of attention in recent years. Fundamentally microwave irradiation is an electromagnetic irradiation in the frequency range of 0.3 to 300 GHz (Buchachenko and Frankevich, 1993).

All domestic microwave ovens and all dedicated microwave reactors for chemical synthesis operate at a frequency of 2.45 GHz (which corresponds to a wavelength of 12.24 cm). The energy of the microwave photon in this frequency region (0.0016 eV) is too low to break chemical bonds and is also lower than the energy of Brownian motion. It is therefore clear that microwaves cannot induce chemical reactions. However, microwave-enhanced chemistry is based on the efficient heating of materials by “microwave dielectric heating” effects. This phenomenon is dependent on the ability of a specific material (solvent or reagent) to absorb microwave energy and convert it into heat. The electric component of an electromagnetic field causes heating by two main mechanisms: dipolar polarization and ionic conduction. Irradiation of the sample at microwave frequencies results in the dipoles or ions aligning in the applied electric field. As the applied field oscillates, the dipole or ion field attempts to realign itself with the alternating electric field and, in the process, energy is lost in the form of heat through molecular friction and dielectric loss. The amount of heat generated by this process is directly related to the ability of the matrix to align itself with the frequency of the applied field. If the dipole does not have enough time to realign, or reorients too quickly with the applied field, no heating occurs. The allocated frequency of 2.45 GHz used in all commercial systems lies between these two extremes and gives the molecular dipole time to align in the field, but not to follow the alternating field precisely (Kappe, 2004). In publications over the last decade, we have described the utility of β-enaminones as precursors to polyfunctional aromatic and heteroaromatic compounds (Ghozlan et al., 2005; Al-Saleh et al., 2006). In addition, the considerable efforts given to studies of nicotinic acid derivatives have attracted significant interest in their use as dye intermediates (Shen et al., 2011; Karapinar et al., 2007; Taylor and Renfrew, 1990; Mørkved et al., 2009; Liu et al., 1991). Enaminones, nicotinates have biological importance were they have been reported of having clinical benefit in the treatment of cancer (Ojugon et al., 2010). In this publication, we report the results of our most recent work on the chemistry of enaminones and nicotinates which has led to the development of novel routes for the preparation of enedienes and

arylhydrazono-nicotinates. When appropriate, in the reaction sequences we have utilized chitosan as an eco-friendly heterogeneous catalyst and microwave as the energy source.

2. MATERIALS AND METHODS

All reactions were conducted under microwave irradiation conditions in heavy-walled Pyrex tubes (capacity 10 mL). 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 300 W, 300 ℃ and 300 bsi, respectively. Melting points were recorded on Gallenkamp apparatus and are reported uncorrected. Infrared spectra (KBr) were determined on a Perkin-Elmer 2000 FT-IR system. NMR measurements were determined on a Bruker DPX spectrometer, at 600 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR, in DMSO-d_6 as solvent and using TMS as internal standard. Mass spectra were measured on MS 30 and MS 9 (AEI) spectrometers, with EI 70 eV. Elemental analyses were measured by means of LECO CHNS-932 Elemental Analyzer. Copies of original data can be provided upon requisite.

The antimicrobial activities of the compounds prepared in this study were evaluated using Agar-well diffusion technique (Isaacson and Kirschbaum 1986) 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 37°C for 24 hours while PDA plates were incubated at 25°C for 48 hours. The zones of inhibition around the wells were determined and the averages based on triplicate measurements were recorded.

2.1 General Procedure for the Preparation of Compounds 2a and 2b

A mixtures of 2-Acetylpyrrole or Phthalimidoacetone (0.01 mol) and DMFDMA (1.19 g, 0.01 mol) were irradiated by focused microwave at 120 ℃ for 10 min for product 2a and 180 ℃ for 20 min for product 2b, (completion of reaction 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 50 ℃. The reaction mixture left to cool to room temperature and then treated with a mixture of EtOH/dioxane (3:1). The solid product was collected by filtration and crystallized from dioxane to afford compounds 2a,b.

2.1.1 3-Dimethylamino-1-(1H-pyrrol-2-yl)propenone 2a

This compound was obtained as orange crystals, yield 86%, (mp 199-200 ℃). IR (KBr): υ = 3252 (NH), 1625 (CO) (cm^{-1}). ^{1}H NMR (DMSO-d_6): δ = 2.88 (s, 3H, CH_3), 3.03 (s, 3H, CH_3), 5.62 (d,1H, J = 12.4 Hz, CH), 6.08-6.10 (m, 1H, pyrrolyl-H), 6.76-6.78 (m, 1H, pyrrolyl-H),

6.86-6.88 (m, 1H, pyrrolyl-H), 7.68 (d,1H, J = 12.4 Hz, CH), 11.41 (s, 1H, NH). MS (EI): m/z (%) 164[M^+]. Anal. Calcd. for $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.06; Found: C, 65.82; H, 7.91; N, 17.06.

2.1.2 2-(4-Dimethylamino-2-oxo-but-3-enyl)isoindole-1,3-dione 2b

This compound was obtained as yellow crystals, yield 77%, (Lit. mp 159-162 °C (Al-Mousawi et al., 2009)); mp 162 °C. IR (KBr): υ 1769, 1714, 1660 (CO) (cm^{-1}). ^{1}H NMR (DMSO-d_6): δ = 2.72 (s, 3H, CH_3), 3.05 (s, 3H, CH_3), 4.40 (s, 2H, CH_2), 5.04 (d,1H, J = 12 Hz, CH), 7.61 (d,1H, J = 12 Hz, CH), 7.85-7.91 (m, 4H, phthalimidyl-H). MS (EI): m/z (%) 258[M^+]. 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.

2.2 General Procedure for the Preparation of Compounds 7a and 7b

Mixtures of equimolecular amounts of each of the enaminones 2a or 2b (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 150 °C 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 50 °C. The precipitated product was collected by filtration and crystallized from dioxane.

