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Chitosan as an eco-friendly heterogeneous catalyst for Michael type addition reactions. A simple and efficient route to pyridones and phthalazines

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ABSTRACT

Depending on their nature, nitrile activated methylene compounds add readily to *β*-enaminones in presence of chitosan to yield dienamides, pyridones or pyridine thiones. The dienamides, formed in this manner, can be readily converted to pyridones by stirring in refluxing acetic acid. Reaction of pyridazinones with a mixture containing benzaldehyde, malononitrile and chitosan affords phthalazines that are also produced by reaction of pyridazinone with benzylidene-malononitrile.

1. Introduction

Chitosan is readily prepared via aqueous alkali promoted hydrolysis of chitin. Being hydrophilic and possessing basic moieties, [1-3] chitosanhas been utilized as heterogeneous eco-friendly basic catalyst for reactions carried out in protic media [4]. Studies conducted in the 1970's and 1980's showed that active methylene ketones as well as phenols undergo addition reactions with benzylidene-malononitriles. Investiga-tions at that time showed that some of the compounds generated by using this process are biological active. In reviewing this work, we realized that it would be valuable to replace homogeneous catalysts used previously by eco-friendly heterogeneous base catalysts as promoters of these reactions. In previous studies, [5] we observed that chitosan serves as a catalyst for Michael addition reactions of active methylene compounds with arylidene-malononitriles. This process can be used to synthesize condensed pyrans, benzopyrans, naphtha-pyrans, pyranopyrazoles as well as thiazolopyridine in yields similar to those obtained earlier when piperidine was used as the catalyst.

In the present investigation, we demonstrated that chitosan can be employed as a heterogeneous basic catalyst to promote addition reactions of active methylene compounds with β-enaminones as well as additions of pyridazinylcarbonitriles to arylidene-malononitriles (Scheme 1). The results of this effort are presented and discussed below.

2. Experimental

2.1. Instrumentation

Melting points were recorded on Gallenkamp apparatus and are uncorrected. Infrared spectra (KBr) were determined on a Perkin-Elmer 2000 FT-IR system. NMR measurements were determined on a Bruker DPX spectrometer, at 400 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. The chitosan was supplied by Aldrich Company (from shrimp shells and with ≥ 75% deacetylated). Copies of original data can be provided upon request.

2.2. Reaction of enaminone 9a,b with malononitrile and with ethyl cyanoacetate

A solution of the enaminone 9a or 9b (10 mmol) and 10 mmol of active methylene compound (malononitrile, ethyl cyanoacetate or benzoyl acetophenone) containing a suspension of chitosan (10% by wt.) in 20 mL absolute ethanol was stirred at reflux for 4 h. The hot reaction mixture was filtered remove insoluble chitosan and the filtrate was concentrated in vacuo giving a residue, which was crystallized from ethanol to yield pure product (Scheme 2).

2-Cyano-5-dimethylamino-5-phenyl-penta-2,4-dienoic acid amide (**12a**): Yellow crystals. Yield: (chitosan: 80%, piperidine 67%). M.p.: 258 °C (literature [6], M.p.: 258 °C). IR (KBr, cm^{-1}): 3390 and 3340 ν(NH_2), 2181 ν(CN), 1672 ν(CO). ^{1}H NMR (400 MHz, DMSO-d_6, δ): 2.51 (s, 3H, CH_3), 3.36 (s, 3H, CH_3), 5.63 (d, 1H, *J*=12.6 Hz, H-4), 6.84 (s, 2H, NH2), 7.26–7.55 (m, 5H, phenyl-H), 7.92 (d, 1H, *J*=12.6 Hz, H-3). ^{13}C NMR (125 MHz, DMSO-d_6, δ): 39.8 ($N(CH_3)_2$), 91.6 (C), 104.7 (C), 118.2 (CN), 129.6, 136.4, 137.2, 143.8 (aromatic carbons), 147.3 (C), 164.6 (C-$N(CH_3)_2$), 165.13 (CO). MS (m/z (%)): 241.1 (M^+, 100), 179.1(76). Anal. Calcd. for $C_{14}H_{15}N_{30}$: C, 69.69; H, 6.27; N, 17.41. Found: C, 69.61; H, 6.22; N, 16.92.

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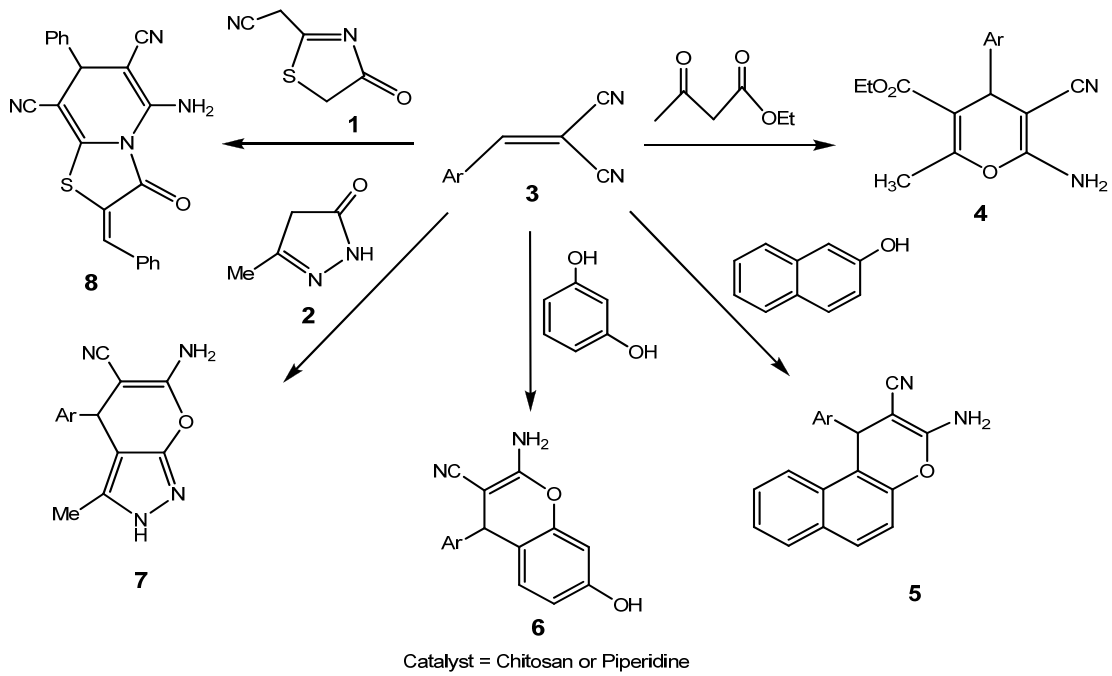


