A New Domino Synthesis of Polyfunctionalized Pentasubstituted Pyridines

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The reaction of *N*-vinylisocyanate **1** and ynamine **2** in the temperature range 0–25 °C affords pyridines **3** and **4** regioselectively; the intermediate azanorbornadiene **7** has been isolated and spectroscopically characterized.

Pyridines are well known to have a wide range of applications,[1] and their synthesis have been extensively reviewed.[2] Polysubstituted derivatives containing several functionalities are a subgroup of prime importance but their syntheses usually involve lengthy processes with poor regioselectivity and/or low yields.[3] Diels–Alder reactions remain one of the most useful approaches to these heterocycles in terms of regiocontrol and simplicity. Methods with the nitrogen atom within the dienic or dienophilic framework have also been reported,[4] 2-azabutadienes being mostly preferred either as open chain synthons[5] or preformed in an heterocyclic nucleus.[6]

In this context, *N*-vinylheterocumulenes are of particular interest because of their ability to act as azadienes in [4 + 2] cycloadditions and as activated double bonds in heterocyclization processes.[7] A combination of both reactivities has been reported by Dondoni *et al.*[8] in the synthesis of 2- and 4-pyridones or pyridinthiones from *N*-vinylisocyanates or isothiocyanates and ynamines; however, low yields of mixtures of regioisomers are obtained.

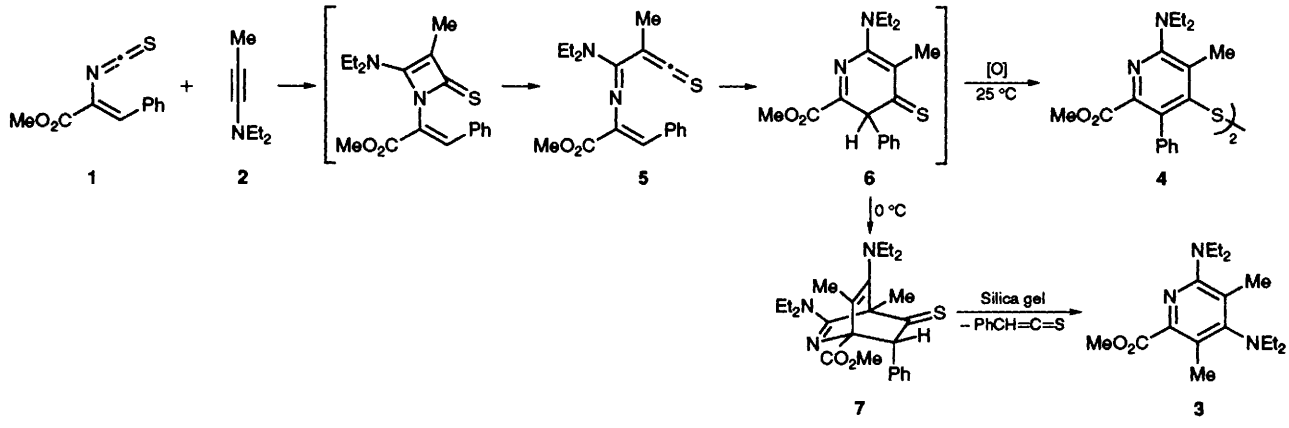
Herein we describe our first results on the regioselective synthesis of pentasubstituted polyfunctionalized pyridines starting from readily available *N*-vinylisothiocyanate[9] **1** and ynamine **2**. Depending on the temperature two different domino[10] reactions can be promoted with full regiochemical control and in almost quantitative yields. Thus, the addition of 2 equiv. of 1-diethylamineprop-1-yne **2** to **1** at 0 °C in THF or chloroform affords, after 12 h of reaction and work-up, the pyridine **3** as the sole product (Scheme 1). When a 1:1 stoichiometry was used the same pyridine is obtained, together with the corresponding amount of unreacted heterocumulene. However, by stirring a 1:1 mixture of **1** and **2** at room temp. for 24 h in the above-mentioned solvents, the dimer **4** is isolated‡ in 95% yield (Scheme 1). The reaction time can be reduced in a factor two by carrying out the process at the solvent reflux temperature, although the yield is slightly decreased (83%) probably due to the self-polymerization of the ynamine.

The structural assignment have been made according to their mass, ^{1}H and ^{13}C NMR spectra, including NOE difference and proton detected heteronuclear 2D correlation experiments (HMQC[11] and HMBC[12]). The dimeric nature of **4** is clearly ascertained from the molecular peak found in its EI-MS spectrum[13] and from the NOE enhancement measured for the diethylamino (3%) and phenyl (3%) substituents after selective presaturation of the methyl protons on the C-3 ring atom.