2.2.1 2-Cyano-5-dimethylamino-5-(1H-pyrrol-2-yl)penta-2,4-dienoic acid amide 7a

This compound was obtained as orange crystals (76%) (mp 236 °C). IR (KBr): υ 3398, 3259 (NH_2), 3211 (NH), 2190 (CN), 1640 (CO) (cm^{-1}). ^{1}H NMR (DMSO-d_6): δ = 2.98 (s, 6H, $N(CH_3)_2$), 5.55 (d, 1H, J = 12.4, H-4), 6.21-6.23 (m, 2H, pyrrolyl-H), 6.81 (s, 2H, NH_2, D_2O exchangeable), 7.04-7.05 (m, 1H, pyrrolyl-H), 7.56 (d, 1H, J = 12.4, H-3), 11.39 (s, 1H, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6): δ = 165.0 ($CONH_2$), 158.0 (C-5), 153.6 (C-3), 122.5, 121.4, 119.2, 113.6, 108.7, 97.7, 87.1, 40.9 ($N(CH_3)_2$). MS (EI): m/z (%) 230.1 [M^+, 18%], 186 (38), 171 (22), 147 (56), 107 (100), 92 (91), 80 (77), 64 (68). Anal. calcd. for $C_{12}H_{14}N_4O$: (230.27): C, 62.59; H, 6.13; N, 24.33. Found: C, 62.60; H, 6.03; N, 23.95.

2.2.2 2-Cyano-5-dimethylamino-6-(1,3-dioxo-1,3-dihydroisoindol-2-yl)hexa-2,4-dienoic acid amide 7b

This compound was obtained as pale green crystals (67%) (mp 262-64 °C). IR (KBr): υ 3443, 3144 (NH_2), 2191 (CN), 1720 (CO), 1671 (CO) (cm^{-1}).^{1}H NMR (DMSO-d_6): δ = 3.04 (s, 6H, $N(CH_3)_2$), 4.80 (s, 2H, CH_2), 5.43 (d, 1H, J = 12.8, CH), 6.99 (s, 2H, NH_2, D_2O exchangeable), 7.85-7.90 (m, 4H, phthalimidyl-H), 8.22 (d, 1H, J = 12.8, CH). ^{13}C NMR (DMSO-d_6): δ = 167.4 ($CONH_2$), 165.1 (CO), 157.8, 150.0, 134.7, 131.6, 123.2, 118.6, 97.5, 90.1, 43.7 (CH_2), 35.2 ($N(CH_3)_2$). MS (EI): m/z (%) 324.1 [M^+, 100%], 280 (68), 261 (17), 164 (63), 133 (52), 104 (42), 94 (32), 76 (29). Anal. calcd. for $C_{17}H_{16}N_4O_3$: (324.33): C, 62.95; H, 4.97; N, 17.27. Found: C, 62.84; H, 4.65; N, 17.03.

2.3 6-(1,3-Dioxo-1,3-dihydroisoindol-2-ylmethyl)-2-oxo-2H-pyran-3-carbonitrile 10

A mixture of 2b (2.58 g, 0.01 mol) and cyanoacetic acid (0.85 g, 0.01 mol) in acetic anhydride (2 mL), was irradiated by using a focused microwave at 160 °C for 10 min

(monitored by TIC testing using ethyl acetate: petroleum ether 1:1 until completion). The mixture was cooled and then poured onto ice-water. The solid product was collected by filtration and crystallized from ethanol and obtained as an orange powder (66%) (mp 180-82 °C). IR (KBr): υ = 3443 (NH), 2231 (CN), 1772 (CO), 1719 (CO) (cm^{-1}). ^{1}H NMR (DMSO-d_6): δ = 4.73 (s, 2H, CH_2), 6.77 (d, J = 7.8, 1H, CH), 7.90-7.98 (m, 4H, phthalimidyl-H), 8.38 (d, J = 8.8, 1H, CH). MS (EI): m/z (%) 280 ([M]$^+$, 100), 262 (12), 238 (32), 198 (16), 160 (36), 104 (86), 76 (74). Anal. calcd. for $C_{15}H_8N_2O_4$: (280.24): C, 64.29; H, 2.88; N, 10.00. Found: C, 64.20; H, 3.23; N, 9.69.

2.4 4-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-3-oxo-2-(phenylhydrazono)-butyraldehyde 13

A cold solution of diazonium salt [prepared by adding a cold solution of sodium nitrite (0.69 g, 0.01 mol) in small amount of water to a solution of aniline (0.93 g, 0.01 mol) and HCl (3 mL)] was added to a solution of pyranone 10 (2.80 g, 0.01 mol) in ethanol (10 mL) containing sodium acetate (4 g). After addition of the diazonium salt, the reaction mixture was stirred at room temperature for 1 h. The solid was collected by filtration and crystallized from ethanol. To give an orange powder (78%) (mp 209-10 °C). IR (KBr): υ = 3442 (NH), 1172(CO), 1720(CO), 1683 (CO) (cm^{-1}). ^{1}H NMR (DMSO-d_6): δ = 5.06 (s, 2H, CH_2), 7.29-7.75 (m, 5H, phenyl-H), 7.90-7.98 (m, 4H, phthalimidyl-H), 9.67 (s, 1H, CHO), 14.24 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ = 189.7 (CHO), 185.7 (CH_2CO), 167.5 (CO), 141.3, 134.7, 130.7, 129.5, 126.6, 123.2, 119.8, 117.3, 42.4 (CH_2). MS (EI): m/z (%) 335 [M$^+$, 69%]. Anal. Calcd. for $C_{18}H_{13}N_3O_4$: C, 64.48; H, 3.91; N, 12.53. Found: C, 64.44; H, 3.91; N, 12.68.