Scheme 1

2-Carbamoyl-5-dimethylamino-5-phenyl-penta-2,4-dienoic acid ethyl ester (**12b**): Yellow powder. Yield: (chitosan: 68%, piperidine: 64%). IR (KBr, cm^{-1}): 3350 and 3330 ν(NH_2), 1685 ν(CO, ester), 1664 ν(CO, amide). ^{1}H NMR (400 MHz, DMSO-d_6, δ): 1.32 (t, 3H, *J*=7 Hz, CH_3), 2.86 (s, 6H, $N(CH_3)_2$), 4.05 (q, 2H, *J*=7 Hz, CH_2), 5.44 (d, 1H, *J*=12.4 Hz, diene CH), 6.42 (s, 2H, NH_2), 7.10–7.52 (m, 5H, phenyl-H), 8.06 (d, 1H, *J*=12.4 Hz, diene CH). ^{13}C NMR (125 MHz, DMSO-d_6, δ): 15.2 (CH_3), 37.1 ($N(CH_3)_2$), 62.7 (CH_2), 88.3, 124.5, 126.8, 126.9, 129.1, 140.0, 146.2 (aromatic carbons), 164.7 (CO), 165.2 (CO). MS (m/z (%)): 288.1 (M^+, 68), 215.1 (100). Anal. Calcd. for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.72. Found: C, 66.58; H, 6.67; N, 9.81.

2-Cyano-5-dimethylamino-hexa-2,4-dienoic acid amide (**12c**): Yellow crystals. Yield: (chitosan: 82%, piperidine: 76%), M.p.: 243 °C. IR (KBr, cm^{-1}): 3340 and 3320 ν(NH_2), 2180 ν(CN), 1670 ν(CO, amide). ^{1}H NMR (400 MHz, DMSO-d_6, δ): 1.14 (CH_3), 2.78 (s, 6H, $N(CH_3)_2$), 5.29 (d, 1H, *J*=12.6 Hz, diene CH), 5.82 (s, 2H, NH_2), 7.84 (d, 1H, *J*=12.6 Hz, diene CH). ^{13}C NMR (125 MHz, DMSO-d_6, δ): 17.6 (CH_3), 38.9 ($N(CH_3)_2$), 118.1 (CN), 98.3, 104.9, 145.2, 147.6 (diene carbons), 164.8 (CO). MS (m/z (%)): 179.1 (M^+, 100), 135.1 (58). Anal. Calcd. for $C_9H_{13}N_{30}$: C, 60.32; H, 7.31; N, 23.45. Found: C, 59.88; H, 7.22; N, 23.18.

2-Carbamoyl-5-dimethylamino-hexa-2,4-dienoic acid ethyl ester (**12d**): Pale yellow solid. Yield: (chitosan: 68%, piperidine: 74%). M.p.: 271 °C. IR (KBr, cm^{-1}): 3355 and 3340 ν(NH_2), 1689 ν(CO, ester), 1660 ν(CO, amide). ^{1}H NMR (400 MHz, DMSO-d_6, δ): 1.17 (t, 3H, *J*=7 Hz, CH_3), 1.82 (s, 3H, CH_3), 2.67 (s, 6H, $N(CH_3)_2$), 4.11 (q, 2H, *J*=7 Hz, CH_2), 5.84 (d, 1H, *J*=12.5 Hz, diene CH), 6.70 (s, 2H, NH_2), 8.26 (d, 1H, *J*=12.5 Hz, diene CH), 7.18 – 7.61 (m, 5H, phenyl-H). ^{13}C NMR (125 MHz, DMSO-d_6, δ): 14.9 (CH_3), 18.6 (CH_3), 41.0 ($N(CH_3)_2$), 58.7 (CH_2), 102.1, 113.3, 141.0 (diene carbons), 162.8 (CO), 163.9 (CO). MS (m/z (%)): 226.1 (M^+, 18), 181.1 (100). Anal. Calcd. for $C_{11}H_{18}N_2O_3$: C, 58.39; H, 8.02; N, 12.38. Found: C, 58.15; H, 7.92; N, 12.14.

2.3. Cyclization of enaminone 12c,e

A solution of enaminone**12c** or **12e** (1.79 g, 10 mmol) in 30 mL glacial acetic acid was stirred at reflux for 5 h. The resulting solution was cooled and neutralized with aq. Na_2CO_3, causing the formation of a solid product 14, which was purified by crystallization from ethanol (Scheme 2).

