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Synthesis of substituted pyrano[3,2-*c*]pyridines via Diels–Alder reaction of 3-methylenepyridin-4-one

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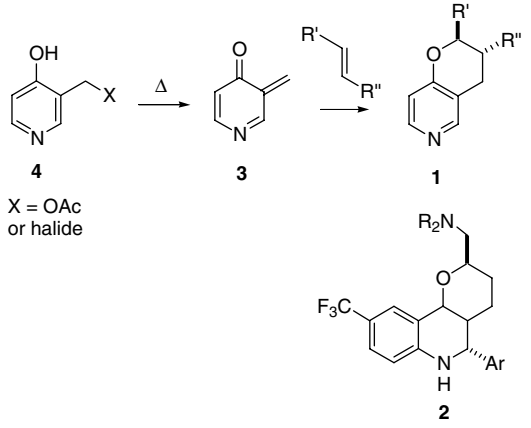
Abstract—On heating, the di-Boc-pyridin-4-one derivative **7** gave an unstable 3-methylenepyridin-4-one intermediate **3**, which underwent a rearomatising Diels–Alder cycloaddition with activated alkenes to give substituted pyrano[3,2-*c*]pyridines in moderate yields.

Pyrano[3,2-*c*]pyridine **1** derivatives are known to possess various important biological properties such as anti-allergic, anti-inflammatory and estrogenic activities.[1] Several biologically active naturally occurring alkaloids of plant origin contain a pyranopyridine moiety.[2] Most recently pyranoquinolines like **2** were shown to inhibit Eg5 proteins and their application in cancer treatment is currently under investigation.[3]

It was our expectation that pyrano[3,2-*c*]pyridine derivatives **1** can be synthesised via a reverse electron demand rearomatising Diels–Alder reaction of 3-methylenepyridin-4-one **3** with alkenes (Scheme 1). Previously, we demonstrated application of such cycloaddition reactions of tropolone-methides and *ortho*-quinone-methides in biomimetic syntheses of natural products.[4] We anticipated, based on our previous findings, that the reactive intermediate **3** will be accessed on thermal treatment of a 4-hydroxy-pyridine derivative **4**, possessing a good leaving group substituent X on the methylene at C3.



Scheme 1. Diels–Alder approach to pyranopyridines **1**.

Our synthesis of the cyclisation precursor started with commercially available 4-methoxypyridine (Scheme 2). Formylation of the 3-position was achieved following a literature method,[5] which we modified to obtain a higher yield of the crude aldehyde **5**,[6] which was used in the following step without column chromatography. Reduction of the aldehyde was carried out according to our previously established method.[4d] Next demethylation was addressed based upon a previously reported method[7] for demethylation of 4-methoxypyridine. We found that in our case demethylation occurred at a milder temperature of 100 °C (lit.,[7] 180 °C).

Isolation of the highly polar **6** was problematic and we decided instead upon an in situ protection. Addition of excess Boc-anhydride and triethylamine to the crude reaction mixture resulted in formation of the di-Boc-pyridin-4-one **7**, which was obtained as a pale yellow oil after column chromatography.

Next, we attempted a direct reaction of **7** with dihydropyran, hoping that the nitrogen deprotection would occur under heating. To our delight, the reaction yielded

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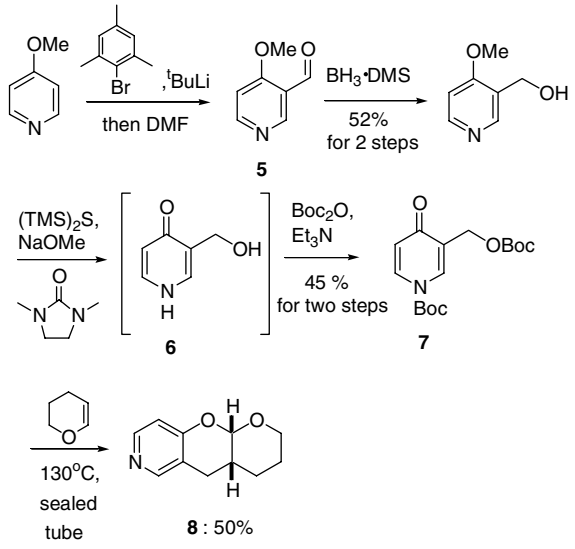


Scheme 2. Synthesis of the cycloaddition precursor **7**.

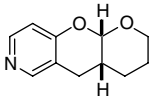
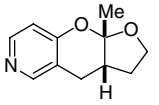
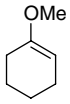
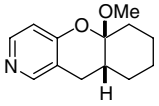
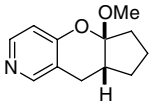
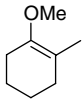
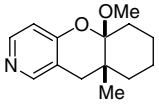
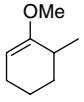
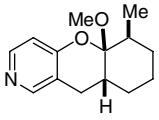
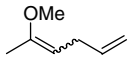
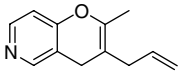
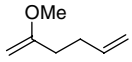
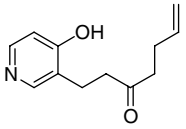
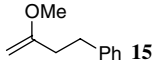
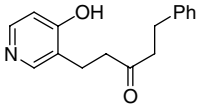
the desired cycloadduct **8** as a single stereoisomer. The relative stereochemistry at the ring junction was established by NOE analysis.

