**Nitriles in Heterocyclic Synthesis:**

The Reaction of 2-Thiocarbamoyl Cinnamonitriles with Active Methylene Reagents

Abdel Moneim El-Torgoman, Salah Mohamed El-Kousy

Chemistry Department, Faculty of Science, Menoufiya University, Menoufia, Egypt

Zaghoul El-Shahat Kandeel*

Chemistry Department, Faculty of Science, Cairo University, Giza, Egypt


Heterocyclic Synthesis, 2-Thiocarbamoyl Cinnamonitriles

Substituted pyridin-2-thiones, 2-pyridones, thiopyrans and pyranoazoles could be synthesized via the reaction of 2-thiocarbamoyl cinnamonitriles with some active methylene reagents.

α,β-Unsaturated nitriles are versatile reagents that have been extensively used in heterocyclic synthesis [1]. Recently the reaction of α-substituted cinnamonitriles with active methylene reagents has been utilized for the synthesis of a variety of otherwise not readily accessible polyfunctionally substituted heterocycles [2–4].

Whereas Daboun and Raid [5] have claimed the isolation of dihydropyridines from the reaction of cinnamonitriles with cyanothioacetamide, Soto and Co-workers [6] have reported that the products of this reaction are pyridin-2-thiones. Recently [7] it has been shown that thiopyrans are the kinetically formed reaction products and their thermal rearrangements affords pyridin-2-thiones. Since we were interested to see if the reaction of cinnamonnitrile, with cyanothioacetamide can be extended to afford differently substituted thiopyrans and pyridines, we studied the behaviour of 2-thiocarbamoyl nitrile, with cyanothioacetamide can be extended to yield the pyridin-2-thione with 2a.

It has been found that 1a reacts with cyanothioacetamide (2a) to yield a product of molecular formula C_{13}H_{10}N_{2}O_{5}. Two isomeric structures (cf. structures 3 and 4) seemed possible for the reaction product (cf. Scheme 1). Structure 3 was however readily eliminated as the reaction product proved to be different from the product of the reaction of anisaldehyde or p-chlorobenzaldehyde with 4,6-diamino-3-cyano-5,5-dihydro-pyridin-2-thione (5).

Compound 1a reacted with 2-cyanoacetamide (2b) to yield a yellow product of molecular formula C_{14}H_{10}N_{2}O_{5}. Again two theoretically possible structures can be suggested for this reaction product (cf. Scheme 2). However, structure 7 was established on the basis of 3H NMR which revealed a pattern that can be interpreted in terms of structure 7 but not 8 (cf. Table II). Compound 7 is assumed to be formed via addition of the amide to the double bond in 1a, cyclization via hydrogen sulphide elimination and then aromatization under the reaction conditions [9].

This work has been digitalized and published in 2013 by Verlag Zeitschrift für Naturforschung in cooperation with the Max Planck Society for the Advancement of Science under a Creative Commons Attribution 4.0 International License.
Compound 1a reacted with ethyl acetoacetate to yield a product which was formulated as the 2-hydroxypyridine derivative 9 based on the IR spectrum which revealed the absence of absorption for ring CO group. The possibility that 9 was formed through the intermediacy of the pyran 11 was ruled out as 11, synthesized via reaction of ethyl acetoacetate and 1c could not be rearranged under similar conditions.

1a reacted also with acetylacetone to yield the thiopyrane 12 as was inferred from its analytical and spectral data and is assumed to be formed via the sequence in Scheme 3.

1a reacted with 3-methylpyrazol-5-one (13) to yield the thiopyrane 15. The formation of 15 is assumed to take place via the intermediacy of the Michael adduct 14 which cyclizes via water elimination. The formation of thiopyrano[2,3-c]pyrazoles in this manner contributes an interesting approach for this ring system. Only very few derivatives of this ring system are known. Similarly the thiopyrano[2,3-c]isoxazole 17 was obtained from 1a and 3-methylisoxazol-5-one (16).

