Synthesis and Properties of 3-Aminoacrylonitriles

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Abstract

3-Aminoacrylonitriles, enamines, were obtained from the reaction of 3-methoxyacrylonitrile with aliphatic amines in appropriate solvent, in sealed tube in the presence of aqueous sodium hydroxide, or under reflux, in satisfactory yields. The reactions of 3-aminoacrylonitriles with isocyanates or isothiocyanates gave 3-amino-2-cyanoacrylamides or 3-amino-2-cyanoacrylthioamides, respectively.

1. Introduction

Since 3-aminoacrylonitriles (1) are important intermediate for the synthesis of biologically active substances, several procedures for the syntheses of 1 have already been offered in the literature, particularly in the patent. For example, 1 have been obtained from the reaction of 3-chloroacrylonitrile with aliphatic amines (2), (3) cyanoacetylene with 2, (4) and sodium alkoxide of 3-hydroxyacrylonitrile with 2. (5) Condensation of N, N-dimethylformamide acetal with acetonitrile, and catalytic dehydrogenation of 3-(dimethylamino)propanenitrile gave same 1. (6) Cleavage of 1-alkyl- or 1-arylpzrazoles with sodium amide (7) or under UV irradiation (8) gave also 1. Furthermore, plasmoysis of 2 gave 1 with 2-aminoacetonitrile and 3-aminopropionitrile. (9)

Incidentally, it was already described in some patents that the amination of 3-alkoxyacrylonitriles, which are prepared from sodium alkoxide of 3-hydroxyacrylonitrile with alkyl halide, with 2 gave 1. (10) In this paper, we wish to report on the syntheses of 1 by the reaction of 3-methoxyacrylonitrile (3) with 2 in more detail, and some chemical properties of obtained 1.

2. Results and Discussion

2.1. Syntheses of 3-Aminoacrylonitriles (1)

The reactions of 3 (mixture of cis and trans isomers) with 2 in appropriate solvent in sealed tube in the presence of aq. NaOH, or under reflux for many hours gave 1 in satisfactory yields. The results are summarized in Table 1. Attempts to prepare the

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products 1i, 1k and 1n were unsuccessful.

Geometry of 1 was confirmed as trans by 1H NMR measurements. That is, the coupling constants between two ethylene protons showed J = 13-15 Hz, and the chemical shifts of these protons appeared in relatively lower region (e.g., δ values of geminal proton for the amino group: δ = 6.8-7.1 ppm; see Experimental) (Tobey-Simon rule). It can be considered that the reaction passes may be controlled to lead the thermodynamically stable trans form.

2.2. Reactions of 1 with Isocyanates

Because the reactions of 1 with heterocumulene as yet are hardly known in the literature, first we choiced isocyanates (4) as heterocumulene. Thus, the reactions of 1

\[ 1 + R\text{-NCO} \rightarrow R^1 \]

with 4 in benzene under reflux gave N-substituted 3-amino-2-cyanoacrylamide derivatives (5). The results are summarized in Table 2.

We confirmed the geometry of 5 as E-form by their 1H NMR behavior. That is, the chemical shifts of ethylene proton appeared in lower region (δ = 7.5-8.3 ppm; see Experimental) (Tobey-Simon rule).

2.3. Reactions of 1 with Isothiocyanates

The reactions of 1 with isothiocyanates (6) in benzene or toluene under reflux gave N-substituted 3-amino-2-cyanoacrylthioamide derivatives (7). The results are summarized in Table 3. The chemical shifts of ethylene proton appeared in lower region (δ = 8-9 ppm; see Experimental). Thus, according to Tobey-Simon rule, we confirmed the geometry of 7 as E-form.
2.4. Attempted Cycloadditions of 1 with 1,3-Dipoles

Attempts to prepare some heterocyclic compounds from 1 with 1,3-dipoles such as nitron, nitrile-ylide, nitrile-imine, and azomethine-ylide in appropriate solvents were unsuccessful.

2.5. Attempts to Prepare Pyrazole Derivatives from 5 or 7 with Hydrazine

We had tried to prepare pyrazole derivatives having cyano group from 5 (or 7) with hydrazine. However, only hydrazones of 5 (or 7) were obtained.

3. Experimental

All the melting points are uncorrected. $^1$H NMR spectra were recorded on a JEOL-MH-100 spectrometer. The IR spectra were measured on a JASCO IRA-1 spectrometer.

