

NITRILES IN HETEROCYCLIC SYNTHESIS: NEW ROUTES FOR SYNTHESIS OF PYRAN,  
PYRIDINE AND PYRROLE DERIVATIVES

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**Abstract**- Synthesis of pyran, pyridine and pyrrole derivatives utilising cinnamoylacetonitrile as starting component is reported.

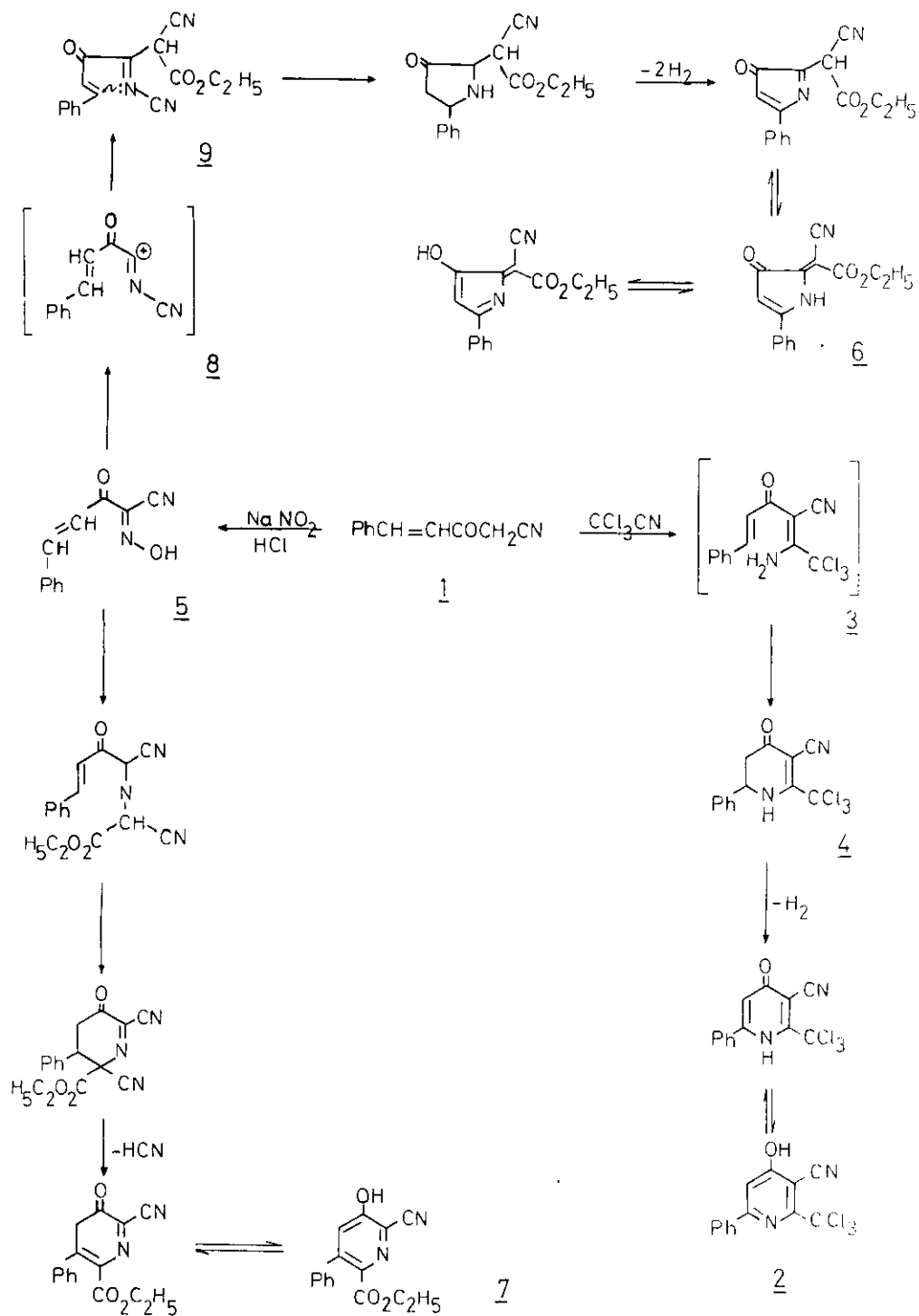
3-Oxoalkanonitriles are versatile reagents and their chemistry has received a considerable attention<sup>1</sup>. In recent years several new synthesis of pyrans<sup>2</sup>, pyridines<sup>3</sup>, pyrimidines<sup>4</sup> and other heterocycles<sup>5-7</sup> has been reported. In all these syntheses benzoylacetonitrile was utilized as the starting materials. We have been interested to see if the above described synthesis can be extended to constitute general routes to the above mentioned ring systems. In the present paper we report our investigations on the utility of cinnamoylacetonitrile (1) in heterocyclic synthesis utilizing procedures similar to those described utilizing benzoylacetonitrile. It has been found that 1 reacts with trichloroacetonitrile to yield a product of molecular formula  $C_{13}H_9N_2OC1_3$  (*m/e* 313). Structure 2 was suggested for the reaction product based on spectral data. The formation of 2 from 1 is assumed to proceed via intermediacy of the enaminketone 3. Formation of an enaminketone from reaction of benzoylacetonitrile with trichloroacetonitrile has been previously reported<sup>8</sup>. The formed enaminketone 3 underwent ready cyclization into 4 which underwent ready oxidation under the reactions conditions to yield the hydroxypyridine derivative 2. The formation of pyridine derivatives from reaction of 1 with trichloroacetonitrile constitutes a new synthesis of pyridine derivatives.

