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Synthesis of pyridone and pyridine rings by [4+2] hetero-cyclocondensation

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Abstract—Substituted pyridones and pyridines have been synthesised efficiently by employing iminium salt as a key precursor. These compounds were prepared using tandem [4+2] cycloaddition/deamination between azabutadiene and dienophiles.

The development of new methods for the synthesis of substituted pyridines and pyridones is a topic of current interest because of their presence in numerous natural products along with the wide spectrum of physiological activities displayed by this class of compounds.[1–3] It is well known that these heterocycles are valuable building blocks in natural products synthesis. Many methods for the preparation of these heterocyclic rings systems and their fused analogues have been described in the literature.[4–7] The most versatile and useful strategy to produce pyridine derivatives is the cyclocondensation between 1,3-dicarbonyl compounds and a 3-aminoenone, 3-aminoacrylate or cyanoacetamide.[8–10] In addition, construction of pyridine and pyridone rings by metal-mediated [2+2+2] cycloaddition of alkynes with nitriles or isocyanates, is an efficient method and has been largely developed.[11] On the other hand, a hetero-Diels–Alder methodology employing azadienes represents a straightforward approach to build nitrogen heterocycles.[12–15] In this communication, we report our new approach to synthesise the title compounds using hetero-Diels–Alder reactions with versatile diazadienium salt forming substrates.

We recently reported that 2,4-diaminothiabutadiene **1** was used as useful building block in the synthesis of various thiopyrans and thiophenes.[16] In a view to extend this work to the preparation of pyridines we decided to investigate the behaviour of this chain, when alkylated, towards dienophiles. Indeed, alkylation of compound **1** using methyl iodide provides *S*-methyl salt **2** which presents the azadiene chain. In our previous paper, we described the reactivity of this diazadienium iodide **2** with glycosylisothiocyanates for the preparation of pyrimidine nucleoside analogues.[17] With these considerations in mind, we have further developed an efficient approach to a variety of 3,6-disubstituted pyridin-2-ones **3** and di- or trisubstituted pyridines **4**,**7** starting from *S*-methyl salt **2**. As shown in Scheme 1, reaction of vinylthioamide **1** with excess of methyl iodide at 25 °C in THF for 18 h afforded the corresponding *S*-methyl salt **2** as the sole product due to the preferential alkylation of the more nucleophilic sulfur atom.

Treatment of compound **2** with a range of ketenes, obtained from the corresponding acid chlorides, led to [4+2] cyclocondensation which gave 6-methylsulfanyl-pyridin-2(1*H*)-ones **3a**–**c**. The heterocyclisation occurred in a regiocontrolled manner by the action of excess (3 equiv) of ketene at room temperature, and by addition of 4 equiv of triethylamine to neutralise the hydracids (HI and HCl) generated in the reaction.[18] The final step consisted of deamination of the supposed intermediary cycloadduct giving aza-lactams **3a**–**c** with moderate yields. It is noteworthy that IR and ^{13}C NMR spectra indicated that compounds **3a**,**b** existed in the 2-hydroxypyridine form probably due to the presence of internal hydrogen bonding between the OH and ester group to increase the stability. The proof of the structure of compounds **3a**–**c**, so the total regioselectivity, was determined by the ^{13}C NMR spectra where the carbon

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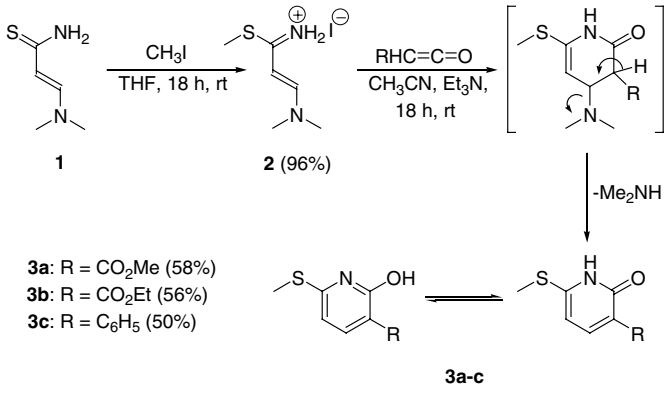
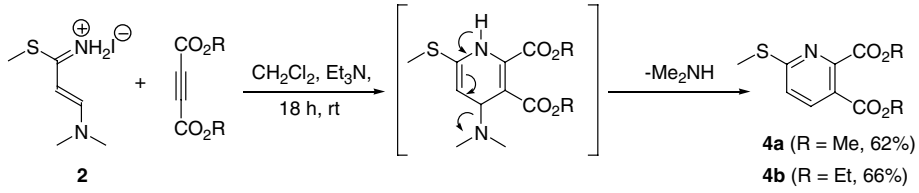


Scheme 1.



Scheme 2.