3.1.1. 3-(1-Pyrrolidinyl)acrylonitrile (1q); General Procedure under Reflux Conditions

To a solution of 3-methoxyacrylonitrile (3) (8.30g, 0.1mol) in methanol (50ml) was
### Table 1 Syntheses of 3-Aminoacrylonitriles R'R-N-CH=CH-CN (1)

<table>
<thead>
<tr>
<th>Product 1</th>
<th>Reaction conditions</th>
<th>Solvent (Additive)</th>
<th>Yield (%)</th>
<th>Mp (°C) or Bp(°C/mm Hg)</th>
<th>Literature</th>
</tr>
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<td>R²</td>
<td>Time/h</td>
<td>Temp/°C</td>
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<td></td>
</tr>
<tr>
<td>1a</td>
<td>CH₃</td>
<td>H</td>
<td>48</td>
<td>100⁽⁄⁾</td>
<td>CH₂OH</td>
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<tr>
<td>1b</td>
<td>C₆H₅</td>
<td>H</td>
<td>24</td>
<td>65⁽⁄⁾</td>
<td>H₂O</td>
</tr>
<tr>
<td>1c</td>
<td>CH₃</td>
<td>CH₃</td>
<td>16</td>
<td>rt</td>
<td>H₂O/Ether</td>
</tr>
<tr>
<td>1d</td>
<td>C₆H₅</td>
<td>C₆H₅</td>
<td>84</td>
<td>150⁽⁄⁾</td>
<td>Dioxane (aq NaOH)</td>
</tr>
<tr>
<td>1e</td>
<td>C₆H₅</td>
<td>H</td>
<td>84</td>
<td>150⁽⁄⁾</td>
<td>Dioxane (aq NaOH)</td>
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<tr>
<td>1f</td>
<td>iso-C₆H₇</td>
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<td>26</td>
<td>150⁽⁄⁾</td>
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<tr>
<td>1g</td>
<td>C₆H₆</td>
<td>H</td>
<td>72</td>
<td>150⁽⁄⁾</td>
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<tr>
<td>1h</td>
<td>s-C₆H₅</td>
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<td>150⁽⁄⁾</td>
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<td>1i</td>
<td>t-C₆H₅</td>
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<td>150⁽⁄⁾</td>
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<tr>
<td>1j</td>
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<td>90⁽⁄⁾</td>
<td>Dioxane</td>
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<tr>
<td>1l</td>
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<td>H</td>
<td>72</td>
<td>150⁽⁄⁾</td>
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<tr>
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<td>H</td>
<td>H</td>
<td>49</td>
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<td>CH₂OH</td>
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<tr>
<td>1n</td>
<td>H</td>
<td>H</td>
<td>24</td>
<td>reflux</td>
<td>Dioxane (aq NaOH)</td>
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<tr>
<td>1o</td>
<td>H</td>
<td>H</td>
<td>48</td>
<td>reflux</td>
<td>Dioxane</td>
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<tr>
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<td>25</td>
<td>reflux</td>
<td>C₆H₅-CH₃</td>
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a) Yield of isolated product.

b) Reaction was carried out in sealed tube.
Table 2 Reaction of 1 with Isocyanates

<table>
<thead>
<tr>
<th>Product 5</th>
<th>Reactuon conditions</th>
<th>Solvent</th>
<th>Yield (％)</th>
<th>Mp (℃)</th>
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</thead>
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<td>R^2</td>
<td>R</td>
<td>Time/h</td>
<td>Temp/C</td>
</tr>
<tr>
<td>5a</td>
<td>p-Cl-C_6H_4</td>
<td>48</td>
<td>reflux</td>
<td>benzene</td>
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<tr>
<td>5b</td>
<td>p-Me-C_6H_4-SO_2</td>
<td>few min.</td>
<td>rt</td>
<td>benzene</td>
</tr>
<tr>
<td>5c</td>
<td>C_6H_5</td>
<td>104</td>
<td>reflux</td>
<td>benzene</td>
</tr>
<tr>
<td>5d</td>
<td>α-naphthyl</td>
<td>96</td>
<td>reflux</td>
<td>benzene</td>
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<tr>
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<td>p-Cl-C_6H_4</td>
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<td>reflux</td>
<td>benzene</td>
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<tr>
<td>5f</td>
<td>H</td>
<td>p-Cl-C_6H_4</td>
<td>48</td>
<td>reflux</td>
</tr>
<tr>
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<td>C_6H_5CH_3</td>
<td>H</td>
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<td>50</td>
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a) Yield of isolated product.