Compound 1 reacted with nitrous acid to yield the oximino derivative 5. Although 5 contains a cyano group, the IR spectra did not show any signals in the range from 2200-2280  $cm^{-1}$ . This finds parallelism to reported absence of cyano absorption in cyano compounds carrying adjacent oxygenated groups<sup>9</sup>.

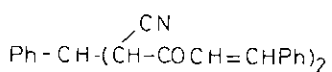
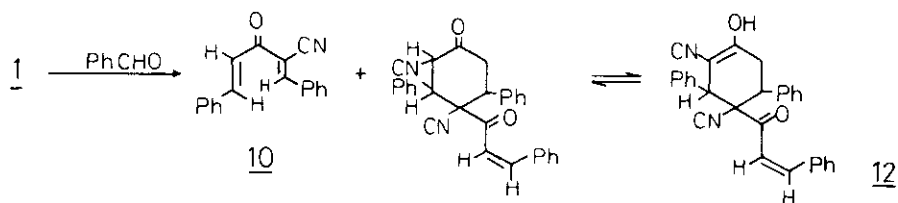
Compound 5 reacted with ethanolic ethyl cyanoacetate in presence of catalytic amount of piperidine to yield a product of molecular formula  $C_{15}H_{12}N_2O_3$  (m/e 268). Two structures seemed possible for the reaction product (cf. structures 6 and 7) and a plausible mechanism to account for their formation could be suggested (cf. scheme 1). Structure 6 seems most likely based on the spectral data which revealed a pyrrole ring signal at  $\delta$  6.00 ppm. If this product was the pyridine derivative 7 one would expect ring signal at higher field. Moreover the IR spectrum of the reaction product revealed ester CO absorption at  $1685\text{ cm}^{-1}$ . If this product was 7 ester group absorption at  $1720\text{--}1750\text{ cm}^{-1}$  would have been observed<sup>10</sup>. In addition the product of reaction is highly coloured (red) which is anticipated for a molecule of structure 6 but not for 7. The formation of 6 is assumed to proceed via initial base catalysed Beckman rearrangement of 5 to yield the intermediate 8. This latter reacts with the carbanion of ethyl cyanoacetate to yield 9 which affords 6 via cyclization, CN elimination and oxidation. Similar base catalysed Beckman rearrangement of oximinonitriles has been previously reported<sup>11</sup>.

