# New Routes for Novel Pyrazolo[3,4-*b*][1,6]-naphthyridine, Pyrazolo[3,4-*b*]pyridine and Pyrazolo[3,4:2,3]pyrido[6,1-*a*]benzimidazole Derivatives

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Pyrazolo[3,4-*b*][1,6]naphthyridine, pyrazolo[3,4-*b*]pyridine and pyrazolo[3,4:2,3]pyrido[6,1-*a*]benzimidazole derivatives are synthesized starting from the isomeric 3-substituted 5-chloro-1-phenylpyrazole-4-carbaldehyde.

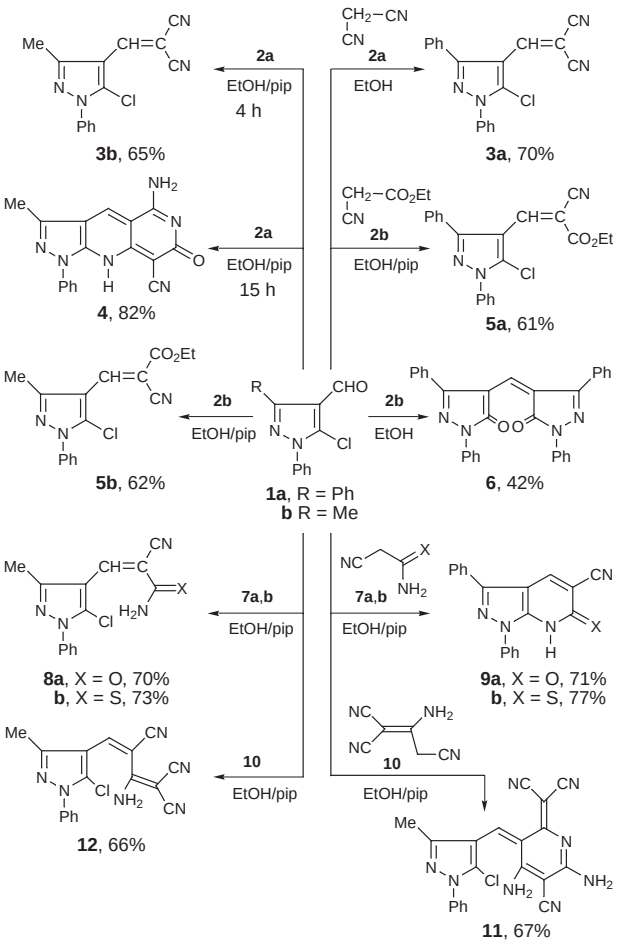
Diverse biological activities have been reported for polyfunctional substituted pyrazoles.[6] The condensation of hydrazines with $\alpha,\beta$-unsaturated aldehydes, ketones and nitriles is regarded as one of the most useful methods for pyrazoline synthesis.[9] Here, we report the effect of catalyst, reaction times and substituents on the reactivity of 5-chloro-3-substituted-1-phenylpyrazole-4-carbaldehyde **1** which has attracted attention as a precursor.[11]

Thus, compound **1a** (R = Ph) condensed readily with malononitrile **2a** in refluxing ethanol to afford **3a** in 70% yield. By contrast, **1b** (R = Me) was recovered virtually unreacted when refluxed with **2a** in ethanol, however, ylidene **3b** was formed when the reaction was carried out in the presence of piperidine either at room temperature or at reflux for 2–4 h. Alternatively, **1b** reacted with **2a** in ethanolic piperidine at reflux for 15 h to yield a product formulated as a pyrazolo[3,4-*b*][1,6]naphthyridine derivative **4** (Scheme 1). It was thus assumed that **1b** condensed with malononitrile **2a** to give **3b**, which readily reacted with the malononitrile dimer **10** which formed *in situ*, to yield an intermediate Michael adduct **I** which cyclized into intermediate **II** which finally loses malononitrile[15] and HCl to give **4** (Chart 1).

