Nitriles in Heterocyclic Synthesis: A Novel Synthesis of Polyfunctionally Substituted Pyrrole Derivatives

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The utility of organic cyano compounds in heterocyclic synthesis has recently received considerable attention [1, 2]. Our group has been involved in the last years in a program aiming to develop efficient procedures for synthesis of polyfunctionally substituted azoles [3, 4], azines [5, 6] and their condensed derivatives [7, 8] utilizing simple and readily obtainable polyfunctionally substituted nitriles. During this phase of our research we could show that whereas ethylidenemalononitrile derivative 1a does not couple with aromatic diazonium salts, the presence of cyano substituent on the methyl moiety (as in 1b) sufficiently activates the adjacent methylene group for coupling [9]. The resulting hydrazones could be utilized for synthesis of pyridazine-6-imine derivatives [10]. It seemed to us of value to see if the presence of other functional substituent on the methyl moiety in 1 can effect similar activation. In the present paper we report synthesis of β-thiocyanatomethyl cinnamonicitriles 1c, e and their conversion into 2-substituted-3-cyano-4-phenyl-5-thiocyanatopyrrole derivatives 5a, b. Thus, it has been found that 1d reacts with potassium thiocyanate to yield the thiocyanato derivative 1c. Compound 1e has been previously obtained [11] via reaction of phenacylthiocyanate with malononitrile under conditions very similar to those reported in a recent patent [12] in which it is suggested that the reaction affords the thiadiazole derivative 2. Compound 1f reacts similarly with KSCN to afford the thiocyanato derivative 1e. Compound 1e has also been previously reported by us [13] via another route but in a very poor yield.

Compound 1c coupled with aromatic diazonium salts to yield the corresponding coupling products which may be formulated as the hydrazone 3 or the azo derivatives 4a–c.

\[
\begin{align*}
1a: & \quad R=CH_3, R'=C_6H_5, X=CN \\
1b: & \quad R=CH_2CN, R'=NH_2, X=CN \\
1c: & \quad R=CH_2SCN, R'=C_6H_5, X=CN \\
1d: & \quad R=CH_2Br, R'=C_6H_5, X=CN \\
1e: & \quad R=CH_2SCN, R'=C_6H_5, X=CO_2Et \\
1f: & \quad R=CH_2Br, R'=C_6H_5, X=CO_2Et \\
4a: & \quad Ar=C_6H_4, X=CN \\
4b: & \quad Ar=C_6H_4CH_3-p, X=CN \\
4c: & \quad Ar=C_6H_4Cl-p, X=CN \\
4d: & \quad Ar=C_6H_4, X=CO_2Et \\
4e: & \quad Ar=C_6H_4CH_3-p, X=CO_2Et \\
4f: & \quad Ar=C_6H_4Cl-p, X=CO_2Et
\end{align*}
\]

\[^1H\text{NMR}\] spectra revealed that the reaction product exists mainly in the arylazo form 4. Thus \[^1H\text{NMR}\] revealed aromatic multiplet at \(\delta\) 7.35—8.40 ppm. If this product is the hydrazone 3, at least three of the aromatic protons, being shielded by resonance of hydrazone lone electrons on the aromatic ring, should have appeared at \(\delta\) value higher than 7.3 ppm. The assigned structure finds further support from chemical reactivity of the reaction product. Thus compounds 4a–c did not cyclize into either pyridazin-6-imine or thiadiazoles at conditions reported to effect cyclizations of hydrazones of structures very similar to that of 3.

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Compound 1e coupled similarly with aromatic diazonium salts to afford the corresponding coupling products 4d–f. Analytical and spectral data are in good agreement with these structures.

Compounds 4a–f could be reduced with Zinc and acetic acid into the pyrrole derivatives 5. The formation of 5 is assumed to proceed via reductive cleavage of the azo link followed by cyclization through internal Michael addition of NH₂ to CN to afford 5a or through loss of ethanol to afford 5b (Chart 1). The structure of compounds 5a, b was inferred from both analytical and spectral data (see Experimental).

Compounds 5 seem to be interesting starting material for further chemical transformations as well as for biological activity studies.

Experimental

All melting points are uncorrected. IR spectra were recorded as KBr discs using a Pye-Unicam SP-1100 spectrophotometer. Absorption values are expressed as v cm⁻¹. ¹H NMR spectra were recorded on a Varian A-60 spectrometer using TMS as internal standard. Chemical shifts are expressed in δ ppm. Analytical data were obtained from the microanalytical centre at Cairo University.

Preparation of the azo compounds 4a–f (general procedure)

To a cold solution of either 1c or 1e (0.01 mole) and sodium acetate (3 g) in ethanol (50 ml) was added, dropwise a solution of diazotized amine (aniline, p-toluidine or p-chloroaniline respectively; 0.01 mole), while stirring. The addition took 30 min, after which stirring was continued for further 3 h. The solid precipitates formed were collected by alternation, washed with cold water, dried and recrystallized from the proper solvent (cf. Table I), to afford compounds: 4a 2.3 g, 4b 2.6 g, 4c 1.9 g, 4d 2.2 g, 4e 2.5 g, 4f 2.0 g, respectively (see Table I).