2.5 6-(1,3-Dioxo-1,3-dihydroisoindol-2-ylmethyl)-2-oxo-5-phenylazo-1,2-dihydropyridine-3-carboxylate 17

A mixture of 13 (3.35 g, 0.01 mol) and ethyl cyanoacetate (1.13 g, 0.01 mol) in presence of ammonium acetate (1 g) and acetic acid (1 mL) was irradiated by using a focused microwave at 140 °C for 5 min (monitored by TLC using ethyl acetate: petroleum ether 1:1). The reaction mixture was cooled and then was poured onto ice-water. The solid formed was collected by filtration and crystallized from ethanol to give brown powder (56%) (mp 188-90 °C). IR (KBr): υ = 3443 (OH), 1773 (CO), 1718 (CO) (cm^{-1}). ^{1}H NMR (DMSO-d_6): δ = 1.29 (t, 3H, J = 6.8 Hz, CH_3), 4.32 (q, 2H, J = 6.8 Hz, CH_2), 5.12 (s, 2H, CH_2), 7.50-7.62 (m, 4H, arom-H), 7.69-7.77 (m, 2H, arom-H), 7.80-7.95 (m, 3H, arom-H), 8.40 (s, 1H, OH), 8.45 (s, 1H, pyridyl-H). ^{13}C NMR (DMSO-d_6): δ = 164.5 (CO), 163.6 (CO), 152.6 (CO), 134.9, 132.6, 130.7, 128.9, 118.7, 96.8, 88.3, 55.9 (CH_2), 18.5 (CH_3). MS (EI): m/z (%) 360.2 ([M]$^+$, 20), 402 (25), 359 (14), 322 (22), 282 (42), 160 (100), 77 (48). Anal. calcd. for $C_{23}H_{18}N_4O_5$: (430.41): C, 64.18; H, 4.22; N, 13.02. Found: C, 63.90; H, 4.20; N, 15.08.

2.6 General Procedure to Syntheses of Compounds 21a and 21b

Mixtures of 18 (1.76 g, 0.01 mol) and each of the arylidenemalonitriles 19a or 19b (0.01 mol of each) in presence of catalytic amount of chitosan [Catalog number C0831 from TCI America] (1 g) in ethanol (3 mL), were irradiated by using a focused microwave at 120 °C for 30 min. The build-up of pressure in the closed reaction vessel was carefully monitored. After irradiation, the reaction tubes were cooled with high-pressure air through an inbuilt system in the instrument until the temperature had fallen below 50 °C. The formed solid products were recrystallized from dioxane.

2.6.1 6-Acetyl-3-amino-5-(4-methoxyphenyl)-2-p-tolyl-2,5-dihydropyridazine-4-carbonitrile 21a

This compound was obtained as dark yellow crystals (68%) (mp 168 °C). IR (KBr): υ = 3423, 3319 (NH_2), 2191 (CN), 1685 (CO) (cm^{-1}). ^1H NMR (DMSO-d_6): δ = 2.29 (s, 3H, $COCH_3$), 2.37 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 4.67 (s, 1H, CH), 5.96 (s, 2H, NH_2, D_2O exchangeable), 6.89 (d, 2H, J = 8.8, arom-H), 7.09 (d, 2H, J = 8.4, arom-H), 7.32-7.38 (m, 4H, arom-H). ^{13}C NMR (DMSO-d_6): δ = 195.8 (CO), 158.4 (CO), 150.2, 143.9, 137.6, 137.4, 134.3, 129.9, 127.9, 125.7, 120.6, 114.2, 56.7, 55.0, 38.8 (OCH_3), 20.6 (CH_3), 18.5 ($COCH_3$). MS (EI): m/z (%) 360.2 [M^+, 30%], 317 (100), 290 (24), 253 (40), 133 (8), 91 (12). Anal. calcd. for $C_{21}H_{20}N_4O_2$: (360.41): C, 69.98; H, 5.59; N, 15.55. Found: C, 69.50; H, 5.78; N, 15.21.

2.6.2 6-Acetyl-3-amino-5-(4-chlorophenyl)-2-p-tolyl-2,5-dihydropyridazine-4-carbonitrile 21b

This compound was obtained as dark yellow crystals (53%) (mp 186 °C). IR (KBr): υ = 3409, 3326 (NH_2), 2185 (CN), 1681 (CO) (cm^{-1}). ^1H NMR (DMSO-d_6): δ = 2.30 (s, 3H, $COCH_3$), 2.37 (s, 3H, CH_3), 4.76 (s, 1H, CH), 6.02 (s, 2H, NH_2, D_2O exchangeable), 7.20 (d, 2H, J = 8.4, arom-H), 7.32-7.42 (m, 6H, arom-H). ^{13}C NMR (DMSO-d_6): δ = 195.7 (CO), 150.3 (CO), 143.1, 141.1, 137.6, 137.5, 131.8, 129.9, 128.9, 128.7, 125.8, 120.3, 56.0, 35.4, 24.5 (CH_3), 20.6 ($COCH_3$). MS (EI): m/z (%) 364.1 [M^+, 22%], 321 (83), 294 (23), 253 (100), 106 (10), 91 (22). Anal. calcd. for $C_{20}H_{17}ClN_4O$: (364.83): C, 65.84; H, 4.70; N, 15.36. Found: C, 65.68; H, 4.88; N, 15.03.

2.7 6-Acetyl-5-(4-chlorophenyl)-3-oxo-2-p-tolyl-2,3-dihydropyridazine-4-carbonitrile 22

A mixture of 21b (3.64 g, 0.01 mol), acetic acid (3 mL) and hydrochloric acid (1 mL), was irradiated by using a focused microwave at 130 °C for 3 min. The build-up of pressure in the closed reaction vessel was carefully monitored. After irradiation, the reaction tube was cooled with high-pressure air through an inbuilt system in the instrument until the temperature had fallen below 50 °C. The formed solid product was collected by filtration and crystallized from dioxane, to give brown crystals (70%) (mp 214-16 °C). IR (KBr): υ = 2234 (CN), 1708 (CO), 1675 (CO) (cm^{-1}). ^1H NMR (DMSO-d_6): δ = 2.41 (s, 3H, $COCH_3$), 2.47 (s, 3H, CH_3), 4.40 (d, 1H, J = 8, arom-H), 7.45-7.49 (m, 3H, arom-H), 7.59-7.62 (m, m, 4H, arom-H). ^{13}C NMR (DMSO-d_6): δ = 194.2 (CO), 156.1 (CO), 149.2, 140.7, 139.1, 137.8, 134.5, 130.2, 129.6, 128.4, 125.1, 115.1, 113.2, 26.9 (CH_3), 20.7 ($COCH_3$). MS (EI): m/z (%) 363 [M^+, 90%], 320 (15), 286 (10), 119 (18), 91 (100), 65 (15). Anal. calcd. for $C_{20}H_{14}ClN_3O_2$: (363.80): C, 66.03; H, 3.88; N, 11.55. Found: C, 66.04; H, 3.88; N, 10.98.