In contrast to the behaviour 13 and 16, 1-phenyl-3-methyl-2-pyrazolin-5-one (18) afforded the py-
rano[2,3-c]pyrazole 20 when treated with 1a. It is clear that several polysubstituted pyridines, thiopyrans, thiopyran[2,3-c]pyrazole, and thiopyran- [2,3-c]isoxazole, are now available from easily prepared starting materials and under simple experimental conditions.

**Experimental**

All melting points are uncorrected. IR spectra were measured as KBr discs using a Pye-Unicam SP 1100 spectrophotometer. $^1$H NMR were obtained on an EM-390, 90 MHz Spectrometer, DMSO ($d_6$) as a solvent and TMS as an internal standard. Elemental analyses (±0.3%) were performed in the Microanalytical Center in Cairo University.

**6-Amino-3,5-dicyano-4-(p-methoxy phenyl)pyridin-2(1H)-thione (4a)**

To a solution of 2.02 g. (10 mmole) of 1a in 50 ml ethanol was added 0.86 g. (10 mmole) of cyanothioacetamide (2a) and 3 drops of triethyl amine. The reaction mixture was then heated under reflux till H$_2$S ceased to evolve (lead acetate paper; 2–3 h). The solvent was then removed by evaporation in vacuo and the solid product formed on standing was
<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>Yield [%]</th>
<th>M.P. °C</th>
<th>Mol. Formula (M.W.)</th>
<th>Analysis [%] Found/Calcd C</th>
<th>H</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>82</td>
<td>265</td>
<td>C₁₀H₁₀N₂O₄S       (282.318)</td>
<td>60.02/59.56</td>
<td>3.71</td>
<td>20.10</td>
</tr>
<tr>
<td>4b</td>
<td>71</td>
<td>110</td>
<td>C₁₀H₁₀N₂SCl*       (186.785)</td>
<td>54.60/54.45</td>
<td>2.50</td>
<td>19.70</td>
</tr>
<tr>
<td>7</td>
<td>84.2</td>
<td>205</td>
<td>C₁₀H₁₀N₂O₂        (266.256)</td>
<td>63.40/63.16</td>
<td>4.00</td>
<td>21.10</td>
</tr>
<tr>
<td>9</td>
<td>85.5</td>
<td>181–182</td>
<td>C₁₀H₁₀N₂O₄        (312.318)</td>
<td>65.50/65.38</td>
<td>5.00</td>
<td>9.21</td>
</tr>
<tr>
<td>12</td>
<td>78.4</td>
<td>238–239</td>
<td>C₁₀H₁₀N₂O₂S       (300.371)</td>
<td>64.10/63.98</td>
<td>5.18</td>
<td>9.51</td>
</tr>
<tr>
<td>15a</td>
<td>48.9</td>
<td>251</td>
<td>C₁₀H₁₀N₂OS        (198.361)</td>
<td>60.50/60.38</td>
<td>4.61</td>
<td>19.00</td>
</tr>
<tr>
<td>15b</td>
<td>54.6</td>
<td>140</td>
<td>C₁₀H₁₀N₂SCl**      (302.828)</td>
<td>55.27/55.53</td>
<td>3.78</td>
<td>18.34</td>
</tr>
<tr>
<td>17</td>
<td>60.7</td>
<td>240</td>
<td>C₁₀H₁₀N₂O₂S       (299.344)</td>
<td>60.05/60.19</td>
<td>4.50</td>
<td>14.15</td>
</tr>
<tr>
<td>20</td>
<td>91.2</td>
<td>210</td>
<td>C₁₀H₁₀N₂O₂        (358.396)</td>
<td>70.30/70.19</td>
<td>5.16</td>
<td>15.54</td>
</tr>
</tbody>
</table>

Table I. Physical data for the prepared compounds.

Table II. IR and ¹H NMR spectra for the prepared compounds.