Compound 1 condensed with benzaldehyde in acetic acid in presence of triethylamine to yield a mixture of the ylidene derivative 10 and other product of molecular formula  $C_{29}H_{22}N_2O_2$  (m/e 430) which was considered to be either the arylidene bis derivative 11 or one of its cyclization products 12 or 13. Structure 12 was established based on IR and <sup>1</sup>HNMR. Thus, IR spectra revealed absence of signal for  $NH_2$  function and show two carbonyl bands at  $1680$  and  $1715\text{ cm}^{-1}$ . Moreover, <sup>1</sup>HNMR revealed a pattern that can be intelligibly interpreted only for structure 12. Thus, spectral data revealed  $CH_2$  protons of cyclohexene structure 12 at  $\delta$  3.10 ppm, two methine protons at  $\delta$  4.2 ppm and 4.8 ppm. Similar by-product has been isolated from the reaction of benzoylacetonitrile with benzaldehyde and could be recently identified by Soto et al.<sup>12</sup>

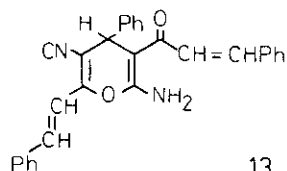
Compound 10 reacted with malononitrile to yield the pyran derivative 14, compound 14 could be synthesized on reacting 1 with benzylidenemalononitrile 15. On the other hand the reaction of 10 with ethyl cyanoacetate failed to afford isolable products, only methylbenzylidenecyanoacetate 16 could be traced in the reaction mixture. The pyran derivative 17 could be however synthesized via the reaction of 18 with 1 and assumed to be formed via the Micheal adduct, although, the



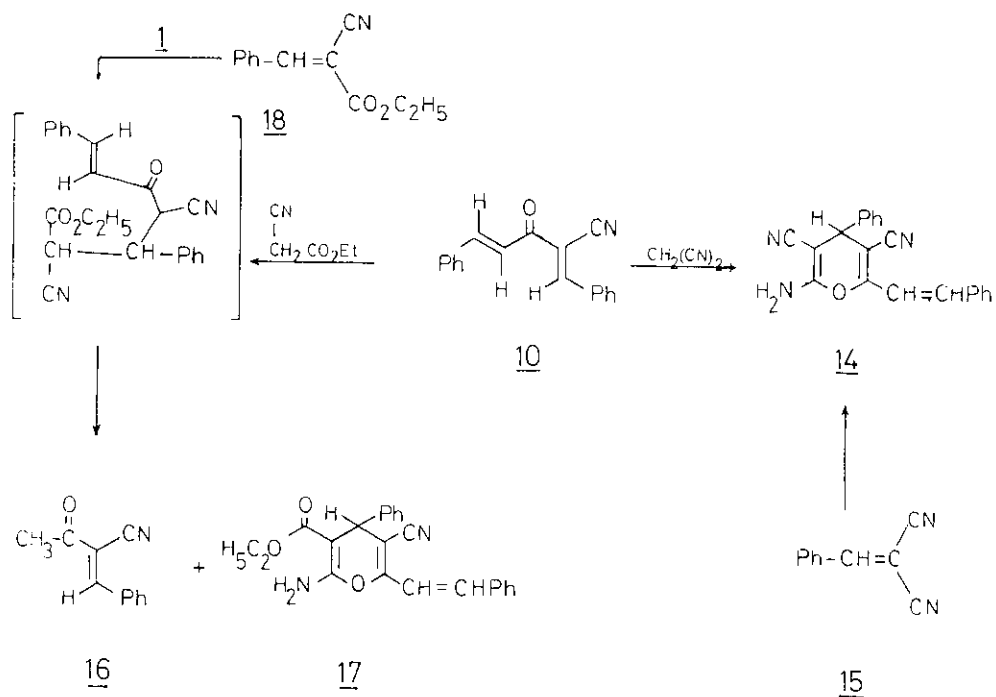
Scheme 1



11



13



Scheme 2

same Michael adduct is assumed to be formed on the way of formation of 16 from reaction of ethyl cyanoacetate with 10, our failure to isolate pyran derivative 17 via this route may be attributed to the assumption that the cinnamoyl moiety competes in the Michael reaction, thus, a mixture of several products is formed in this case.

