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Studies with 3-Oxoalkanenitriles: Synthesis of New Pyrazolo[1,5-*a*]pyrimidines and Pyrazolo[5,1-*c*]-1,2,4-triazines and Reactivity of 4-Phenyl-3-oxobutanenitrile Derivatives

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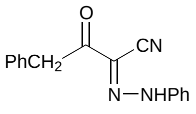
4-Phenyl-3-oxobutanenitrile is synthesized *via* the reaction of ethyl phenylacetate with acetonitrile in the presence of sodium hydride and identified by isolating its 2-phenylhydrazone and dimethylaminomethylidene derivatives; both the hydrazone and dimethylaminomethylidene derivatives prove versatile starting materials for the synthesis of a variety of polyfunctionally substituted heterocycles.

The synthesis of 4-phenyl-3-oxobutanenitrile **6** and its characterization in the form of its hydrazone **4** and its dimethylaminomethylidene derivative **5** are reported. The utility of both derivatives for the synthesis of a variety of new heterocycles of potential biological activity is also described.

Ethyl phenylacetate reacted with acetonitrile in refluxing toluene in the presence of sodium hydride to yield an oily mixture consisting of two major products. Triturating this oily mixture with ethanol afforded ethyl 2,4-diphenyl-3-oxobutanoate **8** in 30% yield as a solid, which was separated by filtration. Evaporation of the ethanol afforded an oil consisting mainly of 3-phenyl-3-oxobutanenitrile **6**. Although this compound could not be obtained in pure form, it could be utilized to produce the phenylhydrazone derivative **4** and the dimethylaminomethylidene derivative **5** *via* treatment with benzenediazonium chloride and *N*,*N*-dimethylformamide dimethyl acetal (DMF DMA), respectively. Both **4** and **5** were characterized by elemental and spectral data.



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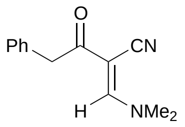

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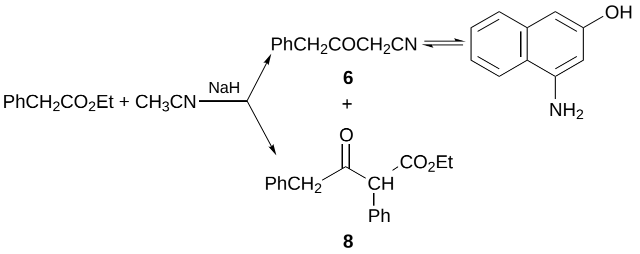
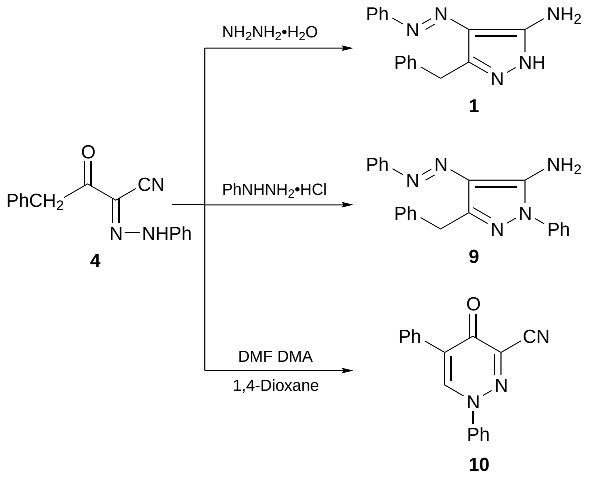
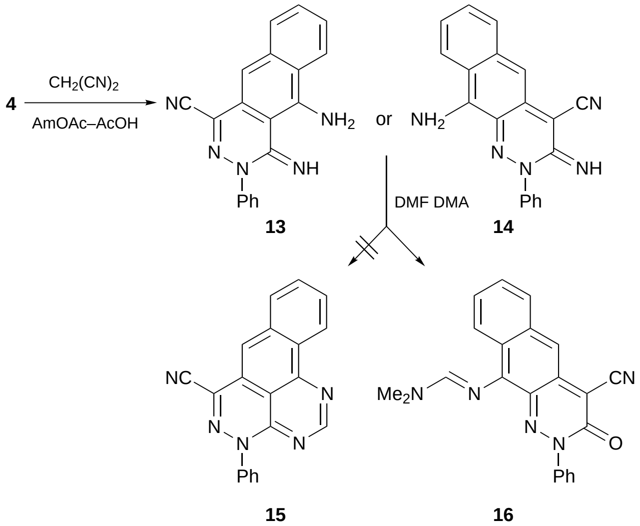