3. RESULTS AND DISCUSSION

In the first phase of this effort, we found that condensation of methylketones 1a,b with dimethylformamide dimethyl acetal (DMFDMA) without solvent in focused microwave oven at 120-180 °C for 10-20 min has afforded enaminones 2a and b in 86% and 77% yields, respectively. Recently heating neat reactants in ionic liquid has been reported to afford compound 2a in an 86% yield (Martins et al., 2008) (Scheme 1).

Enaminones 2a,b reacted with malononitrile in ethanolic piperidine to yield products whose analytical and spectroscopic properties agree well with the revised structures 7a,b as well as those originally assigned to these substances. Unambiguous assignment of the structure of 2-cyano-5-dimethylamino-5-(1H-pyrrol-2-yl)-penta-2,4-dienoic acid amide 7a was made by using X-ray crystallographic analysis (Figure 1) (CCDC , 2010). It should be noted that, Al-Mousawi (Al-Mousawi et al., 2009) and Gorobets (Gorobets et al., 2009) reached the same conclusion about the structures of the products of these reactions based on the results of X-ray crystallographic analysis.

In the processes leading to 7a,b, it appears that malononitrile initially undergoes 1,4 addition to the unsaturated ketone functions in 2a,b, yielding the adduct 4 that cyclizes to form aminopyran 5 followed by rearrangement to generate 7a,b via a 1,3-shift of the dimethylamino-moiety in intermediate 6 (Scheme 1).

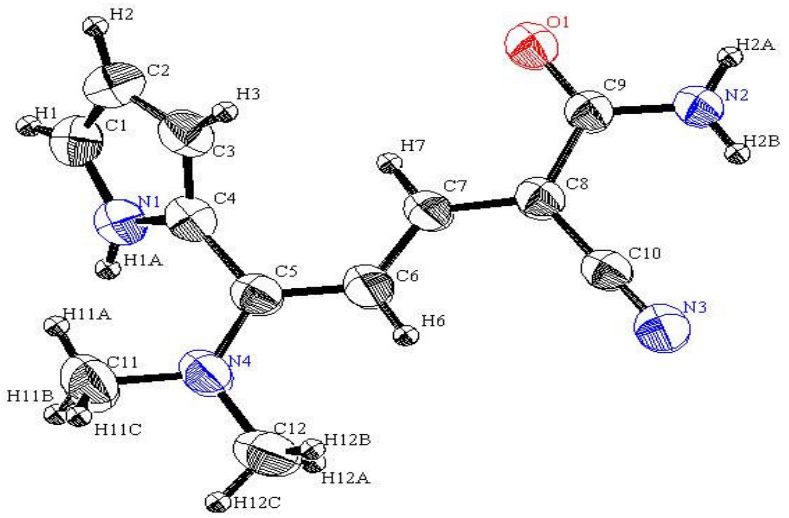
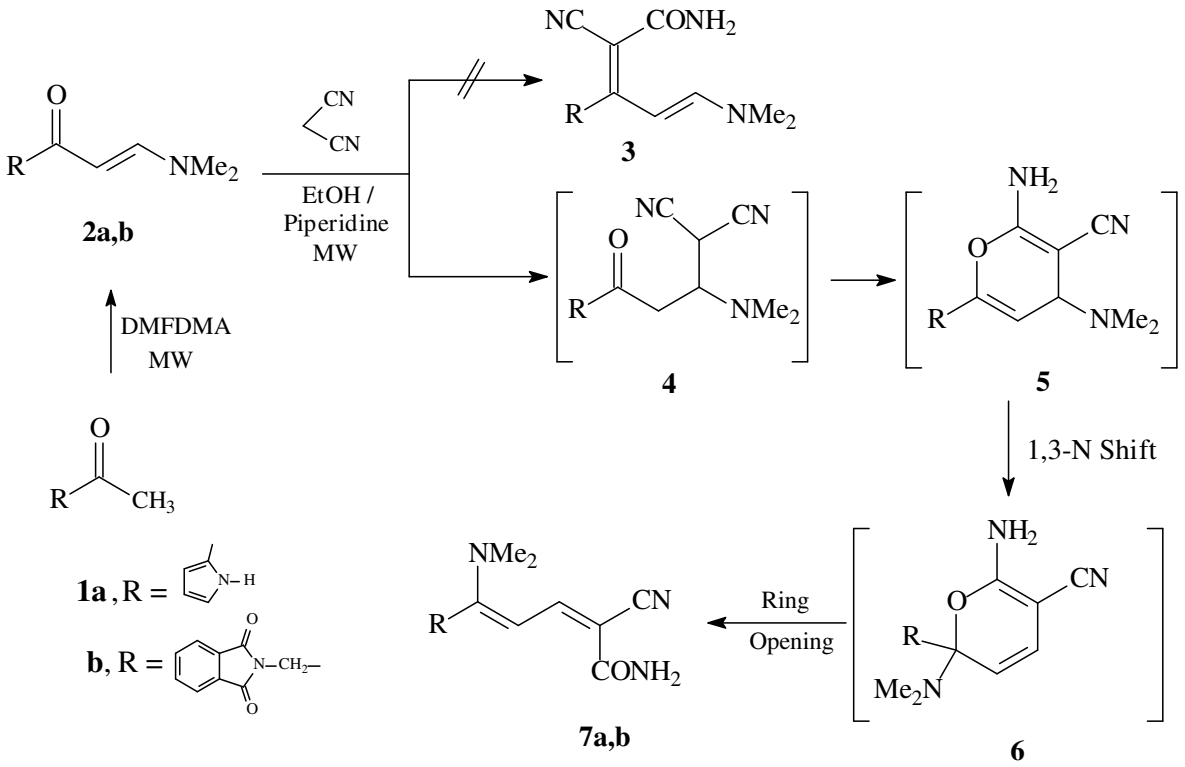


