Chemoselective reaction of malononitrile with imine-ones and antifungal potential of products

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Condensation of malononitrile with 1-[4-(benzylideneamino)phenyl]ethanones 1-10, the compounds containing both carbon-nitrogen and carbon-oxygen double bonds, in equimolar ratio results in the formation of solid products, identified as 2-benzylidenemalononitrile and its derivatives 1a-10a on the basis of elemental analysis and spectral studies. The reaction of 1-10 with two moles of malononitrile also yields the same products 1a-10a by a chemoselective attack of malononitrile on carbon-nitrogen double bond only rather than on both the reactive centres. The synthesized compounds 1a-10a have been evaluated for antifungal potential against *Alternaria alternata*, *Colletotrichum capsici*, *Fusarium oxysporum*, *Myrothecium roridum* and *Ustilago tritici*. Some of the compounds have been found to possess promising antifungal potential against the test fungi.

Keywords: 1-[4-(Benzylideneamino)phenyl]ethanones, malononitrile, imine-ones, 2-benzylidenemalononitriles, antifungal potential

Chemistry of multiple bonds has achieved a dramatic development in the past decades because these compounds have been used as substrates in the synthesis of industrial and biologically active compounds. Moreover, the compounds containing carbon-nitrogen, carbon-oxygen and/or carbon-carbon double bond are known to possess biological activities such as antimicrobial, antifungal, antitumor and nematicidal. Malononitrile reacts with carbonyl compounds to give condensation products whereas such a reaction with imines have been reported to yield either addition-elimination products or compounds containing heterocyclic rings. The carbon-nitrogen double bond is intermediate in reactivity between carbon-oxygen and carbon-carbon double bonds. In continuation of earlier work on imine-ones, i.e. 1-(4-(benzylideneamino)phenyl)ethanone and its C-phenyl derivatives, this communication describes the chemoselective reaction of malononitrile with 1-(4-(benzylideneamino)phenyl)-ethanones and evaluation of products for antifungal activity.

Condensation of malononitrile with 1-[4-(benzylideneamino)phenyl] ethanone and its C-phenyl derivatives 1-10, the compounds synthesized by condensing 1-(4-aminophenyl) ethanone with aryl aldehydes, in equimolar ratio in the presence of catalytic amount of pyridine resulted in the formation of crude solids which were purified by recrystallization from suitable solvent. The IR spectra of the products contained absorption bands at ~2230 and 1590 and 850 cm⁻¹ indicating the presence of cyano group and -CH=C < linkage, respectively. In addition to above bands, the absorption bands at ~ 3400 cm⁻¹ were also observed in IR spectra of compounds 3a, 7a and 8a and around 1540 and 1360 cm⁻¹ in the IR spectra of 9a and 10a which were assigned to phenolic and nitro groups respectively.

In the ¹H NMR spectra of the products, the protons resonated in the expected field. Multiplet signals of integration corresponding to 6 protons in compound 1a; five protons in compounds 2a, 3a, 4a, 9a and 10a; four protons in products 5a, 7a and 8a and three protons in the compound 6a observed between δ 7.0-7.9 accounted for aromatic protons alongwith one olefinic proton. In addition to above signals, the functional group signals of the respective product were also observed. Mass spectra of the compounds revealed that the molecular ion peak also constituted the base peak. On the basis of elemental and spectral data analysis, the products 1a-10a have been characterized as 2-benzylidenemalononitrile and its derivatives. The 2-benzylidenemalononitriles along with their physical characteristics and spectral data are recorded in Table I.

Condensation of two moles of malononitrile with one mole of 1-[4-(benzylideneamino)phenyl] ethanone and its C-phenyl derivatives 1-10 also yielded the same products 1a-10a. The formation of 2-benzylidenemalononitriles 1a-10a can be explained due to the attack of the carbanion formed from malononitrile on carbon-nitrogen double bond of 1-[4-(benzylideneamino)phenyl]ethanone, to give unstable addition products which lose 1-(4-amino-
phenyl) ethanone to give the stable addition-elimination products (Scheme I).

Malononitrile, thus, reacted unexpectedly with carbon-nitrogen double bond of 1-[4-(benzylidene-phenyl) phenyl] ethanones only leaving carbon-oxygen double bond, considered to be more reactive, intacted under the reaction conditions, leading to the formation of mono addition-elimination products rather than bis attack at both the reactive centres, even when the reaction was carried out with two moles of malononitrile. Thus condensation of malononitrile is a chemoselective reaction with 1-[4-(benzylidene-phenyl) phenyl] ethanones.

The products 1a-10a were evaluated in vitro for the antifungal potential against *Alternaria alternata, Colletotrichum capsici, Fusarium oxysporum, Myrothecium roridum* and *Ustilago tritici* by spore germination inhibition technique \(^{11}\) at various concentrations. The results have been expressed in terms of ED\textsubscript{50} values \textit{i.e.} the effective dose at which 50 per cent spore germination inhibition is caused (Table II).