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>IR [cm⁻¹]</th>
<th>¹H NMR [° ppm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>3340, 3290 (−NH₂), 2950 (aromatic CH), 2225, 2205 (two CN) and 1650 (C=N)</td>
<td>3.8 (s, 3H, OCH₃), 7.2–7.5 (m, 4H, aromatic protons), 7.7 (s, 2H, NH₂) and 8.2 (s, 1H, NH)</td>
</tr>
<tr>
<td>4b</td>
<td>3330, 3200 (−NH₂), 2950 (aromatic CH), 2220 (CN) and 1640 (C=N)</td>
<td>3.8 (s, 3H, OCH₃), 7.2–7.7 (m, 4H, aromatic protons), 7.8 (s, 2H, NH₂) and 8.1 (s, 1H, NH)</td>
</tr>
<tr>
<td>7</td>
<td>3240, 3100 (conj. −NH₂), 2850 (aromatic CH), 2240, 2210 (two CN) and 1690 (ring CO)</td>
<td>3.8 (s, 3H, OCH₃), 7.1–7.7 (m, 4H, aromatic protons), 7.8 (s, 2H, NH₂) and 8.2 (s, 1H, NH)</td>
</tr>
<tr>
<td>9</td>
<td>3480–3390 (br, OH), 2490 (aromatic CH), 2200 (CN) and 1700 (ester CO)</td>
<td>3.8 (s, 3H, OCH₃), 7.2–7.5 (m, 4H, aromatic H) and 8.2 (s, 1H, OH)</td>
</tr>
<tr>
<td>12</td>
<td>3400, 3380 (NH₃), 2940 (aromatic CH), 2200 (CN) and 1680 (CO)</td>
<td>–</td>
</tr>
<tr>
<td>15a</td>
<td>3319, 3210 (NH₃), 2290 (aromatic CH), 2220 (CN) and 1640 (C=N)</td>
<td>1.8 (s, 3H, CH₃), 3.8 (s, 3H, OCH₃), 6.6 (s, 1H, thiopyran H-4), 7.3–7.7 (m, 4H, aromatic protons) and 8.1, 8.2 (s, 3H, NH and NH₂)</td>
</tr>
<tr>
<td>15b</td>
<td>3330, 3200 (NH₃), 2220 (CN) and 1650 (C=N)</td>
<td>–</td>
</tr>
<tr>
<td>17</td>
<td>3300, 3280 (NH₃), 2940 (aromatic CH), 2240 (CN) and 1680 (C=N)</td>
<td>–</td>
</tr>
<tr>
<td>20</td>
<td>3450, 3360 (NH₃), 2960 (aromatic CH), 2210 (CN) and 1640 (C=N)</td>
<td>1.8 (s, 3H, CH₃), 3.8 (s, 3H, OCH₃), 6.4 (s, 1H, pyran H-4), 7.2–7.5 (m, 9H, aromatic protons) and 8.2 (s, 2H, NH₂)</td>
</tr>
</tbody>
</table>
collected by filtration, washed with water several
times and then recrystallized from ethanol. Orange
crystals, m.p. 265 °C.

Using this procedure, the compounds enlisted in
Table I could be obtained via the reaction of
equimolar amounts (10 mmole) of 1a with the equiv-
alent amount of the methylene active reagents
(2a–c), ethyl acetoacetate, acetylacetone, 3-methyl-
5-pyrazolone (13), 3-methyl-isoxazol-5-one (16) and
3-methyl-1-phenyl-5-pyrazolone (18).

Elgemeie, Heterocycles 20, 519 (1983).
A. Monforte, and M. Quinterio, J. Chem. Soc. Perkin
Trans 1 1985, 1681.
and M. H. Elnagdi, Synthesis 1985, 432.
[4] Z. E. Kandeel, K. H. Hilmy, F. M. Abdel Razek, and
Heterocycles 20, 783 (1983).
687 (1986).
[9] Z. E. Kandeel, K. M. H. Hilmy, N. A. Ismail, and