

# Utility of 3-Aminocrotononitrile in the Synthesis of New Methyl 1,4-Dihydropyridine, Methylquinoline and Thiophene Derivatives: Reactivity of the Methyl Function in Alkyl 1,4-Dihydropyridine and Methyl Quinoline Derivatives Towards Some Electrophilic Reagents

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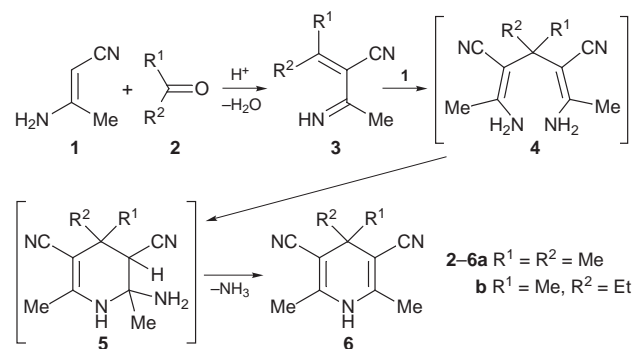
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The methyl function in some newly prepared methyl 1,4-dihydropyridine and methyl quinoline derivatives proves to be highly active towards some electrophiles.

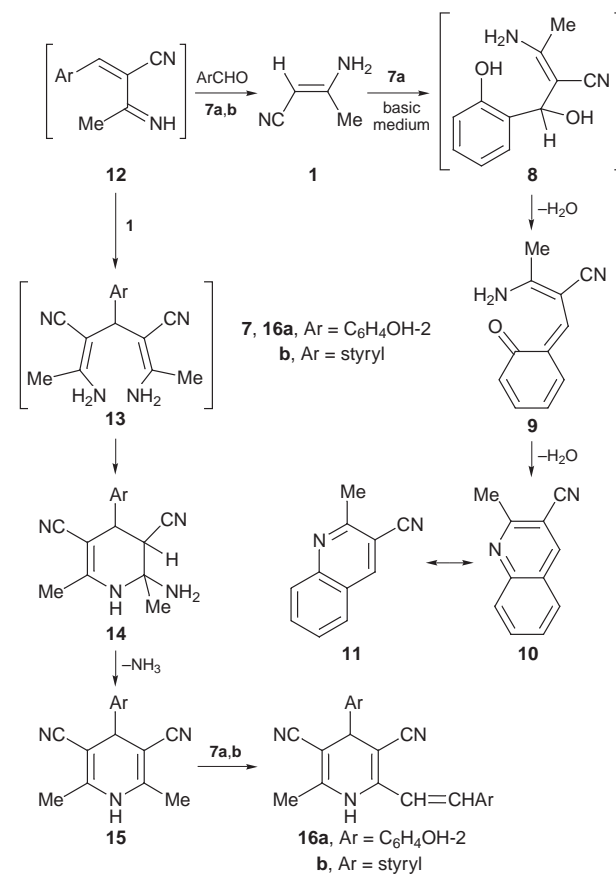
A literature survey revealed that 2-aminocrotononitrile condenses with aromatic aldehydes to afford 1,4-dihydropyridine derivatives.<sup>15</sup> Recently, we have found that heteroaromatic aldehydes condense with 3-aminocrotononitrile **1** to afford pyridine derivatives.<sup>16</sup> This result promoted us to focus on the behaviour of 3-aminocrotononitrile towards some other carbonyl compounds. Thus, it has been found that acetone **2a** condensed readily with 3-aminocrotononitrile **1** to afford a 1:2 adduct formulated as the 2,4,4,6-tetramethyl-1,4-dihydropyridine derivative **6a**. Establishing structure **6a** was based on its spectral data. Formation of compound **6a** is assumed to be *via* initial condensation of acetone with one molecule of **1** to yield the unstable ylidene derivative **3a** which, in turn, reacts with another molecule of **1** giving intermediate **4a** which cyclizes into **5**, which then loses NH<sub>3</sub> to yield **6a**. Similarly, butanone condenses with **1** to afford 1,4-dihydro-4-ethyl-2,4,6-trimethylpyridine-3,5-dicarbonitrile **6b** (Scheme 1).