2-Amino-4-dimethylamino-benzonitrile (**14**): Yellow solid. Yield: 54%. M.p.: 162 °C. IR (KBr, cm^{-1}): 3450 and 3330 ν(NH_2), 2181 ν(CN). ^{1}H NMR (400 MHz, DMSO-d_6, δ): 2.81 (s, 6H, $N(CH_3)_2$), 5.61 (s, 2H, NH_2), 6.80–7.57 (m, 3H, phenyl-H). ^{13}C NMR (125 MHz, DMSO-d_6, δ): 40.9 ($N(CH_3)_2$), 117.8 (CN), 106.0, 113.7, 133.4, 141.6, 142.8 (aromatic carbons). MS (m/z (%)): 161.1 (M^+, 100), 117.1 (46). Anal. Calcd. for $C_9H_{11}N_3$: C, 67.06; H, 6.88; N, 26.07. Found: C, 66.91; H, 6.74; N, 25.84.

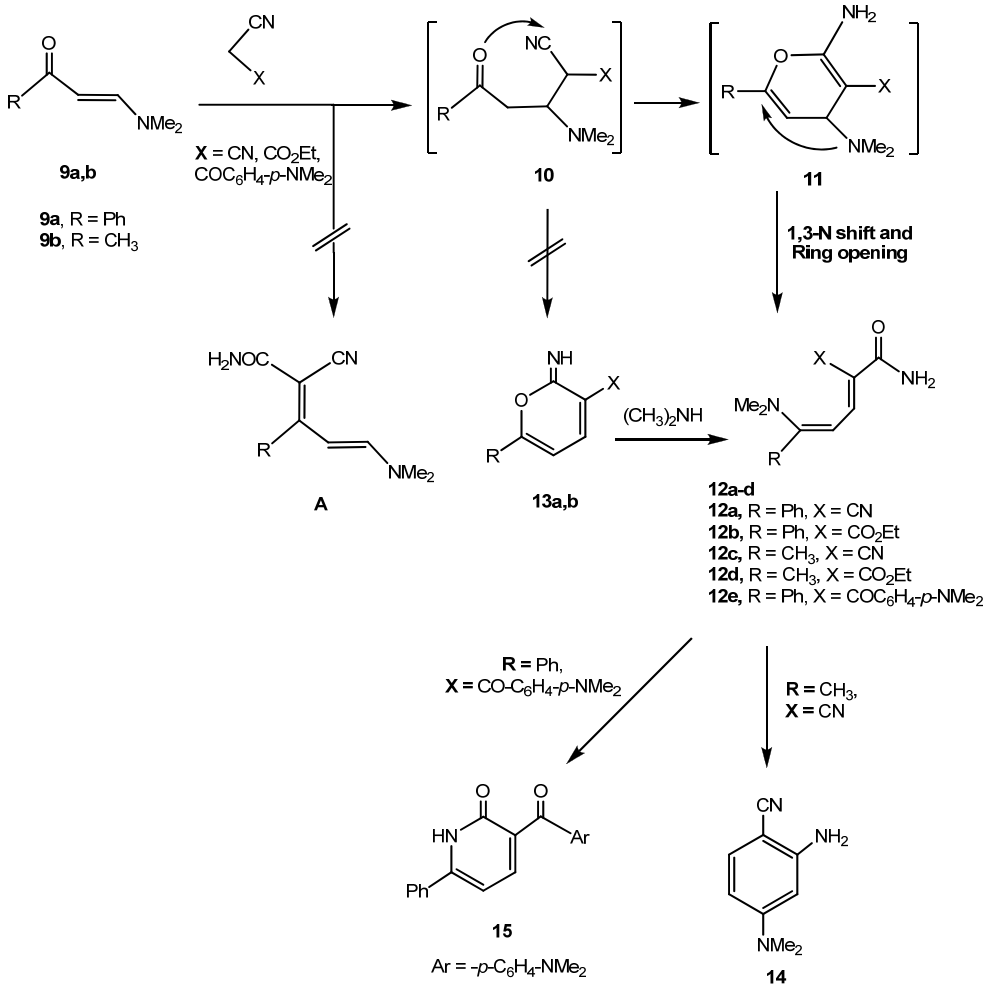
3-(4-Dimethylamino-benzoyl)-6-phenyl-1H-pyridin-2-one (**15**): Yellow solid. Yield: 58%. IR (KBr, cm^{-1}): 3400 ν(NH), 1680 and 1678 ν(CO).^{1}H NMR (400 MHz, DMSO-d_6, δ): 2.86 (s, 6H, $N(CH_3)_2$), 6.76 (m, 11H, Aromatic H), 8.79 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6, δ): 41.1 ($N(CH_3)_2$), 97.3, 101.1, 113.5, 129.7, 136.7, 137.4, 143.6, 144.8, 145.8, 151.4 (aromatic carbons), 169.4 (CO), 184.3 (CO). MS (m/z (%)): 318.1 (M^+, 100), 171.1 (66). Anal. Calcd. for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.27; H, 5.61; N, 8.54.

2.4. Reaction of enaminones 9a,b with ethylacetoacetate

A mixture of enaminones**9a** or **9b** (10 mmol) and 1.3 g (10 mmol) of ethyl acetoacetate was dissolved in 30 mL absolute ethanol in presence of catalytic amount of chitosan (10% by wt.). The reaction mixture was stirred at reflux for 6 h and filtered to remove chitosan. The residue obtained by concentration in vacuo was crystallized from ethanol (Scheme 3).