On the other hand, **1a**,**b** reacted smoothly with ethyl cyanoacetate **2b** in ethanolic piperidine at reflux to afford the acrylate derivatives **5a**,**b**. However, the methylidene **6** was isolated in 42% yield when the reaction was carried out in the absence of piperidine. **1a** reacted with cyanoacetamide **7a** and/or cyanothioacetamide **7b** in ethanolic piperidine to yield acyclic buta-1,3-diene derivatives **8a**,**b**. The chemical structures of **8a**,**b** were established based on IR and $^1$NMR spectroscopy, MS and elemental analysis. By contrast, **1b** reacted with **7a**,**b** under the same reaction conditions to afford 1,3-diphenylpyrazolo[3,4-*b*]pyridine derivatives **9a**,**b**. The chemical structure of **9a** was confirmed by IR, $^1$H and $^{13}$C NMR, MS and elemental analysis.

Compound **1a** condensed with malononitrile dimer **10** in ethanolic piperidine to yield a product formulated as **11**. The formation of **11** is believed to proceed *via* elimination of one molecule of malononitrile from the initial butadiene intermediate, which recombined once more[15] to yield the final product **11**. On the other hand, **1b** readily condensed with **10** under the same reaction conditions to give the acyclic buta-1,3-diene derivative **12**. The chemical structures of **11** and **12** were confirmed based on elemental and spectral data (Scheme 1).

Compound **1a** reacted with 2-cyanomethylbenzimidazole **13** in ethanolic piperidine at reflux to yield the new 1,3-diphenylpyrazolo[3,4:2,3]pyrido[6,1-*a*]benzimidazole **15**




**Scheme 1**

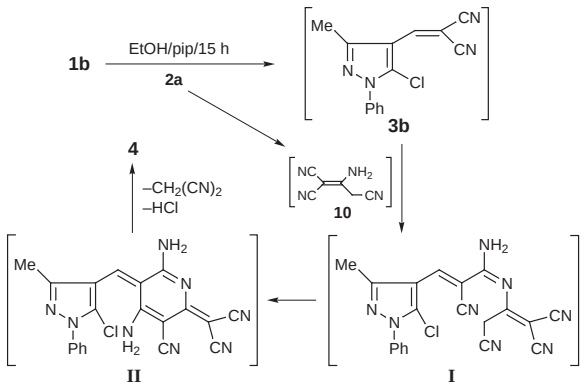
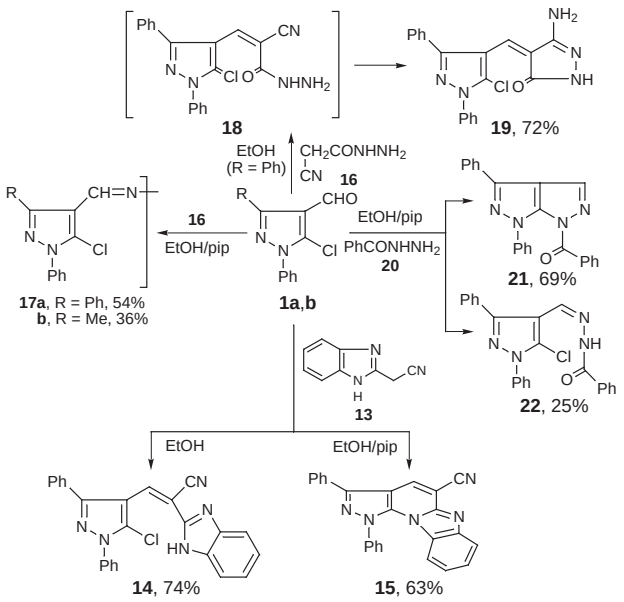



**Chart 1**

* To receive any correspondence.




**Scheme 2**

as the only isolable product as confirmed by IR, $^{1}$H and $^{13}$C NMR, MS and elemental analysis. However, intermediate **14** was isolated in 74% yield in the absence of piperidine. Furthermore, **1a**,**b** reacted directly with cyanoacetohydrazide **16** in ethanolic piperidine at reflux to yield the dimeric azines **17a**,**b** which were identified by comparison with authentic samples.[11] However, **1b** was recovered unreacted with **16** in the absence of piperidine, while **1a** afforded **19**, which is assumed to be formed *via* initial formation of the carbohydrazide intermediate **18**. The IR spectrum of **19** showed no indication of a cyano function. Finally, **1a** reacted with benzoic acid hydrazide **20** in ethanolic piperidine at reflux to yield **22** (25%). Treatment of the filtrate yielded **21** in 69% yield, with elemental and spectral data consistent with the proposed structures (Scheme 2).

Techniques used: IR, $^{1}$H and $^{13}$C NMR, mass spectrometry

References: 24

Schemes: 3

Charts: 3

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