We performed the reaction of **7** with a number of activated cyclic and non-cyclic alkenes and the results of our investigation are presented in Table 1. Whereas dihydropyran (entry 1) and 2-methyldihydrofuran (entry 2) are commercially available, cyclic methoxyalkenes **9** and **10** were prepared in a single step procedure from the corresponding ketones.[8] Preparation of methoxyalkenes **12**–**15** required synthesis of the dimethoxy ketals[9] followed by a mild conversion into the methoxyalkenes employing an excess of tri-isobutyl aluminium.[10] All reactions with such cyclic activated alkenes gave Diels–Alder products in moderate yields as single stereoisomers. Interestingly, when we attempted to prepare the methoxyalkene **12** according to the single-step procedure,[8] we ended up with a 4:1 mixture of **12** and the isomeric form **11**. We expected the Diels–Alder reaction to prefer the less hindered double bond of **12**; surprisingly, **3** showed a high preference for the tetrasubstituted double bond of **11**. A single stereoisomer was also formed in the reaction with pure **12**, this time prepared via a two-step procedure,[10] showing a high level of stereocontrol by the centre adjacent to the alkene. Reaction of the trisubstituted alkene **13** resulted in further elimination (entry 7), while terminal enol ethers **14** and **15** gave quinone-methide Michael addition products.[11]

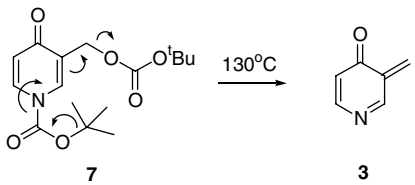
All reactions proceeded with full consumption of the starting material and a white highly polar solid was recovered in every case accounting for the consumed starting material. It is presumed that it consisted of products of oligomerisation, which were not characterised on this occasion. Finally, the reaction with methyl cyclohexene (entry 10) gave no isolated cycloaddition product but instead evidence of oligomerisation.

Our proposed mechanism for in situ formation of 3-methylenepyridine-4-one **3** is presented in Scheme 3.

Table 1. Results of reactions of **7** with alkenes

	Alkene	Product	Yield (%)
1		 **8**	50
2			55
3	 **9**		65
4	 **10**		55
5[a]	 **11**		70
6	 **12**		52
7[b]	 **13**		51
8	 **14**		79
9	 **15**		77
10		No reaction	—

All reactions were carried out according to the example synthesis of **9**,[12] but (a) the reaction was carried out using a 4:1 mixture of enolates **12** and **11**; (b) **13** consisted of a 1:1 mixture of *E* and *Z* enolates.



Scheme 3. Proposed mechanism for formation of **3**.

In conclusion, we have demonstrated the first examples of a Diels–Alder reaction of 3-methylenepyridin-4-one with activated alkenes. The reaction proceeded with formation of substituted pyrano[3,2-*c*]pyridines in moderate yields with high levels of stereocontrol. Further

investigations will centre on reactions in polar solvents with a wider range of alkenes. The influence of Lewis acids and the possibility of an intramolecular Diels–Alder reaction of a derivative of **7** possessing a tethered alkene moiety will also be investigated.

Acknowledgements

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References and notes

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12. Cycloaddition of **7** with dihydropyran: An argon filled sealed tube was charged with a solution of di-Boc-pyridin-4-one **7** (100 mg, 0.31 mmol) in 3,4-dihydropyran (2 ml, 21.8 mmol). The reaction mixture was stirred at 130 °C for 3 h. Removal of volatiles in vacuo was followed by column chromatography of the residue (SiO_2, ethyl acetate with 1% triethylamine) to give cycloadduct **8** as a pale yellow oil (29.6 mg, 50%). *m*/*z* (CI^+) found 192.1022, $C_{11}H_{14}NO_2$ ($M+H^+$) requires 192.1025; ν_{max}/cm^{-1} (film) 2939, 1580, 1490, 1273, 1165, 1100, 936, 909, 830; δ_H (500 MHz, $CDCl_3$) 1.60 (1H, m), 1.68–1.77 (3H, m), 2.25 (1H, m), 2.68 (1H, dd, *J* 16.5, 4.5), 2.94 (1H, dd, *J* 16.5, 6.0), 3.77 (1H, m), 4.00 (1H, m), 5.42 (1H, d, *J* 2.5), 6.80 (1H, d, *J* 5.5), 8.25 (1H, s), 8.28 (1H, d, *J* 5.5); δ_c (125 MHz, $CDCl_3$) 23.5, 24.0, 26.1, 31.3, 62.5, 97.1, 111.6, 116.3, 149.0, 150.7, 159.7.