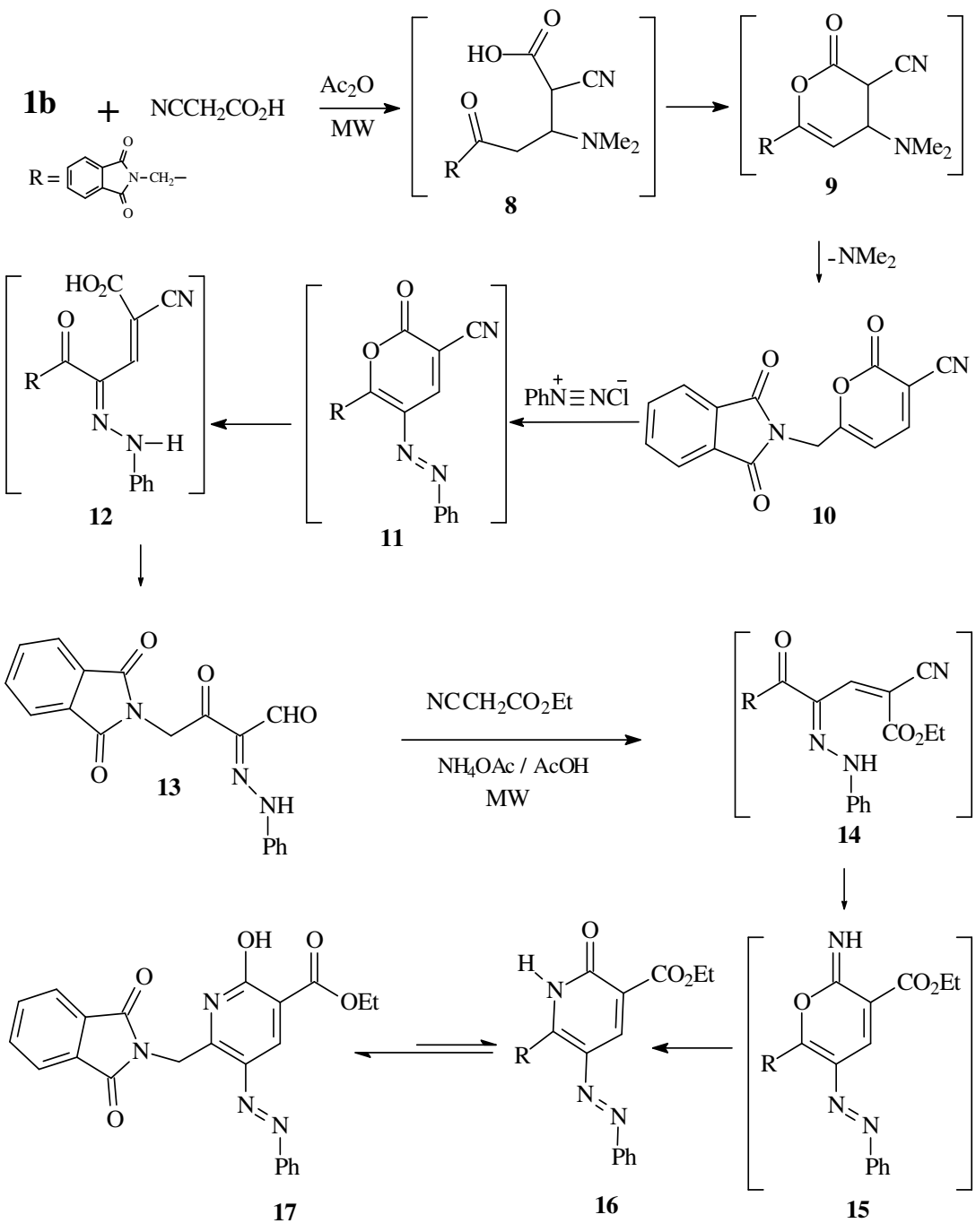
Fig. 1. Ortep plot of the x-ray crystallographic data for 7a.

In contrast to the observed behavior with malononitrile, reaction of 1b with cyanoacetic acid in acetic anhydride afforded pyranone 10 (cf. Scheme 2). It is assumed that the initially formed Michael adduct 8 undergoes cyclization to produce 9 that then eliminates dimethylamine to yield 10. Pyranone 10 was readily converted into phenylhydrazone 13 when reacted with benzenediazonium chloride. It is believed that the initially formed azo compound 11 undergoes ring opening to generate 12, which hydrolyzes under the coupling reaction conditions to yield phenylhydrazone 13.

Condensation of the 2-arylhydrazonoketone 13 with ethyl cyanoacetate afforded the 5-arylazonicotinate 16. It is believed that the mechanism for this process involves initial condensation of 13 with ethyl cyanoacetate to afford the intermediate 14 which cyclizes to produce the pyran-2-imine intermediate 15. Dimroth type rearrangement of 15 then gives ethyl 5-arylazonicotinate 16, which exists in prototropic equilibrium with 17 (Scheme 2). A similar observation has been recently reported in our laboratory in which the H-bonding postulate was supported by the results of X-ray crystallographic analysis. A contrasting result has come from an investigation by Al-Mousawi, which showed that a similar analogue exists in its enol-form rather than keto-form in solution (Al-Mousawi et al., 2011).