3-Acetyl-6-phenyl-pyran-2-one (**17a**):Yellow solid. Yield: 75%. IR (KBr, cm^{-1}): 1714 ν(CO, lactone), 1709 ν(CO, ketone). ^{1}H NMR (400 MHz, DMSO-d_6, δ): 1.88 (s, 3H, CH_3), 6.69 (d, 1H, *J*=8 Hz, lactone-CH), 7.83 (d, 1H, *J*=8 Hz, lactone-CH), 7.13–7.61 (m, 5H, phenyl ring). ^{13}C NMR (125 MHz, DMSO-d_6, δ): 16.7 (CH_3), 86.5, 122.4, 123.1, 123.6, 134.3, 136.2 141.9, 146.8 (aromatic and lactone carbons), 158.4 (lactone CO), 171.6 (CO). MS (m/z (%)): 214.1 (M^+, 100), 199.1 (67). Anal. Calcd. for $C_{13}H_{10}O_3$: C, 72.89; H, 4.71. Found: C, 72.61; H, 4.65.

3-Acetyl-6-methyl-pyran-2-one (**17b**): Yellow solid. Yield: 70%. IR (KBr, cm^{-1}): 1719 ν(CO, ester), 1711 ν(CO, ketone).



Scheme 2

^{1}H NMR (400 MHz, DMSO-d_6, δ): 1.87 (s, 3H, CH_3), 1.92 (s, 3H, CH_3), 6.44 (d, 1H, *J*=8 Hz, lactone CH), 7.58 (d, 1H, *J*=8 Hz, lactone CH). ^{13}C NMR (125 MHz, DMSO-d_6, δ): 14.3 (CH_3), 15.7 (CH_3), 97.8, 127.6, 138.4, 143.4 (lactone carbons), 162.1 (lactone CO), 176.9 (CO). MS (m/z (%)): 152.1 (M^+, 100), 137.1 (42). Anal. Calcd. for $C_8H_8O_3$: C, 63.15; H, 5.30. Found: C, 62.97; H, 5.23.

2.5. Reaction of enaminones 9a,b with ethyl cyanoacetate and elemental sulfur

A mixture of enaminones **9a** or **9b** (10 mmol), 1.13 g (10 mmol) of ethyl cyanoacetate and 10 mmol of elemental sulfur was dissolved in 30 mL absolute ethanol. The solution was stirred at reflux for 4 h in presence of catalytic amount of chitosan (10% by wt.). Chitosan was removed by filtration and the filtrate was concentrated in vacuo giving a residue which was crystallized from ethanol (Scheme 4).

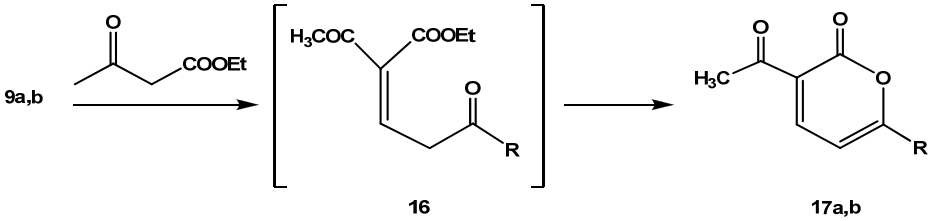
2-Amino-5-benzoyl-thiophene-3-carboxylic acid ethyl ester (**19a**): Yellow crystals. Yield: 76%. M.p.: 142 °C (literature [16] Mp 142 °C). IR (KBr, cm^{-1}): 3450 and 3320 ν(NH_2), 1680 ν(CO), 1635 ν(CO). ^{1}H NMR (400 MHz, DMSO-d_6, δ): 1.33 (t, 3H, *J*=8 Hz, CH_3), 4.52 (q, 2H, *J*=8 Hz, CH_2), 6.70 (br., 2H, NH_2, D_2O exchangeable), 7.38–7.69 (m, 6H, Ar-H, thiophene-CH). ^{13}C NMR (125 MHz, DMSO-d_6, δ): 13.7 (CH_3), 64.8 (CH_2), 104.9, 122.7, 129.1, 130.5, 158.7 (aromatic carbons), 162.1 (CO), 168.0 (CO). MS (m/z (%)): 275.1 (M^+, 100), 231.1 (17). Anal. Calcd. for $C_{14}H_{13}NO_3S$: C, 61.07; H, 4.76; N, 5.09; S: 11.65. Found: C, 60.85; H, 4.59; N, 4.88; S: 11.61.

5-Acetyl-2-amino-thiophene-3-carboxylic acid ethyl ester (**19b**): Yellow solid. Yield: 80%. M.p.: 94 °C. IR (KBr, cm^{-1}): 3460 and 3340 ν(NH_2), 1712 ν(CO), 1708 ν(CO). ^{1}H NMR (400 MHz, DMSO-d_6, δ): 1.18 (s, 3H, CH_3), 1.29 (t, 3H, *J*=8 Hz, CH_3), 4.16 (q, 2H, *J*=8 Hz, CH_2), 6.21 (br., 2H, NH_2, D_2O exchangeable), 7.78 (s, 1H, thiophene-CH). ^{13}C NMR (125 MHz, DMSO-d_6, δ): 13.2 (CH_3), 16.4 (CH_3), 61.3 (CH_2), 106.1, 122.4, 132.5, 142.4 (thiophene carbons), 163.4 (CO), 176.2 (CO). MS (m/z (%)): 213.1 (M^+, 100), 168.1 (35). Anal. Calcd. for $C_9H_{11}NO_3S$: C, 50.69; H, 5.20; N, 6.57; S: 15.04. Found: C, 50.18; H, 5.06; N, 6.08; S: 14.94.