Table 3 Reaction of 1 with Isothiocyanates

<table>
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<tr>
<th>Product 7</th>
<th>Reactuon conditions</th>
<th>Solvent</th>
<th>Yield (％)</th>
<th>Mp (℃)</th>
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<tbody>
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<td>R^2</td>
<td>R</td>
<td>Time/h</td>
<td>Temp/C</td>
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<td>benzene</td>
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<td>few min.</td>
<td>rt</td>
<td>benzene</td>
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<tr>
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<td>C_6H_5</td>
<td>120</td>
<td>reflux</td>
<td>toluene</td>
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<tr>
<td>7d</td>
<td>CH_3</td>
<td>240</td>
<td>reflux</td>
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<td>7e</td>
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<td>120</td>
<td>reflux</td>
<td>benzene</td>
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<td>7f</td>
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<td>p-NC-C_6H_4</td>
<td>120</td>
<td>reflux</td>
</tr>
<tr>
<td>7g</td>
<td>C_6H_5CH_3</td>
<td>H</td>
<td>p-NC-C_6H_4</td>
<td>48</td>
</tr>
</tbody>
</table>

a) Yield of isolated product.
added pyrrolidine (8.52g, 0.12mol), and the mixture was refluxed for 48 h. After the reaction mixture was allowed to stand at room temperature, precipitated crystals were filtered, washed with cold petroleum benzene to give 1q as brown plates; yield 8.9 g (73%); mp 52-54 °C. IR (KBr): 2190 cm⁻¹(C≡N); ¹H NMR (CDCl₃) δ = 1.80-2.34 (4H, m, β-pyrrolidinyl methylene), 2.97-3.42 (4H, m, α-pyrrolidinyl methylene), 3.39 (1H, d, =CH-CN), 7.08 (1H, d, N-CH=).

3.1.2. 3-Cycloheptylaminoacylonitrile (1o)
Brown plates; IR (KBr): 2185 (CN), 1640 cm⁻¹(C≡C); ¹H NMR (CDCl₃) δ = 1.09-2.28 (12H, m, cycloheptyl methylene), 2.95-3.44 (1H, m, CH), 3.66 (1H, d, J = 15 Hz, =CH-CN), 4.60-5.14 (1H, m, NH), 6.67 (1H, dd, J = 8 and 15 Hz, N-CH=).

3.1.3. 3-Morpholinoacylonitrile (1r)
Brown plates; IR (KBr): 2185 cm⁻¹(CN); ¹H NMR (CDCl₃) δ = 3.00-3.27 (4H, m, β-morpholino methylene), 3.51-3.75 (4H, m, α-morpholino methylene), 3.87 (1H, d, =CH-CN), 6.77 (1H, d, N-CH=).

3.1.4. 3-Piperidinoacylonitrile (1s)
Orange needles; IR (KBr): 2190 (CN), 1620 cm⁻¹(C≡C); ¹H NMR (CDCl₃) δ = 1.38-2.80 (6H, m, β- and γ-piperidino methylene), 2.84-3.22 (4H, m, α-piperidino methylene), 3.80 (1H, d, J = 13 Hz, =CH-CN), 6.76 (1H, d, J = 13 Hz, N-CH=).

3.1.5. 3-Cyclopentylaminoacylonitrile (1t); General Procedure in Sealed Tube
A mixture of aqueous NaOH (0.05g; H₂O 0.5ml), dioxane (5ml), 3 (1.66g, 0.02mol), and cyclopentylamine (5.10g, 0.06mol) was heated in autoclave at 150 °C for 3 days. The reaction mixture was concentrated, and was dissolved in chloroform (10ml). The chloroform solution was dried over MgSO₄, filtered and was concentrated in vacuo. The obtained residue was distilled under reduced pressure to give 1t as light yellow oil; yield 1.85g (68%); bp 109-112 °C / 4 mmHg. IR (neat): 2245 (CN), 1680 cm⁻¹(C≡C); ¹H NMR (CDCl₃) δ = 1.05-2.23 (8H, m, cyclopentyl methylene), 3.30-3.75 (1H, m, CH), 3.75 (1H, d, J = 14 Hz, =CH-CN), 4.62-5.41 (1H, m, NH), 6.73 (1H, dd, J = 8 and 14 Hz, N-CH=).

3.1.6. 3-Propylaminoacylonitrile (1e)
Colorless oil; IR (neat): 2180 (CN), 1640 cm⁻¹(C≡C); ¹H NMR (CDCl₃) δ = 0.60-1.28 (3H, m, CH₃), 1.28-2.04 (2H, m, CH₂CH₂), 2.75-3.20 (2H, m, CH₂N), 3.85 (1H, d, J = 13 Hz, =CH-CN), 4.64-5.40 (1H, m, NH), 6.85 (1H, dd, J = 9 and 13 Hz, N-CH=).