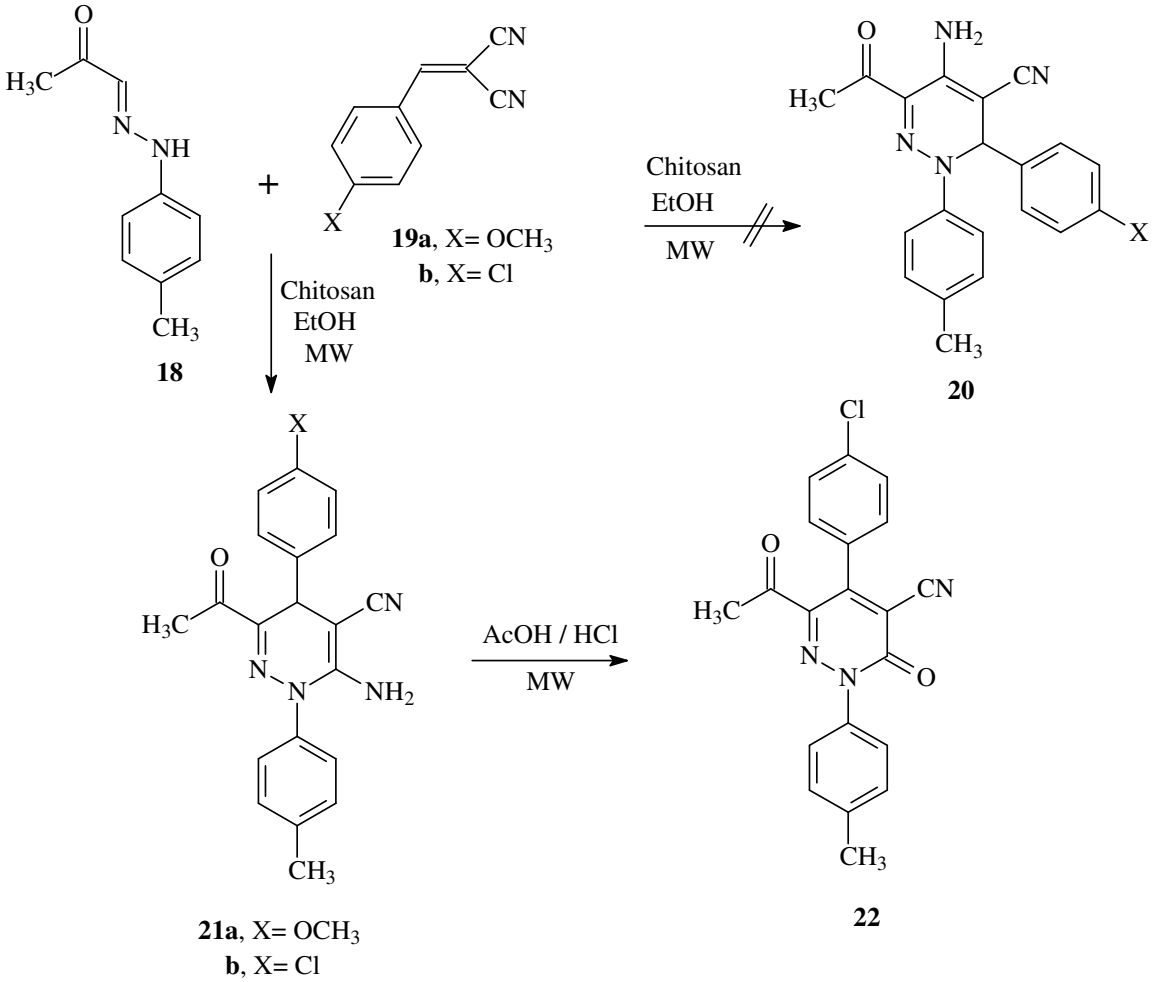
Scheme 1. Synthesis of dienoic acid amides.



Scheme 2. Synthesis of pyranones, phenylhydrazone and 5-arylazonicotinates

Recently Al-Matar et al. reported that arylhydrazonals behave as azaenamines in reactions with benzylidenemalononitrile in the presence of piperidine to yield the corresponding dihydropyridazines (Al-Matar et al., 2007).

In an attempt to extend this methodology, we have explored alternate catalysts for this process. Chitosan has been employed as an efficient, mildly basic, eco-friendly, heterogeneous catalyst in a number of reactions. When the 2-oxoarylhydrazonal 18 and arylidenemalonitriles 19a and b were mixed in ethanolic solutions containing chitosan, the pyridazine-4-carbonitriles 21a and b were formed cleanly. In order to rule out structure 20, X-ray crystallographic analyses were carried out confirming that the product structures are correctly represented by 21a and b (Figures 2 and 3) (CCDC , 2010). Also, in order to further establish its structure, 21b was hydrolyzed by treatment with acetic acid in presence of hydrochloric acid to yield the dihydropyridazinone 22 (Scheme 3).



Scheme 3. Synthesis of pyridazine-4-carbonitriles and dihydropyridazinone

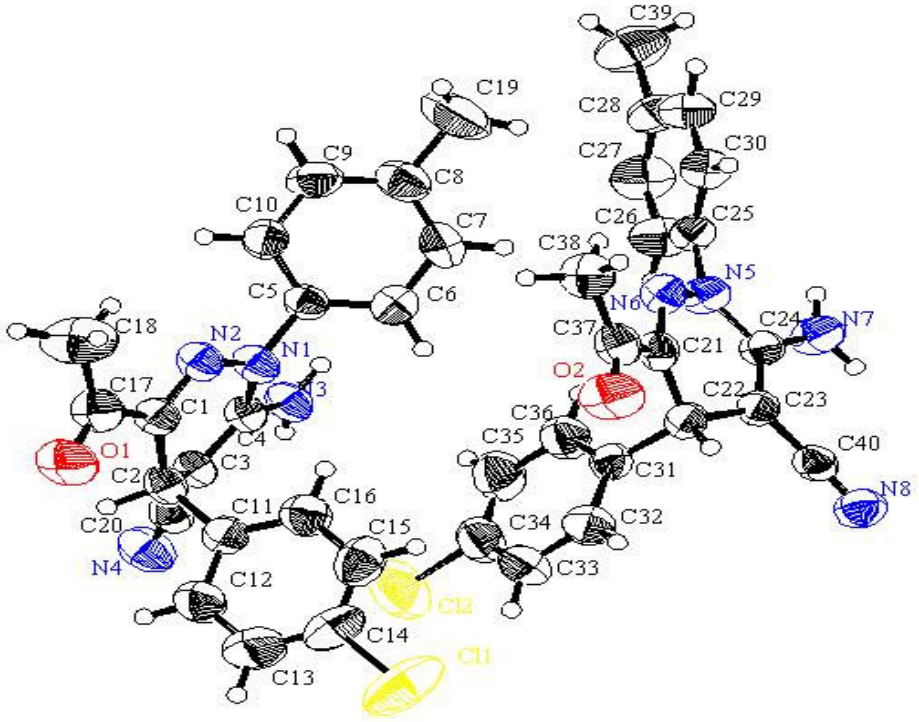


Fig. 3. Ortep plot of the x-ray crystallographic data for 21b

The results of the antimicrobial activity evaluations, given in Table 1, reveal that enaminones 2a and 2b exhibited strong activities against the tested organisms (Gram positive bacteria) *Bacillus subtilus* and *Staphylococcus auerus,* (Gram negative bacteria) *Escherichia coli* and *Serratia sp.* and (Yeast) *Candida albicans* and *Saccharomyces cerevisiae.* On the contrary compound 7b showed activity only towards Gram negative bacteria and one of the Yeast (*Saccharomyces cerevisiae*).