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield [%]</th>
<th>m.p. [°C]</th>
<th>M. F.</th>
<th>M.wt.</th>
<th>Analysis [%]</th>
<th>Table I. Physical data of newly prepared compounds.</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>70</td>
<td>225</td>
<td>AcOH</td>
<td>329</td>
<td>65.65 3.34</td>
<td>21.28</td>
</tr>
<tr>
<td>4b</td>
<td>75</td>
<td>231</td>
<td>AcOH</td>
<td>343</td>
<td>66.47 3.79</td>
<td>20.41</td>
</tr>
<tr>
<td>4c</td>
<td>55</td>
<td>241</td>
<td>AcOH</td>
<td>363.5</td>
<td>59.42 2.75</td>
<td>19.26</td>
</tr>
<tr>
<td>4d</td>
<td>58</td>
<td>260</td>
<td>AcOH</td>
<td>376</td>
<td>63.83 4.26</td>
<td>14.89</td>
</tr>
<tr>
<td>4e</td>
<td>65</td>
<td>189</td>
<td>AcOH</td>
<td>390</td>
<td>64.62 4.62</td>
<td>14.36</td>
</tr>
<tr>
<td>4f</td>
<td>47</td>
<td>&gt;270</td>
<td>AcOH</td>
<td>410.5</td>
<td>58.47 3.65</td>
<td>13.64</td>
</tr>
<tr>
<td>5a</td>
<td>60</td>
<td>235</td>
<td>EtOH</td>
<td>240</td>
<td>60.00 3.33</td>
<td>23.33</td>
</tr>
<tr>
<td>5b</td>
<td>55</td>
<td>209</td>
<td>EtOH</td>
<td>241</td>
<td>59.75 2.90</td>
<td>17.43</td>
</tr>
</tbody>
</table>

* Satisfactory chlorine analysis has been obtained.
Table II. IR and $^1$H NMR data of the newly prepared compounds.

<table>
<thead>
<tr>
<th>Compound</th>
<th>IR $\nu$ cm$^{-1}$ (selected bands)</th>
<th>$^1$H NMR $\delta$ ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>2220 and 2190 (two CN), 2160 (SCN)</td>
<td>2.42 (s, 1H, CH); 7.38–8.3 (m, 10H, arom. protons)</td>
</tr>
<tr>
<td>4b</td>
<td>2210 and 2190 (two CN), 2175 (SCN)</td>
<td>2.4 (s, 1H, CH); 3.7 (s, 3H, CH$_3$); 7.35–8.4 (two groups m, 9H, arom. protons)</td>
</tr>
<tr>
<td>4c</td>
<td>2215 and 2200 (CN groups), 2175 (SCN)</td>
<td>2.41 (s, 1H, CH); 7.4–8.35 (two groups m, 9H, arom. protons)</td>
</tr>
<tr>
<td>4d</td>
<td>2220 (CN), 2170 (SCN), 1720 (CO)</td>
<td>1.9 (t, 3H, CH$_3$); 2.35 (q, 2H, CH$_2$); 2.5 (s, 1H, CH); 7.37–8.1 (m, 10H, arom. protons)</td>
</tr>
<tr>
<td>4e</td>
<td>2190 (CN), 2165 (SCN), 1718 (CO)</td>
<td>1.85 (t, 3H, CH$_3$); 2.4 (q, 2H, CH$_2$); 2.55 (s, 1H, CH); 7.35–8.15 (two groups m, 9H, arom. protons)</td>
</tr>
<tr>
<td>4f</td>
<td>2195 (CN), 2170 (SCN), 1710 (CO)</td>
<td>1.95 (t, 3H, CH$_3$); 2.42 (q, 2H, CH$_2$); 2.48 (s, 1H, CH); 7.4–8.2 (two groups m, 9H, arom. protons)</td>
</tr>
<tr>
<td>5a</td>
<td>3420–3300 (NH and N H$_2$), 2180 (CN), 2080 (SCN)</td>
<td>2.1 (s, 2H, NH$_2$); 2.32 (s, 1H, NH); 7.3–7.6 (m, 5H, arom. protons)</td>
</tr>
<tr>
<td>5b</td>
<td>3500–3280 (NH and OH), 2175 (CN), 2095 (SCN)</td>
<td>3.2 (s, 1H, OH); 7.28–7.85 (m, 5H, arom. protons); 8.3 (s, 1H, NH)</td>
</tr>
</tbody>
</table>

Preparation of 2-substituted 3-cyano-4-phenyl-5-thiocyanopyrrole derivatives 5a, b

To a solution of 0.01 mole of each of the azo compounds 4a–f in acetic acid glacial (50 ml) was added about 3 g of Zinc dust. The reaction mixtures were refluxed for 2 h, during which time the dark azo red colour turns to pale green. The reaction mixtures were filtered while hot and left to cool to room temperature. The precipitated solids were collected by filtration and recrystallized separately from ethanol. It was found that the products of the three azos 4a–c have the same melting point, and no depression has been observed in the mixed melting points between them. Analytical and spectral data confirmed that they are one compound – 5a; the products obtained from the three azos 4d–f were found also to be the same compound 5b (see Tables I and II).