3.1.7. 3-sec-Butylaminoacylonitrile (1h)
Light yellow oil; IR (neat): 2190 (CN), 1640 cm⁻¹(C≡C); ¹H NMR (CDCl₃) δ = 0.76-1.82 (8H, m, CH₃ and C₂H₅), 2.96-3.40 (1H, m, CH), 3.84 (1H, d, J = 14 Hz, =CH-CN), 4.54-5.36 (1H, br., NH), 6.80 (1H, dd, J = 8 and 14 Hz, N-CH=).

3.1.8. 3-iso-Butylaminoacylonitrile (1j)
Light yellow oil; IR (neat): 2185 (CN), 1620 cm⁻¹(C≡C); ¹H NMR (CDCl₃) δ = 0.84-1.
32 (6H, br.d, 2CH₃), 1.48-2.12 (1H, m, CH), 2.62-3.43 (2H, m, CH₂), 3.84 (1H, d, J = 15 Hz, =CH-CN), 5.04-5.60 (1H, m, NH), 6.84 (1H, dd, J = 8 and 15 Hz, N-CH=).

3.2.1. N-(p-Chlorophenyl)-2-cyano-3-(1-pyrrolidinyl)acrylamide (5a): General Procedure

To a solution of 1q (0.37 g, 0.003 mol) in dry benzene (10ml) was added p-chlorophenylisocyanate (0.46g, 0.003ml), and the mixture was refluxed for 48 h. After the reaction mixture was concentrated in vacuo, obtained precipitate was filtered and recrystallized from ethanol to give 5a; yield 0.34 g (41%); mp 207-208 °C. IR (KBr): 2170 (CN), 1655 cm⁻¹(CO);¹H NMR (CDCl₃) δ = 1.56-2.49 (4H, m, β-pyrrolidinyl methylene), 3.51-4.17 (4H, m, α-pyrrolidinyl methylene), 7.17-7.65 (4H, m, aromatic protons), 7.62 (1H, br.s, NH), 8.01 (1H, s, CH=).

3.2.2. 2-Cyano-3-(1-pyrrolidinyl)-N-tosylacrylamide (5b)

Colorless plates; IR (KBr): 2180 (CN), 1680 cm⁻¹(CO);¹H NMR (CDCl₃) δ = 1.68-2.28 (4H, m, β-pyrrolidinyl methylene), 2.40 (3H, s, CH₃), 3.45-4.11 (4H, α-pyrrolidinyl methylene), 7.35, 7.98 (4H, two d, aromatic protons), 7.92 (1H, s, NH), 8.31 (1H, s, CH=).

3.2.3. 2-Cyano-N-phenyl-3-(1-pyrrolidinyl)acrylamide (5c)

Colorless plates; IR (KBr): 2170 (CN), 1655 cm⁻¹(CO);¹H NMR (CDCl₃) δ = 1.65-2.43 (4H, m, β-pyrrolidinyl methylene), 3.48-4.17 (4H, m, α-pyrrolidinyl methylene), 6.93-7.74 (6H, m, aromatic protons and NH), 8.01 (1H, s, CH=).

3.2.4. 2-Cyano-N-(α-naphthyl)-3-(1-pyrrolidinyl)acrylamide (5d)

Colorless plates; IR (KBr): 2175 (CN), 1650 cm⁻¹(CO);¹H NMR (CDCl₃) δ = 1.65-2.31 (4H, m, β-pyrrolidinyl methylene), 3.48-4.14 (4H, m, α-pyrrolidinyl methylene), 7.29-8.28 (9H, m, aromatic protons, NH, and CH=).

3.2.5. N-(p-Chlorophenyl)-2-cyano-3-morpholinoacrylamide (5e)

Colorless plates; IR (KBr): 2175 (CN), 1670 cm⁻¹(CO);¹H NMR (CDCl₃) δ = 3.15-4.47 (8H, m, morpholino methylene), 7.74-7.59 (4H, m, aromatic protons), 7.56 (1H, s, NH), 7.80 (1H, s, CH=).

3.2.6. N-(p-Chlorophenyl)-2-cyano-3-cyclohexylaminoacrylamide (5f)

Colorless needles; IR (KBr): 2205 (CN), 1660 cm⁻¹(CO);¹H NMR (CDCl₃) δ = 1.08-2.43 (10H, m, cyclohexyl methylene), 3.03-3.48 (1H, m, CH), 7.23-8.01 (6H, m, aromatic protons, CH=, and CONH), 8.51-9.01 (1H, m, NH).