Scheme 1

The behaviour of salicylaldehyde **7a** towards **1** was found to be dependent upon the reaction conditions. Thus, salicylaldehyde **7a** reacts with 3-aminocrotononitrile **1** in basic medium to give a 1:1 adduct formulated as the quinoline derivative **11** which has identical properties to that of an authentic sample.<sup>17</sup> Compound **11** is assumed to be formed *via* nucleophilic attack of **1** at the carbonyl carbon and subsequent cyclization *via* loss of two water molecules. In contrast to this and to the reported behaviour of

3-aminocrotononitrile towards aromatic aldehydes,<sup>15</sup> heteroaromatic aldehydes<sup>16</sup> and aliphatic ketones, 3-aminocrotononitrile **1** reacted with salicylaldehyde **7a** in acidic medium to give a 2:2 adduct formulated as the 1,4-dihydropyridine derivative **16a**. Compound **16** is assumed to be formed *via* initial condensation of salicylaldehyde with one molecule of **1** to yield the unstable ylidene derivative **12** which, in turn, reacts with another molecule of **1** giving **13** which cyclizes to **14** and loses NH<sub>3</sub> to afford **15**. Compound **15** reacts further with another molecule of **7a** to give the dihydropyridine derivative **16a**. Attempts to isolate **15** failed (Scheme 2).

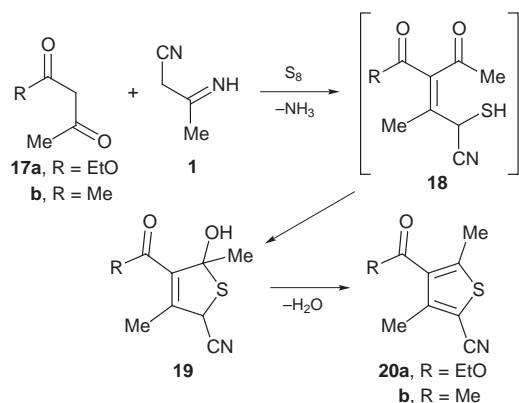


Scheme 2

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Similar to the behaviour of **1** towards salicylaldehyde **7a** in acidic medium, 3-aminocrotononitrile **1** reacted with cinnamaldehyde **7b** to afford the dihydropyridine derivative **16b** (Scheme 2).

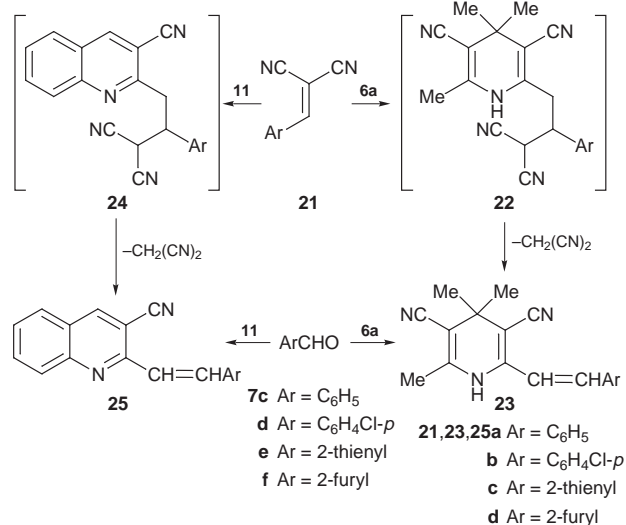
Furthermore, the behaviour of **1** towards active methylene reagents and sulfur was also investigated and found to afford new thiophene derivatives. Thus, when a mixture of **1**, ethyl acetoacetate and sulfur was refluxed in sodium/dioxan, a product with molecular formula  $C_{10}H_{11}NO_2S$  **20a** was obtained.<sup>20</sup> Formation of **20a** from **1**, ethyl acetoacetate and elemental sulfur appears to be an extension of Gewald's synthesis of substituted thiophenes<sup>21</sup> (Scheme 3). Similarly, acetylacetone **17b** reacted with **1** and elemental sulfur to give the thiophene derivative **20b**.



Alkyl functions in  $\pi$ -deficient alkylheteroaromatics are reactive towards electrophiles under mild conditions.<sup>10,22</sup> Encouraged by this, we investigated the reactivity of the methyl functions in **6a** and **11**. Thus, it has been found that, in contrast to the reported formation of benzoazines in the reaction of methylazinylnitriles with arylidenemalononitrile **21**, the reaction of **6a** with arylidenemalononitriles **21a-c** gave ylidene derivatives **23a-d**. Compounds **23a-d** were found to be identical with authentic samples prepared from the condensation of **6a** with aromatic aldehydes **7c-f** (Scheme 4).

Similarly, 2-methylquinoline-3-carbonitrile **11** reacted with arylidenemalononitriles **21a-d** to afford the ylidene derivatives **25a-d** which were identical with authentic

samples prepared from the condensation of **11** with aldehydes **7c-f** (Scheme 4).



**Scheme 4**

Techniques used: IR, <sup>1</sup>HNMR, mass spectrometry and elemental analysis

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