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The Capture of Acetonitrile During a Bischler-Napieralski Cyclisation Reaction of an Oxamide Derivative

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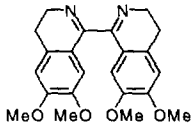
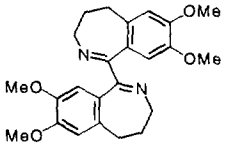
Abstract: *Attempts to extend Bischler-Napieralski reactions of oxamide derivatives to seven-membered ring analogues of 1,1'-bi-isoquinolinyl were problematic and although a 1,1'-bi-benzazepine was obtained in a low yield an imidazolidinone was isolated in high yield as a result of the capture of acetonitrile by a reactive intermediate.*

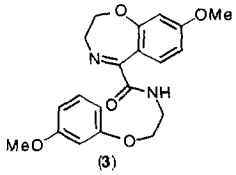
Our use of pyrophosphoryl chloride in Vilsmeier reactions[1] suggested an extension to an intramolecular version, the Bischler-Napieralski reaction.[2] The intermediacy of nitrilium ions has been established for reactions involving derivatives of β-phenylethylamine,[3] however, nitrilium ions have not been detected in reactions involving amides derived from β-arylethylamines that carry electron releasing substituents at appropriate positions and a duality of mechanisms may operate. Retro-Ritter reactions are established in reactions of 1,2-diarylethylamides that are supressed by carrying out the reactions using an appropriate nitrile.[4] These considerations encouraged us to investigate reactions of oxamide derivatives, even though the possible *N*-acylnitrilium ions would be at higher energy than *N*-alkyl- and *N*-arylnitrilium ions. We investigated reactions of oxamide derivatives partly in an attempt to prepare compounds with axial chirality. The formation of benzazepines and benzoxazepines using Bischler-Napieralski type procedures has not been investigated as frequently as the formation of 3,4-dihydroisoquinolines.[5,6] Although alkanonitriles have not been commonly used as solvents for Bischler-Napieralski cyclisation reactions, there are examples where their use has been strongly recommended,[6a-c] and an example of capture by a reactive intermediate.[6d] We report in this letter some of our results, including an example where acetonitrile is intercepted by an intermediate that results in the formation of an imidazolidinone.



(1)



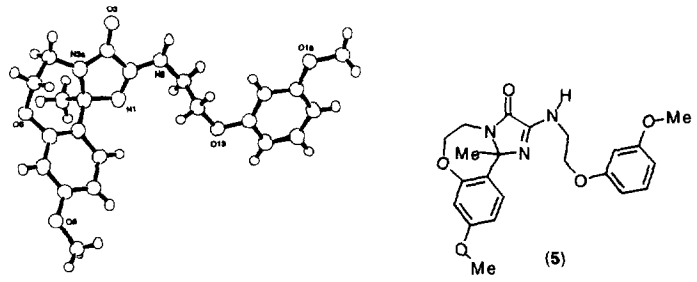
(2)



(3)

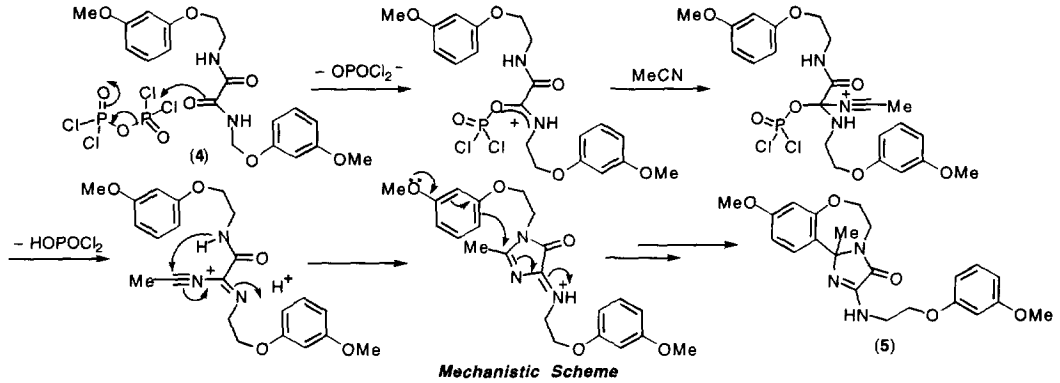
The oxamide derived from 3,4-dimethoxy-β-phenylethylamine was converted into the bi-isoquinolinyl derivative (**1**) in an 84% yield using pyrophosphoryl chloride[7] in acetonitrile. Attempts to extend the reactions to the seven-membered ring analogues of the compound (**1**) were frustrated: we were only able to obtain the 1,1'-bis-(benzazepine) derivative (**2**) in a 21% yield in a reaction using 1,2-dichloroethane as the solvent. The monocyclised product (**3**) was obtained in a 34% yield as the only identified product in an analogous reaction.

On the other hand we isolated a product in 81% yield that had incorporated a molecule of acetonitrile when the oxamide (**4**) was allowed to react with pyrophosphoryl chloride in acetonitrile. We conclude that an intermediate involved in the reaction is sterically congested but that the relatively small cylindrically symmetrical acetonitrile can intercept a reactive intermediate and hence give the stable imidazolidinone (**5**). Elemental analysis established the molecular formula[8] and spectroscopic data suggested the formation of the compound (**5**).[9] This was confirmed by a single crystal X-ray stucture determination as shown below.[10]



X-ray structure representation of the product (**5**)

A plausible mechanistic interpretation of these results is shown in the scheme.



Mechanistic Scheme

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8. Found: C, 63.90, H, 6.25, N, 10.25% M^+ 411.1754; $C_{22}H_{25}N_3O_5$ requires C, 64.20, H, 6.10, N, 10.25% M^+ 411.1794.
9. ν_{max} 1710 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.73 (s, 3H), 3.64-3.67 (m, 1H), 3.68-3.70 (m, 1H), 3.76 (s, 3H), 3.78 (s, 3H), 3.86 (q, 2H, *J* = 5.9 Hz), 4.19 (t, 2H, *J* = 5.9 Hz), 4.31 (m, 1H), 4.46 (m, 1H), 5.56 (br t, 1H, *J* = 5.9 Hz, N*H*), 6.47 - 6.57 (m, 4H), 6.61 (d x d, 1H, *J* = 2.65 and 8.5 Hz), 7.14 - 7.21 (m, 1H), and 7.63 (d, 1H, J = 8.5 Hz) ppm; δ_C (62.86 MHz, $CDCl_3$) 27.87, 41.24, 42.19, 55.26, 55.36, 65.90, 72.00, 84.00, 101.50, 106.57, 106.76, 107.67, 109.50, 127.77, 129.34, 129.94, 154.86, 158.47, 159.71, 160.07, and 160.85 ppm.
10. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited with the Cambridge Crystallographic Data Centre.

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