2.6. Reaction of enaminones 9a,b with cyanothioacetamide and with cyanoacetamide

A mixture of enaminones **9a** or **9b** (10 mmol) and 10 mmol of thioacetamide (or acetamide) was dissolved in 30 mL absolute ethanol containing a catalytic amount of chitosan (10% by wt.). The reaction mixture was stirred at reflux for 4 h. Undissolved chitosan was removed by filtration and the residue obtained by concentration of the filtrate was crystallized from ethanol (Scheme 5, 6).

6-Phenyl-2-thioxo-1,2-dihydro-pyridine-3-carbonitrile (**22a**): Yellow solid. Yield: 74%. M.p.: 255 °C (Lit. [7], M.p.: 255 °C). IR (KBr, cm^{-1}): 3345 ν(NH), 2185 ν(CN), 1684 ν(CO, thioamide).



Scheme 3

^{1}H NMR (400 MHz, DMSO-d_6, δ): 7.09 (d, 1H, *J*=12.6 Hz, H-4), 8.14 (d, 1H, *J*=12.6 Hz, H-5), 7.53–7.78 (m, 5H, phenyl-H), 14.27 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6, δ): 83.4 (C-5, thiopyridone), 113.7 (C-3, thiopyridone), 117.3 (CN), 121.1, 128.6, 130.4, 131.8, 136.3, 142.1, 144.6 (aromatic carbons), 168.2 (C=S). MS (m/z (%)): 212.1 (M^+, 100), 77.1 (26). Anal. Calcd. for $C_{12}H_8N_2S$: C, 67.90; H, 3.80; N: 13.20; S: 15.11. Found: C, 67.46; H, 3.66; N: 12.94; S: 15.03.

6-Methyl-2-thioxo-1,2-dihydro-pyridine-3-carbonitrile (**22b**): Yellow powder. Yield: 67%. M.p.: 237 °C (literature [8], M.p.: 236 °C). IR (KBr, cm^{-1}): 3350 ν(NH), 2180 ν(CN), 1672 ν(CS, thioamide). ^{1}H NMR (400 MHz, DMSO-d_6, δ): 1.73 (s, 3H, CH_3), 6.89 (d, 1H, *J*=12.6 Hz, H-4), 7.76 (d, 1H, *J*=12.6 Hz, H-5), 13.07 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, δ): 18.4 (CH_3), 72.6 (C-5, thiopyridone), 112.5 (C-3, thiopyridone), 117.1 (CN), 147.3 (C-6, thiopyridone), 148.8 (C-4, thiopyridone), 165.2 (C=S). MS (m/z (%)): 150.1 (M^+, 100). Anal. Calcd. for $C_7H_6N_2S$: C, 55.97; H, 4.03; N: 18.65; S: 21.35. Found: C, 55.78; H, 3.82; N: 18.21; S: 21.10.

2-Oxo-6-phenyl-1,2-dihydro-pyridine-3-carboxylic acid amide (**25a**): Yellow powder. Yield: 78%. M.p.: >300°C with decomposition. IR (KBr, cm^{-1}): 3345 and 3330 ν(br. band of NH and NH_2), 1668 and 1658 ν(CO, amide). ^{1}H NMR (400 MHz, DMSO-d_6, δ): 5.47 (s, 2H, NH_2), 6.14 (d, 1H, *J*=12 Hz, H-4), 7.06–7.73 (m, 5H, phenyl-H), 8.22 (d, 1H, *J*=12 Hz, H-3), 8.16 (s, 1H, NH).^{13}C NMR (125 MHz, DMSO-d_6, δ): 103.7, 122.4, 123.6, 124.8, 126.7, 126.9, 134.8, 139.1 (aromatic carbons), 156.7 (CO), 163.2 (CO). MS (m/z (%)): 214.1 (M^+, 100). Anal. Calcd. for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N: 13.08. Found: C, 67.09; H, 4.65; N: 12.87.

2-Oxo-6-phenyl-1,2-dihydro-pyridine-3-carboxylic acid amide (**25b**): Yellow solid. Yield: 64%. M.p.: 300 °C (literature [9], M.p.: 301 °C). IR (KBr, cm^{-1}): 3340 and 3330 ν(br. band of NH and NH_2), 1665 and 1660 ν(CO, amide). ^{1}H NMR (400 MHz, DMSO-d_6, δ): 1.77 (s, 3H, CH_3), 5.20 (d, 1H, *J* = 12 Hz, pyridone CH), 5.96 (s, 2H, NH_2), 7.25 (d, 1H, *J* = 12 Hz, pyridone CH), 8.51 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6, δ): 17.3 (CH_3), 102.7, 129.4, 135.2, 139.8, (pyridone carbons), 164.8 (CO), 167.5 (CO). MS (m/z (%)): 152.1 (M^+, 100). Anal. Calcd. for $C_7H_8N_2O_2$: C, 55.26; H, 5.30; N: 18.41. Found: C, 55.16; H, 5.23; N: 18.28.

2.7. Chitosan catalyzed reaction of 3 with pyridazinone

A mixture of 1.54 g (10 mmol) benzylidene-malononitrile 3a and 2.11 g (10 mmol) was dissolved in 30 mL absolute ethanol containing a catalytic amount of chitosan (10% wt). The reaction mixture was stirred at reflux for 6 h. The product was isolated and purified in the manner described above (Scheme 7).