The test compounds exhibited poor to promising antifungal potential against the test fungi. Compounds 2a and 5a showed promising activity whereas compounds 3a and 9a possessed moderate potency against *A. alternata*. All the test compounds had ED\textsubscript{50} values less than 1000 \(\mu g/mL\) against *C. capsici* and

<table>
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<tr>
<th>Compd</th>
<th>R</th>
<th>m.p. °C</th>
<th>Yield %</th>
<th>(^1)H NMR spectrum (δ) functional group</th>
<th>M** (m/z)</th>
<th>Mol. formula</th>
</tr>
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<tr>
<td>1a</td>
<td>H</td>
<td>130</td>
<td>71</td>
<td>-</td>
<td>154</td>
<td>C(_{10})H(_6)N(_2)</td>
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<tr>
<td>2a</td>
<td>4-Cl</td>
<td>105</td>
<td>62</td>
<td>-</td>
<td>188</td>
<td>C(_{10})H(_6)N(_2)Cl</td>
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<tr>
<td>3a</td>
<td>4-OH</td>
<td>110</td>
<td>59</td>
<td>9.5 (s, 1H, OH)</td>
<td>170</td>
<td>C(_{10})H(_6)N(_2)O</td>
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<tr>
<td>4a</td>
<td>4-OCH(_3)</td>
<td>121</td>
<td>59</td>
<td>4.1 (s, 3H, OCH(_3))</td>
<td>184</td>
<td>C(_{11})H(_6)N(_2)O</td>
</tr>
<tr>
<td>5a</td>
<td>3-OCH(_3), 4-OCH(_3)</td>
<td>78</td>
<td>60</td>
<td>4.0 (s, 6H, 2 × OCH(_3))</td>
<td>214</td>
<td>C(<em>{12})H(</em>{10})N(_2)O(_2)</td>
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<tr>
<td>6a</td>
<td>3-OCH(_3), 4-OCH(_3), 5-OCH(_3)</td>
<td>97</td>
<td>55</td>
<td>4.0 (s, 9H, 3 × OCH(_3))</td>
<td>244</td>
<td>C(<em>{13})H(</em>{12})N(_2)O(_3)</td>
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<tr>
<td>7a</td>
<td>3-OCH(_3), 4-OH</td>
<td>91</td>
<td>64</td>
<td>4.1 (s, 3H, OCH(_3)) 9.4 (s, 1H, OH)</td>
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<td>C(_{11})H(_6)N(_2)O (_2)</td>
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<tr>
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<td>3-OCH(_2)(_2), 4-OH</td>
<td>79</td>
<td>59</td>
<td>4.4 (q, 2H, OCH(_2)CH(_3)) 1.5 (t, 3H, OCH(_2)CH(_3)) 9.5 (s, 1H, OH)</td>
<td>214</td>
<td>C(<em>{12})H(</em>{10})N(_2)O (_2)</td>
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<td>9a</td>
<td>2-NO(_2)</td>
<td>60</td>
<td>58</td>
<td>-</td>
<td>199</td>
<td>C(_{10})H(_5)N(_3)O(_2)</td>
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<tr>
<td>10a</td>
<td>3-NO(_2)</td>
<td>90</td>
<td>60</td>
<td>-</td>
<td>199</td>
<td>C(_{10})H(_5)N(_3)O(_2)</td>
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Table I — Characteristics and spectral data of 2-benzylidenemalononitriles

Scheme I

![Scheme I](image)
the compound 3a possessed better potential with ED₅₀ value of 150 µg/mL. The test compounds 1a-8a showed ED₅₀ values less than 1000 µg/mL against F. oxysporum and compounds 1a and 5a had better potency with ED₅₀ value of 180 and 120 µg/mL respectively. Three test compounds viz. 5a, 3a and 1a have been found to possess promising activity against M. roridum with ED₅₀ value of 60, 70 and 130 µg/mL. Six test compounds presented moderate activity against U. tritici.

Experimental Section

The purity of the products was checked by TLC. The melting points were determined on electric melting point apparatus and are uncorrected. The compounds gave satisfactory elemental analysis. The IR spectra were recorded on a Perkin-Elmer FT-IR spectrometer using KBr disc. The ¹H NMR spectra were recorded on a Bruker Spectrospin 300 MHz spectrometer in CDCl₃ with TMS as internal standard. Mass spectra were recorded on Perkin-Elmer Clarus 500 Mass Spectrometer.

General procedure for reaction of malononitrile with 1-[4-(benzylideneamino)phenyl] ethanones. 1-(4-(Benzylideneamino)phenyl)ethanone/its derivative (1-10) (0.01 mole) was taken in dry benzene (20 mL) in a conical flask (100 mL). Then malononitrile (0.01 mole) and a few drops of pyridine were added to the above solution. The reaction mixture was heated and shaken briskly for 15 min. The flask was then cooled, stopped and allowed to stand at room temperature overnight when a crude solid separated out which was filtered and purified by recrystallisation from suitable solvent to get pure 2-benzylidenemalononitrile/its derivatives 1a-10a. Evaporation of the solvent from the filtrate yielded jelly like mass, TLC of which indicated the presence of 1-(4-aminophenyl)ethanone and unreacted starting materials.

Condensation of malononitrile with 1-(4-(benzylideneamino)phenyl)ethanones 1-10 in 2:1 molar ratio was also carried out by following the above procedure.

In vitro screening for antifungal potential. The stock solution of each compound was prepared by dissolving each chemical (20 mg) in absolute alcohol (0.5 mL) and the volume was made to 10 mL with sterilized distilled water. The stock solution of 2000 µg/mL of each compound thus prepared on active ingredient basis was kept in refrigerator till use. The required dilutions were subsequently made from the stock solution by adding sterilized distilled water as and when required.

Small droplets (0.02 mL) of test solution and spore suspension in equal amount were seeded in the cavity slides. These slides were kept in petriplates lined with moist filter paper and incubated for 24 hr at 25±1°C. The slides were checked for germination and per cent spore germination inhibition was determined from which ED₅₀ values were calculated using Polo Software Program.

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References