In addition, the results displayed in Table 1 indicated that compounds 7a and 22 have moderate growth inhibitory activities against Gram negative bacteria as revealed by the diameters of their inhibition zones. Among these compounds 7a and 22 show moderate growth inhibitory effects against one of the Yeast (*Saccharomyces cerevisiae*). Of the compounds tested, the data on Table 1 indicated that compounds 13, 16, 21a, and 21b exhibited weak antimicrobial activities against the tested organisms. In general, the enaminones to be proved more biologically active than pyridazines derived from them. Overall, the results showed that three of the heterocycles prepared in this study exhibited strong antimicrobial activities with significant zones of inhibition (≥ 10 mm) against at least three of the tested organisms.

The compound 2b is of special interest since it showed inhibition for *Candida albicans* when cycloheximide failed to do so. Also 2a is of significant important since it showed inhibition zone for certain bacterial strains equivalent to that resulted from 100 mg of penicillin.

Table 1. 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
2a*	11	NI	15	9	-	29
2b	1 (0)	5.6 (1.1)	3 (0)	3.6 (1.1)	9.3 (2.3)	14.3 (2.3)
7a*	3	NI	5	7	-	9
7b*	NI	NI	3	7	-	13
13	3 (0)	1.6 (0.1)	0.3 (0.6)	1 (1.7)	NI	6.3 (1.1)
17	NI	1 (0)	1 (0)	2.3 (1.1)	2 (0)	2.3 (1.1)
21a	3 (0)	NI	4.3 (2.8)	3 (0)	NI	5 (0)
21b	5 (0)	NI	2.3 (1.2)	3 (0)	4 (0)	5 (0)
22*	NI	NI	3	5	-	7
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})*

4. CONCLUSION

In conclusion, the results of the investigation described above have confirmed that the route described for formation of dienoic acid amides is general. In addition, the structures of the products of these processes have been firmly established by using X-ray crystal structure determinations. Furthermore, this effort has led to the development of a new and efficient method to synthesize ethyl 5-arylazo-2-hydroxy-6-arylnicotinates. We have shown that chitosan serves as an efficient, basic, heterogeneous catalyst for the addition reactions of arylhydrazonoglyoxalates to arylidenemalononitrile yielding pyridazinone derivatives. Finally, the results of biological activity evaluations demonstrate that members from the prepared compounds have promising antimicrobial activities against Gram positive bacteria, Gram negative bacteria and Yeast. However, more work is needed to determine the cytotoxicity of the synthesized chemicals especially toward eukaryote cells. The fact that yeast had been inhibited by some of the chemicals raise a question about the effect of these chemicals on other eukaryote cells such as human cells. Therefore, cytotoxicity tests are consider a must if the chemicals to be used in industry.

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REFERENCES

Al-Matar, H.M., Riyadh, S.M., Elnagdi, M.H. (2007). Studies with enamines: reactivity of N,N-dimethyl-N-[(E)-2-(4-nitrophenyl)-1-ethenyl]amine towards nitrilimine and aromatic diazonium salts. J. Heterocycl. Chem., 44, 603-607.

Al-Mousawi, S.M., Moustafa, M.S., Abdelhamid, I.A., Elnagdi, M.H. (2011). Reassignment of the structures of condensation products of α -keto α'-formylarylhydrazones with ethyl cyanoacetate: A novel route to ethyl 5-arylazo-2-hydroxynicotinates. Tetrahedron Lett., 52, 202-204.

Al-Mousawi, S.M., Moustafa, M.S., Abdelkhalik, M.M., Elnagdi, M.H. (2009). Enaminones as building blocks in organic syntheses: on the reaction of 3-dimethylamino-2-propenones with malononitrile. Arkivoc, 11, 1-10.

Al-Mousawi, S.M., El-Apasery, M.A., Elnagdi, M.H. (2010). Enaminones in heterocyclic synthesis: a novel route to tetrahydropyrimidines, dihydropyridines, triacylbenzenes and naphthofurans under microwave irradiation. Molecules, 15, 58-67.

Al-Saleh, B., Makhseed, S., Hassaneen, H.M.E., Elnagdi, M.H. (2006). Studies with functionally substituted enamines: the reactivity of enaminals and enamino esters toward naphthoquinone, hydrazonoyl halides, aminoazoles and hippuric acid. Synthesis, 1, 59-62.

Blache, Y., Chavignon, O., Sinibaldi-Troin, M.E., Gueiffier, A.,Teulade, J.C., Troin, Y., Gramain, J.C. (1994). Synthesis of azacarbazoles. Heterocycles, 38, 1241-1246

Bradamante, S., Pagani, G.A. (1996). Benzyl and heteroarylmethyl carbanions: structure and substituent effects. Adv. Carbanion Chem., 2, 189-263.

Buchachenko, A.L., Frankevich, E.L. (1993). Chemical Generation & Reception of Radio & Microwaves, Wiley-VCH Verlag GmbH (November). Weinheim, Germany.

CCDC 805227, 805935 and 804724 contain the supplementary crystallographic data for compound 7a, 21a and 21b in this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk

De Oliveira, H.C.B., Fonseca, T.L., Castro, M.A., Amaral, O.A.V., Cunha, S. (2003). Theoretical study of the static first hyperpolarizability of azo-enaminone compounds. J. Chem. Phys., 119, 8417-8423.

Dominguez, E., Ibeas, E., Martinez de Marigorta, E., Palacios, J.K., SanMartin, R. (1966). A Convenient One - Pot Preparative Method for 4 , 5 - Diarylisoxazoles Involving Amine Exchange Reactions. J. Org. Chem., 61, 5435-5439.

Edafiogho, I.O., Phillips, O.A., Udo, E.E., Samuel, S., Rethish, B. (2009). Synthesis, antibacterial and anticonvulsant evaluations of some cyclic enaminones. Eur. J. Med. Chem., 44, 967-975.