5-Amino-4-oxo-3,7-diphenyl-3,4-dihydro-phthalazine-6-carbonitrile (**28**): Yellow solid. Yield: 60%. M.p.: 262 °C (literature [10], M.p.: 261 °C). IR (KBr, cm^{-1}): 3340 and 3300 ν(br., NH_2), 2180 ν(CN), 1625 ν(CO, amide). ^{1}H NMR (400 MHz, DMSO-d_6, δ): 5.66 (s, 2H, NH_2), 7.04–8.19 (m, 12H, aromatic-H). ^{13}C NMR (125 MHz, DMSO-d_6, δ): 117.1 (CN), 100.1, 119.7, 121.0, 121.4, 124.2, 125.7, 127.3, 130.4, 134.8, 139.2, 139.5, 144.6 (aromatic carbons), 162.8 (CO). MS (m/z (%)): 338.1 (M^+, 100). Anal. Calcd. for $C_{21}H_{14}N_4O$: C, 74.54; H, 4.17; N: 16.56. Found: C, 74.42; H, 4.11; N: 16.48.

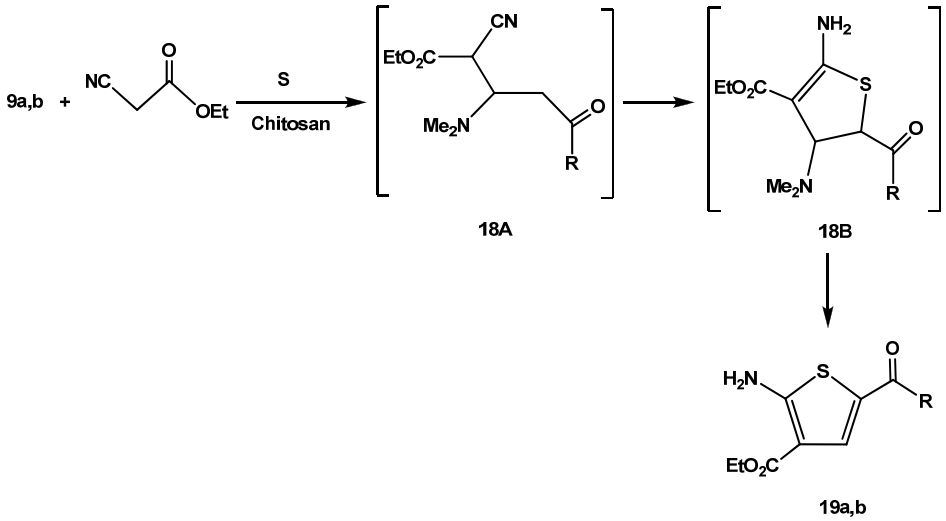
3. Results and discussion

Our studies of chitosan catalyzed addition reactions of active methylene compounds were ultimately aimed at developing synthetic routes for the preparation of potentially biological interesting substances, including enedienes, pyridones, thiopyridones as well as phthalazines. In exploratory studies, we observed that chitosan promoted reactions of *β*-enaminones **9a,b** with malononitrile afford the same products obtained earlier from reactions of the same substrates in presence of piperidine [6,11]. Although it was proposed earlier that these products are conjugated amino nitriles, A, [12], we recently established on the basis of both X-ray and ^{15}N NMR analysis that the products actually are the enedienes **12a,b** (Scheme 2). Recently Abdelrazik [13] and Gorobets [14] have reached the same conclusion based on X-ray crystallographic analysis results. Further support of the newly assigned structures comes from the observation that enediene**12c** undergoes cyclization to give **14** when stirred in refluxing glacial acetic acid.

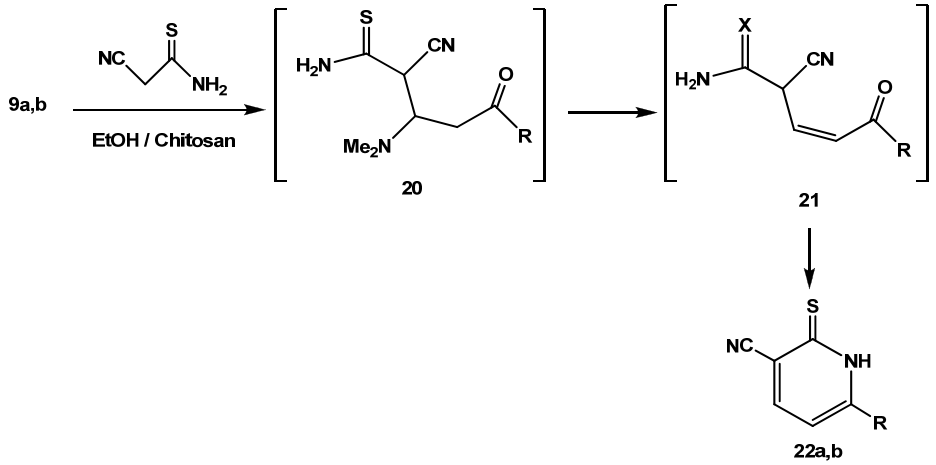
In a similar manner, **9a,b** react with ethyl cyanoacetate and 3-(4-dimethylamino-phenyl)-3-oxo-propionitrile in the presence of chitosan to yield **12a-d**, formed by the sequence shown in Scheme 2. Earlier, we suggested that the mechanistic route involves initial 1,4-addition of malononitrile to the enaminones to produce **10a,b** that cyclize to form **11a,b**, which then undergo a 1,3-nitrogen shift to yield **12a,b**. More recently, Abdelrazik [15] suggested that the pyranimine**13** is initially formed in a closely related piperidine promoted process and that it subsequently adds dimethylamine to form **12**. The mechanism suggested by Abdelrazik seemed unlikely since in his case the reaction was conducted in presence of piperidine, which is more nucleophilic and much less volatile than dimethylamine. Thus, if the Abdelrazikpathway is operating, one would expect the products of piperidine addition to **13** would be produced.