A possible mechanism for the formation of **3** and **4** is depicted in Scheme 1. In the first step a 2-azetin-4-one is obtained through the regiospecific [2 + 2] cycloaddition of the ynamine to the isothiocyanate moiety of **1**, this rearranges to the cumulene **5**, which then undergoes an electrocyclical ring-closure affording the dihydropyridin-4-thione **6**. This key intermediate can react further in two different ways depending on the temperature. At 0 °C the 2-azadienic reactivity is enhanced over that of the thiocarbonyl moiety and a [4 + 2] cycloaddition with a second ynamine molecule takes place yielding the bicyclic heterocycle **7**, that by subsequent retro-Diels–Alder finally gives the pyridines **3**. On the other hand, at room temp. the thiocarbonyl group of **6** would oxidize to the dimer **4**, under the basic conditions[14] of the reaction medium itself.

The proposed mechanism is strongly supported by the fact that once **7** is formed at 0 °C it is stable at room temp. and can be isolated by *in vacuo* solvent evaporation (92%); however, all attempts to purify it failed and the pyridine **3** was obtained instead. Its identification was achieved spectroscopically from the reaction crude following the same procedure previously outlined§. The correlations observed in the HMBC spectrum for the proton singlets at δ 1.74, 1.81 and 4.21 clearly established the bicyclic configuration of **7**, and its stereochemistry was easily deduced from the NOESY spectrum.[15] The regio- and diastereo-specific formation of **7** must be adscribed to the effective steric blockage of the 2-azadiene face on the same side of the phenyl ring, which in turn favours the approach of **2** through the less hindered face of **6**.

The reaction described here affords an extremely simple way of access to pentasubstituted polyfunctionalized pyridines with all the benefits of a domino strategy, *i.e.* consecutive reactions take place as a consequence of the functionalities formed in the previous steps, therefore, high yields can be obtained by drastically reducing the amount of undesired byproducts. Moreover, the concerted character of most of the reactions involved in the synthesis reported, allows **3**, **4** and **7** to be obtained in a regiospecific manner, the most striking



1 2 5 6 4 7 3

Scheme 1

point being the fact that two different cascades of reactions are promoted at a temperature interval as small as 25 °C. Taking into account the nature of the starting materials, this methodology could be applied to a wide range of heterocumulenes and electron-rich olefins.[16]

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Footnotes

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‡ To a solution of the isothiocyanate **1** (0.4 g, 2 mmol) in chloroform or THF (10 ml) at 0 °C 2 equiv. of the ynamine **2** (0.44 g, 4 mmol) were slowly added. The mixture was stirred overnight at this temperature. Solvent evaporation afforded a red oil **7** (92%). Column chromatography (silica gel, diethyl ether as eluent, R_F: 0.8) then gave pyridine **3** quantitatively, that was recrystallised from hexane–chloroform. The same procedure was applied to the synthesis of pyridine **4**, but a 1:1 stoichiometry at $T = 25$ or 80 °C was used instead. Recrystallization of the crude product yielded pure **4** (95%).

Selected spectral data for 2,4-bis(*N,N*-diethylamino)-3,6-dimethyl-6-methoxycarbonylpyridine **3**: ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 1.02 (t, 6 H), 1.09 (t, 6 H), 2.17 (s, 3 H), 2.28 (s, 3 H), 3.14 (q, 4 H), 3.17 (q, 4 H), 3.91 (s, 3 H). ^{13}C NMR (100.61 MHz, $CDCl_3$‘: δ 13.2, 14.2, 15.0, 16.0, 45.0, 46.0, 52.0, 124.6, 125.2, 144.6, 158.1, 160.5, 168.4. MS: 307 (M^+), 278, 218, 72.

For di(*N,N*-diethylamino)-5-methoxycarbonyl-2-methyl-6-phenyl-4-pyridyl disulfide **4**: ^{1}H NMR (400.13 MHz, $CDCl_3$); δ 1.14 (t, 6 H), 2.24 (s, 3 H), 3.21 (q, 4 H), 3.51 (s, 3 H), 6.68 (d, 2 H), 7.12–7.30 (m, 3 H). ^{13}C NMR (100.61 MHz, $CDCl_3$), δ 13.1, 18.4, 44.8, 51.8, 127.2, 127.5, 128.9, 130.0, 132.5, 136.9, 144.9, 146.6, 160.9, 167.3, MS: 658 (M^+), 329, 269, 72; mp: 162–163 °C.

§ *Selected spectral data* for *endo*-2-aza-3,7-diethylamino-4,8-dimethyl-1-methoxycarbonyl-5-thiocarbonylnorborna-2,7-diene **7**: ^{1}H NMR (400.13 MHz, $CDCl_3$); δ 0.75 (t, 3 H), 0.93 (t, 3 H), 1.05 (t, 3 H), 1.74 (s, 3 H), 1.81 (s, 3 H), 2.75–2.99 (m, 4 H), 3.08–3.22 (m, 4 H), 3.62 (s, 3 H), 4.21 (s, 1 H), 6.93–7.12 (m, 5 H). ^{13}C NMR (100.61 MHz, $CDCl_3$): δ 13.22, 13.73, 14.67, 14.77, 16.53, 44.34, 46.28, 47.33, 51.98, 66.68, 75.47, 76.87, 126.80, 127.70, 129.30, 136.84, 141.29, 142.96, 168.51, 171.78, 248.50; MS: 441 (M^+), 382, 310, 278. A detailed structural study will be published elsewhere.

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