Fabiani, M.E. (1999). Angiotensin receptor subtypes: novel targets for cardiovascular therapy. Drug News Perspect., 12, 207-215.

Ghozlan, S.A.S., Abdelhamid, I.A., Gaber, H.M., Elnagdi, M.H. (2005). Studies on enaminonitriles: A new synthesis of 1,3-substituted pyrazole-4-carbonitrile. J. Heterocycl. Chem., 42, 1185-1189.

Gorobets, N.Y., Sedash, Y.V., Shishkina, S.V., Shishkin, O.V., Yermolayev, S.A., Desenko, S.M. (2009). Structure of the intermediate in the synthesis of 6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile. Arkivoc., 13, 23-30.

Isaacson, D.M., Kirschbaum, J. (1986). Assays of antimicrobial substances In: Manual of Industrial Microbiology and Biotechnology (A. L. Demain, A.L., Solomon, N.A. Eds), ASM, Washington., 410-435.

Kappe, C.O. (2004). Controlled microwave heating in modern organic synthesis. Angew. Chem. Int. Ed., 43, 6250-6284.

Karapinar, E., Phillips, D.A.S., Taylor, J.A. (2007). Reactivity, chemical selectivity and exhaust dyeing properties of dyes possessing a 2-chloro-4-methylthio-s-triazinyl reactive group. Dyes Pigments.,75, 491-497.

Le Questel, J., Berthelot, M., Laurence, C. (2000). Hydrogen-bond acceptor properties of nitriles: a combined crystallographic and *ab* initio theoretical investigation. J. Phys. Org. Chem., 13, 347-358.

Liu, D., Gao, K., Cheng, L. (1991), The catalytic effect of tertiary amines on the dyeing of monochlorotriazine dyes at high temperatures in a neutral medium. J. Soc. Dyer. Colour., 107, 319-322.

Loghmani-Khouzani, H., Sabzyan, H., Rezaei-Pooranari, A. (2008). Synthesis and structure of α -azo-2-ketomethylquinolines. Dyes Pigments., 76, 447-454.

Macho, S., Miguel, D., Neo, A.G., Rodriguez, T., Torroba, T. (2005). Cyclopentathiadiazines, new heterocyclic materials from cyclic enaminonitriles. Chem. Commun., 3, 334-336.

Martins, M.A.P., Frizzo, C.P., Moreira, D.N., Rosa, F.A., Marzari, M.R.B., Zanatta, N., Bonacorso, H. G. (2008). Synthesis of β - enaminones by ionic liquid catalysis. A one-pot condensation under solvent - free conditions. Cat. Commun., 9, 1375-1378.

Morkved, E.H., Andreassen, T., Novakova, V., Zimcik, P. (2009). Zinc azaphthalocyanines with thiophen - 2 - yl , 5 - methylthiophen - 2 - yl and pyridin-3- yl peripheral substituents: Additive substituent contributions to singlet oxygen production. Dyes Pigments, 82, 276-285.

Ojogun, V., Knutson, B.L., Vyas, S., Lehmler, H. (2010). Fluorophilicity of alkyl and polyfluoroalkyl nicotinic acid ester prodrugs. J. Fluor. Chem.,131, 784-790

Riyadh, S.M. (2011). Enaminones as building blocks for the synthesis of substituted pyrazoles with antitumor and antimicrobial activities. Molecules, 16, 1834-1853.

Riyadh, S.M., Abdelhamid, I.A., Al-Matar, H.M., Hilmy, N.M., Elnagdi, M.H. (2008). Enamines as precursors to polyfunctional heteroaromatic compounds; a decade of development. Heterocycles, 75, 1849-1905.

SanMartin, R., Martinez de Marigorta, E., Dominguez, E. (1994). A convenient alternative route to α - aminoketones. Tetrahedron., 50, 2255-2264.

Shawali, A.S., Farghaly, T.A., Al-Dahshoury, A.R. (2009). Synthesis, reactions and antitumor activity of new β -aminovinyl β-pyrazolyl ketones. Arkivoc., 14, 88-99.

Sheikhshoaie, I., Fabian, W.M.F. (2009). Theoretical insights into material properties of Schiff bases and related azo compounds. Curr. Org. Chem., 13, 149-171

Shen, L., Zhao, P., Zhu, W. (2011). A ratiometric hydrophilic fluorescent copolymer sensor based on benzimidazole chromophore for microbioreactors. Dyes Pigments, 89, 236-240.

Singh, P., Sharma, P., Bisetty, K., Mahajan, M.P. (2009). Cycloaddition reactions of cross - conjugated enaminones. Tetrahedron., 65, 8478-8485.

Singh, K., Singh, J., Singh, H. (1998). Carbon transfer reactions of functionalized oxazolidines and their open chain enamine tautomers to enamine nucleophiles. A facile synthesis of substituted pyridines and ring annulated derivatives. Tetrahedron, 54, 935-942.

Stanovnik, B., Svete, J. (2004). Synthesis of Heterocycles from Alkyl 3-(Dimethylamino)propenoates and Related Enaminones. Chem. Rev., 104, 2433-2480.

Starh, S., Stanovnik, B. Grdadolnik, S.G. (1997). Alkyl 2-(2-benzoyl-2-ethoxycarbonyl-1-ethenyl)amino-3-dimethylaminopropenoates in the synthesis of heterocyclic systems. J. Heterocycl. Chem., 34, 263-267.

Taylor, J.A., Renfrew, A.H.M. (1990). Reactive dyes for cellulose. An unexpected hydrolysis product of a triazinyl reactive dye with a 3-carboxypyridine (nicotinic acid) leaving group. J. Soc. Dyer. Colour, 106, 230-234.

Tekeuchi, K., Kitagawa, T., Ohga, Y., Nakakimura, A., Munakata, M. (1997). Effects of γ - cyano substituent in allylic bridgehead solvolyses: evidence of cyano π conjugation in carbocations. Tetrahedron., 53, 8155-8164.

Zhu, S., Zhao, K., Su, X., Ji, S. (2009). Microwave - assisted synthesis of new spiro [indoline - 3,4'- quinoline] derivatives via a one-pot multicomponent reaction. Synth. Commun., 39, 1355-1366.

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