In order to gain information about this mechanistic issue, we repeated the reactions explored by Abdelrazik using an excess piperidine. In these processes, not even trace quantities of piperidine incorporated products were formed. Moreover, reactions in the presence of excess diethylamine did not generate even trace quantities of derivatives of **12** in which NEt_2 exits in the place of the NMe_2 group. Finally, even if dimethylamine is formed in the reaction mixture, at the temperature used it should be removed rapidly by evaporation.

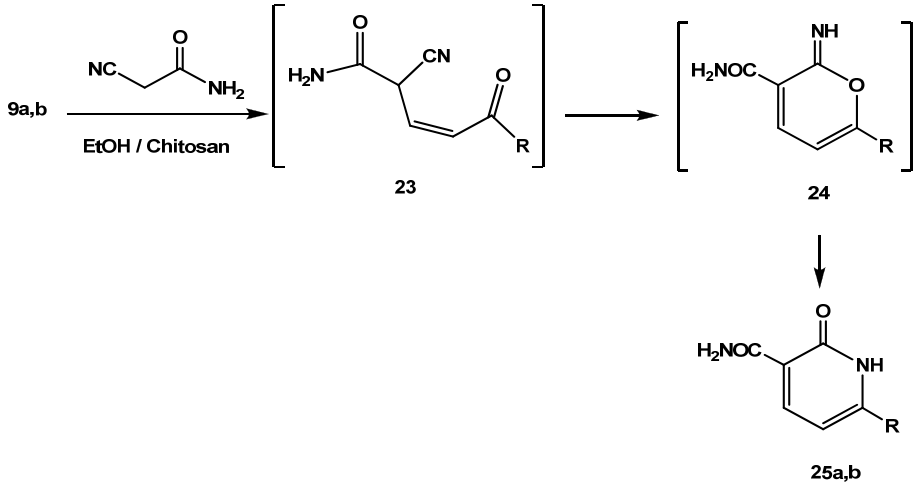
In contrast to the observed behavior with malononitrile and ethyl cyanoacetate, reactions of **9a,b** with ethyl acetoacetate in presence of chitosan as a catalyst produced lactones **17a,b** (Scheme 3). The initial step in this process involve ethyl acetoacetate addition to **9a,b** yielding Michael adducts that readily eliminate dimethylamine to yield **16**. Elimination of ethanol from **16** then affords **17a,b**. Importantly, addition of the eliminated dimethylamine to the pyran ring, as suggested by the Abdelrazik mechanism, did not occur.



Scheme 4

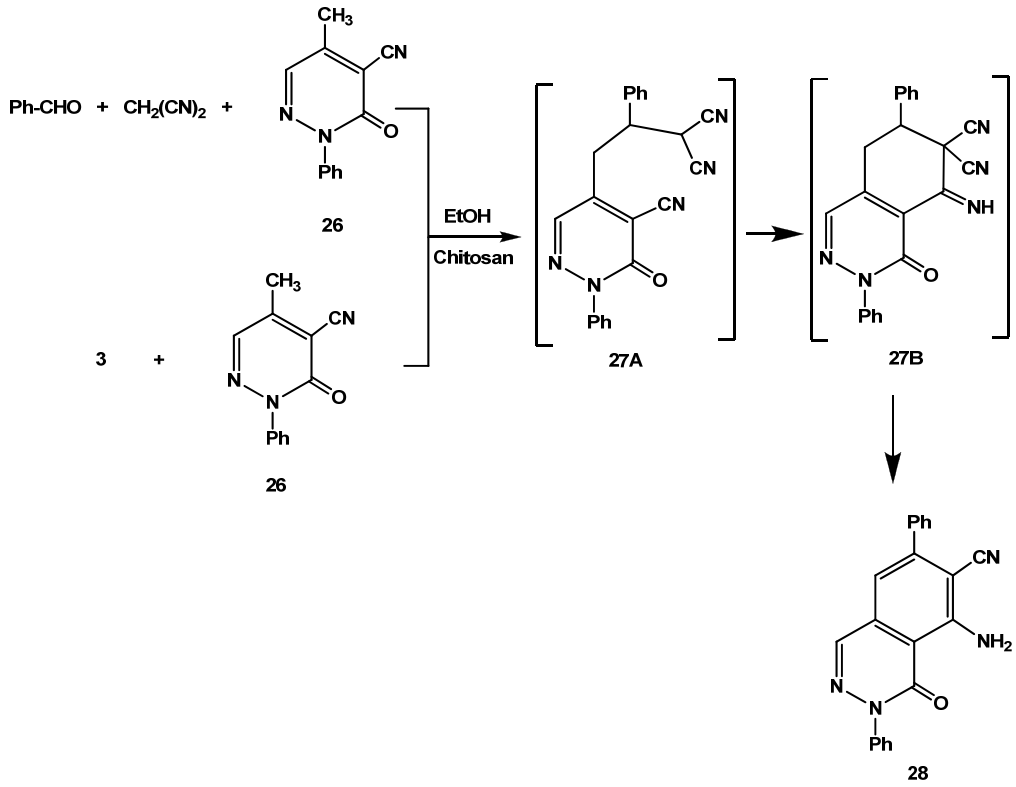


Scheme 5



Scheme 6

Chitosan catalyzed reaction of **9a,b** with ethyl cyanoacetate in a solution containing elemental sulfur afforded the thiophene derivative **19** in 65% yield (Scheme 4). Product formation takes place via the intermediacy of **18A** and **18B**. It should be noted that a previous report [16] described the production of **17** in 68% yield in a similar process utilizing



Scheme 7

piperidine as the catalyst. As proposed by Al-Mousawi*et al.* [16], the initial step in these reactions involves Michael addition of ethyl cyanoacetate to the activated double bonds of **9a,b** to yield intermediate **18A**. This is followed by addition of sulfur to afford **18B**, which is then converted to **19a,b**.