3.2.7. 3-Benzylamino-N-(p-chlorophenyl)-2-cyanoacrylamide (5g)

Colorless plates; IR (KBr): 2175 (CN), 1645 cm⁻¹(CO);¹H NMR (CDCl₃) δ = 4.41 (2H, d, CH₂), 7.05-7.65 (11H, m, aromatic protons, CH=, and CONH), 9.61-10.05 (1H, m, NH).

3.3.1. 2-Cyano-N-(p-cyanophenyl)-3-(1-pyrrolidinyl)acrylthioamide (7a): General Procedure

To a solution of 1q (1.22 g, 0.01 mol) in dry benzene (50 ml) was added p-
cyanophenylisothiocyanate (1.60 g, 0.01 mol), and the mixture was refluxed for 55 h. After the reaction mixture was concentrated in vacuo, obtained precipitates were filtered and recrystallized from ethanol to give 7a; yield 1.15 g (41%); mp 208-211 °C. IR (KBr): 2180 cm⁻¹(CN); ¹H NMR (CDCl₃) δ = 1.86-2.43 (4H, m, β-pyrrolidinyl methylene), 3.63-4.14 (4H, m, α-pyrrolidinyl methylene), 7.65, 7.86 (4H, two d, aromatic protons), 8.70-8.94 (1H, br.s, NH), 8.82 (1H, s, CH =).

3.3.2 2-Cyano-3-(1-pyrrolidinyl)-N-tosylacrylthioamide (7b)
Yellow plates; IR (KBr): 2165 cm⁻¹(CN); ¹H NMR (CDCl₃) δ = 1.53-2.13 (4H, m, β-pyrrolidinyl methylene), 2.39 (3H, s, CH₃), 3.48-3.93 (4H, m, α-pyrrolidinyl methylene), 7.26, 7.68 (4H, two d, aromatic protons), 7.85 (1H, s, NH), 8.16 (1H, s, CH =).

3.3.3 2-Cyano N-phenyl-3-(1-pyrrolidinyl)acrylthioamide (7c)
Yellow needles; IR (KBr): 2170 cm⁻¹(CN); ¹H NMR (CDCl₃) δ = 1.86-2.55 (4H, m, β-pyrrolidinyl methylene), 3.63-4.35 (4H, m, α-pyrrolidinyl methylene), 7.29-7.83 (5H, m, aromatic protons), 8.61 (1H, br.s, NH), 8.94 (1H, s, CH =).

3.3.4 2-Cyano-N-methyl-3-(1-pyrrolidinyl)acrylthioamide (7d)
Colorless columns; IR (KBr): 2170 cm⁻¹(CN); ¹H NMR (CDCl₃) δ = 1.70-2.49 (4H, m, β-pyrrolidinyl methylene), 3.27 (3H, d, CH₃), 3.60-4.17 (4H, m, α-pyrrolidinyl methylene), 7.11-7.77 (1H, br.s, NH), 8.82 (1H, s, CH =).

3.3.5 2-Cyano-N-(p-cyanophenyl)-3-morpholinoacrylthioamide (7e)
Yellow needles; IR (KBr): 2220, 2170 cm⁻¹(CN); ¹H NMR (CDCl₃) δ = 3.48-4.50 (8H, m, morpholino methylene), 7.83 (4H, m, aromatic protons), 8.79 (1H, s, CH =), 8.76-9.15 (1H, br.s, NH).

3.3.6 2-Cyano-N-(p-cyanophenyl)-3-cyclohexylaminoacrylthioamide (7f)
Yellow columns; IR (KBr): 2215, 2175 cm⁻¹(CN); ¹H NMR (CDCl₃) δ = 0.98-2.80 (10H, m, cyclohexyl methylene), 3.03-3.65 (1H, m, CH), 7.46 (1H, d, CH =), 7.59-8.07 (4H, m, aromatic protons), 8.63 (1H, s, CSNH), 11.93-12.38 (1H, m, NH).

3.3.7 3-Benzylamino-2-cyano-N-(p-cyanophenyl)acrylthioamide (7g)
Yellow needles; IR (KBr): 2210,2190 cm⁻¹(CN); ¹H NMR (CDCl₃) δ = 4.56 (2H, d, CH₂), 7.17-8.13 (10H, m, aromatic protons and CH =), 8.73 (1H, s, CSNH), 11.91-12.45 (1H, rt, NH).

References