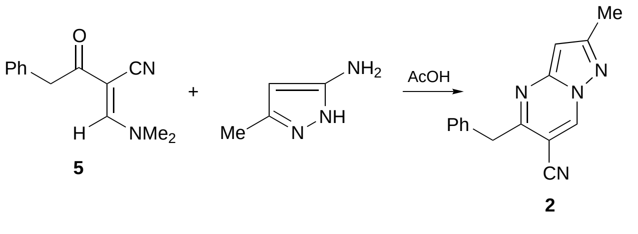


Treatment of the phenylhydrazone **4** with hydrazine hydrate afforded 5-amino-3-benzyl-4-phenylazopyrazole **1** in quantitative yield. Similar treatment of **4** with phenylhydrazine resulted in isomerization of the phenylhydrazone into another compound for which no simple structure could be deduced. However, when **4** was treated with phenylhydrazine hydrochloride in refluxing ethanol, 5-amino-3-benzyl-1-phenyl-4-phenylazopyrazole **9** was obtained. Reaction of **4** with DMF DMA yielded the pyridazinone **10**. A similar pyridazine synthesis has been recently reported by Elnagdi and co-workers.[6]

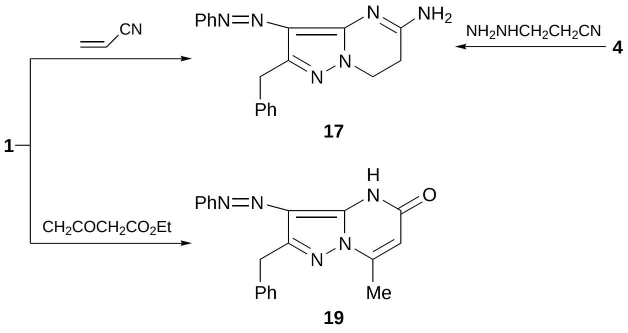
Reaction of **4** with malononitrile afforded a product of condensation that may be formulated as **13** or **14**. Structure **14** is preferred over **13** based on the observation that treatment of the product with DMF DMA did not afford the tetracyclic derivative **15** but rather gave **16**.

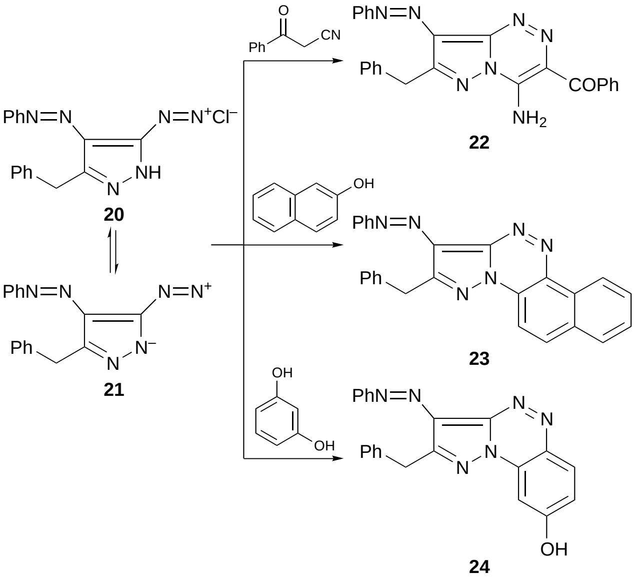
Treatment of **5** with 5-amino-3-methylpyrazole in acetic acid afforded the benzylpyrazolo[1,5-*a*]pyrimidine **2** in quantitative yield.





Compound **1** afforded the 5-aminopyrazolo[1,5-*a*]pyrimidine derivative **17** on treatment with acrylonitrile. Structure **17** was also established for the product from the reaction of the hydrazone **4** with (2-cyanoethyl)hydrazine.





Compound **1** reacted with ethyl acetoacetate in ethanol to afford the 5-oxopyrazolo[1,5-*a*]pyrimidine derivative **19**. Structure **19** is based on literature precedent[7] and on the IR spectrum which revealed a characteristic carbonyl absorption for a 5-oxopyrazolo[1,5-*a*]pyrimidine at 1674 cm^{-1}. The behaviour of **1** towards ethyl acetoacetate is in parallel with that reported for 5-aminopyrazoles towards the same reagent under similar conditions.[8]

Compound **1** was readily diazotized utilizing Elnagdi's diazotization procedure.[8] Although the diazonium salt **20** could not be isolated in pure form, it coupled readily with benzoylacetonitrile, yielding 7-aminopyrazolo[1,5-*a*]triazines **22**. The diazonium salt **20** also reacted under the coupling conditions with 2-naphthol and with resorcinol affording the pyrazolotriazine derivative **23** and the pyrazolotriazine **24** respectively.

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

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