Reactions of **9a,b** with cyanothioacetamide in the presence of chitosan affords the pyridine-thiones **22a,b** (Scheme 5). In the route for product formation, intial addition of **9a,b** to the activated double bond of cyanothioacetamide affords adduct **20** that undergoes subsequent elimination of dimethylamine to yield **21**. Cyclization of **21** via water elimination then affords the observed products **22a,b**.

In contrast to the observations described above, reactions of **9a,b** with cyanoacetamide afford products that arise by dimethylamine elimination. Possible structures of these products include **23** and **24** (Scheme 6). However, the acyclic substance **23** could be readily ruled out on the basis of both IR and ^{13}C NMR spectroscopic properties, which ruled out the presence of a cyano group in the products. However, in spite of reports to the contrary, [13] pyraneimines like **24** are highly unstable substances. This consideration led us to propose that the products of these reactions have the pyridone structures **25a,b**. The results of *NOE* experiments, and in particular the observation that irradiation of the NH proton causes an enhancement in the aryl proton signal intensities and vice versa, support this assignment.

Additional studies showed that chitosan also catalyzes condensation reactions between benzaldehyde, malononitrile and pyridazinone **26** yielding the pthalazinone **28** (Scheme 7) that was reported [17] earlier to be produced in pyridine assisted reactions of the substrates. We believe that the initial step in this process involves benzaldehyde condensation with malononitrile to yield benzylidene-malononitrile, a reaction that has been reported to occur under mild conditions [18, 19]. The benzylidene-malononitrile then adds to **26** to yield Michael adduct **27A** that cyclizes to yield cyclic imine **27B**, which serves as the precursor of 28.

4. Conclusion

The studies described above clearly demonstrate that chitosan serves as an efficient basic heterogeneous catalyst for a variety of Michael addition reactions. Moreover the scope and limitations of enedienes formed in reactions of enaminones with active methylene compounds has been defined.

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References

[1]. Niola, F.; Basora, N.; Chornet, E.; Vidal, P. F. *Carbohyd. Res.* **1993**, *238*, 1-9.
[2]. Bader, H. J.; Birkholz, E. *Prax. Natur. Chem.* **1996**, *45(6)*, 24-30.
[3]. Rege, P. R.; Block, L. H. *Carbohyd. Res.***1999**, *321*, 235-245.
[4]. Gomha, S. M.; Riyadh, S. M. *Arkivoc* **2009**, *11*, 58-68.
[5]. Al-Matar, H. M.; Khalil, K. D.; Meier, H.; Kolshorn, H.; Elnagdi, M. H. *Arkivoc* **2008**, *16*, 288-301.
[6]. Alnajjar, A.; Abdelkhalik, M. M.; Al-Enezi, A.; Elnagdi, M. H. *Molecules* **2009**, *14(1)*, 68-77.
[7]. Al-Saleh, B.; El-Apasery, M. A.; Abdel-Aziz, R. S.; Elnagdi, M. H. *J. Heterocyclic Chem.* **2005**, *42(4)*, 563-566.
[8]. Schmidt, U.; Kubitzek, H. *Chemische Berichte* **1960**, *93*,1559-65.
[9]. Boatman, S.; Harris, T. M.; Hauser, C. R. *J. Org. Chem.* **1965**, *30(11)*, 3593-7.
[10]. Ghozlan, S. A. S.; Abdelhamid, I. A.; Elnagdi, M. H. *Arkivoc* **2006**, *13*, 147-157.
[11]. Al-Mousawi, S. M.; Moustafa, M. S.; Abdelkhalik, M. M.; Elnagdi, M. H. *Arkivoc* **2009**, *11*, 1-10.
[12]. Al-Omran, F.; Al-Awadi, N.; Abdelkhalik, M. M.; Kaul, K.; Elkhair, A. A.; Elnagdi, M. H. *J. Chem. Res.* (S) **1997**, *84,* 601-613.
[13]. Abdelrazek, F. M.; Elsayed, A. N. *J. Heterocyclic Chem.* **2009**, *46*, 949-953.
[14]. Gorobets, N. Y.; Sedash, Y. V.; Shishkina, S. V.; Shishkin, O. V.; Yermolayev, S. A.; Desenko, S. M. *Arkivoc* **2009**, *13*, 23-30.
[15]. Abdelrazek, F. M.; Michael, F. A. *J. Heterocyclic Chem.* **2006**, *43(1)*, 7-10.

[16]. Al-Mousawi, S.; Moustafa, M. S.; Elnagdi, M. H. *Arkivoc* **2008**, *10*, 17-25.
[17]. Al-Saleh, B.; Hilmy, Noha M.; El-Apasery, M. A.; Elnagdi, M. H. *J. Heterocyclic Chem.* **2006**, *43(6)*, 1575-1581.
[18]. Mogilaiah, K.; Rani, J. Uma. Indian *J. Heterocycl. Chem*. **2003**, *13(2)*, 169-170.
[19]. Xu, Da-Zh.; Liu,Y.; Shi S.; Wang, Y.*GreenChem*. **2010**, *12*, 514-517.