Table 1: List of compounds 2, 5, 6, 10, 12, 14 and 17

Compound*	Solvent of cryst.	Colour	Mp (°C)	Yield (%)	Mol. formula	M <sup>+</sup> m/e
<u>2</u>	EtOH	Yellow	194	85	C <sub>13</sub> H <sub>7</sub> N <sub>2</sub> OC <sup>13</sup> <sub>3</sub>	313
<u>5</u>	cyclohexane	colourless	157-159	78	C <sub>11</sub> H <sub>8</sub> N <sub>2</sub> O	200
<u>6</u>	EtOH	red	189	70	C <sub>15</sub> H <sub>12</sub> N <sub>2</sub> O <sub>3</sub>	268
<u>10</u>	EtOH	yellow	148	70	C <sub>18</sub> H <sub>13</sub> NO	259
<u>12</u>	AcOH	yellow	240	80	C <sub>29</sub> H <sub>22</sub> N <sub>2</sub> O <sub>2</sub>	430
<u>14</u>	EtOH	colourless	114	80	C <sub>21</sub> H <sub>15</sub> N <sub>3</sub> O	325
<u>17</u>	EtOH	yellow	221-223	60	C <sub>23</sub> H <sub>20</sub> N <sub>2</sub> O <sub>3</sub>	372

\* Satisfactory elemental analyses for all the newly synthesized compounds were obtained.

Table 2: Spectroscopic data for compounds listed in Table 1

Compound	IR (cm <sup>-1</sup> ) (selected bands)	<sup>1</sup> H NMR δ (ppm)
<u>12</u>	3300 (OH); 2220 (CN)	7.20-7.60 (m, 6H, C <sub>6</sub> H <sub>5</sub> and pyridine H-5); 12.05 (s, 1H, OH)
<u>5</u>	3200-3000 (OH); 1660 (CO); 1600 (C = N)	7.20-7.50 (m, 7H, C <sub>6</sub> H <sub>5</sub> and benzyldene protons)
<u>6</u>	3400 (NH); 2220 (CN); 1680 (CO)	1.4 (t, 3H, CH <sub>3</sub> ); 4.5 (q, 2H, CH <sub>2</sub> ); 6.0 (d, 1H, pyrrole H-3); 7.8-8.00 (m, 6H, C <sub>6</sub> H <sub>5</sub> ); 10.1 (s, br, 1H, NH)
<u>10</u>	2200 (CN); 1670 (CO)	
<u>12</u>	3400 (OH); 2220, 2200 (2CN); 1740 (CO); 1680 (CO)	2.8-3.0 (m, 2H, cyclohexene H-2); 4.10-4.40 (m, 1H, cyclohexene H-3); 4.8 (s, 1H, cyclohexene H-5); 7.0-7.8 (m, 17H, 3C <sub>6</sub> H <sub>5</sub> and benzyldenic protons)
<u>14</u>	3400 (NH <sub>2</sub> ); 2200 (CN);	3.2 (s, br, 2H, NH <sub>2</sub> ); 4.5 (s, 1H, pyran H-4); 7.0-7.8 (m, 7H, C <sub>6</sub> H <sub>5</sub> and benzyldenic protons)
<u>17</u>	3400 (NH <sub>2</sub> ); 2200 (CN); 1685 (CO)	1.15 (t, 3H, CH <sub>3</sub> ); 3.20 (s, br, 2H, NH <sub>2</sub> ); 4.10 (q, 2H, CH <sub>2</sub> ); 4.70 (s, 1H, pyran H-4); 7.0-7.8 (m, 7H, C <sub>6</sub> H <sub>5</sub> and benzyldenic protons)

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