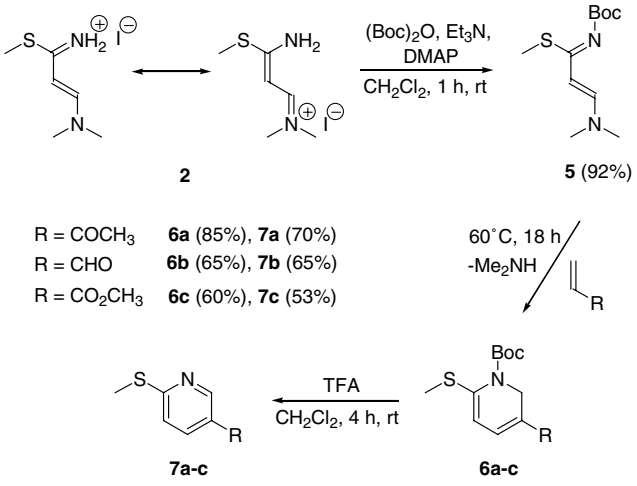
signal in position 2 (≈165 ppm) is unambiguously attributed to iminol (for **3a**,**b**) or amide (for **3c**) function of pyrimidic ring.

Preliminary antiviral and cytotoxic assays for compounds **3** against HSV-1 in Vero (African Green Monkey) cells were performed. Unfortunately, biological tests showed that heterocycles did not display any anti-herpes activity.

We continued our investigations towards pyridines by exposing diene **2** to dialkyl acetylenedicarboxylate. The tandem [4+2] cycloaddition/deamination reaction between compound **2** and acetylenic dienophiles in the presence of triethylamine allowed us to prepare pyridines **4a**,**b** in satisfactory yields (Scheme 2).[19]

To complete this study we investigated the behaviour of cationic aza-1,3-butadiene **2** with acrylic dienophiles. The [4+2] cycloaddition with acrolein, methyl vinyl ketone or methyl acrylate did not occur and we never observed the formation of the pyridine skeleton. This failure was probably due to the relative instability of *S*-methyl salt **2** and the lower reactivity of the acrylic dienophiles relative to the ketenes or acetylenedicarboxylates. To increase the reactivity of iminium salt, which has two mesomeric forms either aza-1,3-diene or aza-2,4-diene and to block the azabuta-1,3-diene form in the heterocyclisation process, we protected the nitrogen atom with *tert*-butoxycarbonyl group (Scheme 3).

The acylation of nitrogen with di-*tert*-butyl dicarbonate in presence of 4-dimethylaminopyridine and triethylamine was performed in dichloromethane at room temperature according to the reported conditions.[16,20]



Scheme 3.

Compound **5** thus obtained in 92% yield was converted to dihydropyridines **6a**–**c** by cycloaddition reaction with acrylic dienophiles and spontaneous deamination. The ^{1}H NMR spectra of **6a**–**c** showed a singlet due to the methylene group in position 2, and thus excluded the regioisomeric 2-substituted structure. After deprotection of compounds **6a**–**c** by trifluoroacetic acid in dichloromethane,[21] which promoted simultaneous aromatisation, pyridines **7a**–**c** were isolated.[22]

Current interest in the pyridine skeleton justifies development of new methods to synthesise compounds with this basic structure. In the approach presented here, we have shown that our method is straightforward, regioselective and applicable to a large range of dienophiles. We are currently investigating the scope of

these reactions by extending them to other dienophiles; the results of these studies will be reported in due course.

Acknowledgements

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18. Experimental procedure for pyridones **3**: diazapentadienium iodide **2** (1 mmol) was added to a solution of acid chloride (3 mmol) in acetonitrile (10 mL). After 15 min of stirring at room temperature, the reaction mixture was cooled to 0 °C and triethylamine (4 mmol) was added. The mixture was stirred at room temperature for an additional 18 h, and then the solvent was removed in vacuo. The resulting residue was partitioned between CH_2Cl_2 (20 mL) and water (2×20 mL). The organic extract was dried ($MgSO_4$), filtered and evaporated. The residue was purified by flash chromatography on silica to give compound **3**.
19. Experimental procedure for pyridines **4**: diazapentadienium iodide **2** (1 mmol) was added to a solution of acetylene dicarboxylate (2 mmol) in CH_2Cl_2 (10 mL). After 15 min of stirring at room temperature, the reaction mixture was cooled to 0 °C and triethylamine (2.4 mmol) was added. The mixture was stirred at room temperature in an additive 18 h. The solution was washed with water (2×10 mL). The organic extract was dried ($MgSO_4$), filtered and evaporated. The residue was purified by flash chromatography on silica to give compound **4**.
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22. Experimental procedure for pyridines **7**: a mixture of azadiene **5** (2 mmol), dienophile (5 mL) and hydroquinone (few crystals) was stirred for 18 h at 60 °C, then evaporated under reduced pressure and chromatographed on silica to give compound **6**. To a solution of dihydropyridine **6** (1 mmol) in anhydride CH_2Cl_2 under Ar atmosphere was added TFA at 0 °C. The solution was stirred at room temperature for 4 h and concentrated in vacuo. The residue was purified by chromatography on silica to give compound **7**.