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Intramolecular Diels–Alder reactions of *N*-alkenyl-2(1*H*)-pyrazinones: generation of a novel type of *cis*-1,7-naphthyridine

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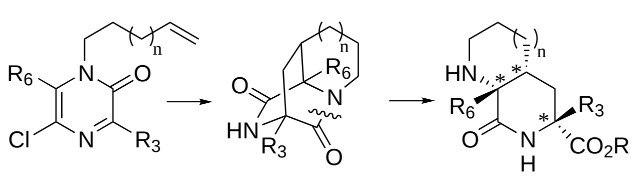
Abstract—The intramolecular Diels–Alder reaction of three 1-(ω-alkenyl)-2(1*H*)-pyrazinones was investigated. Cycloaddition was shown to proceed for 1-(4-pentenyl)- and 1-(5-hexenyl)-2(1*H*)-pyrazinone **5a** and **5b** to give the corresponding tricyclic hydrolysed adducts **7a** and **7b**, but not for the 1-(3-butenyl) derivative **5c**. In contrast to **7b**, the more strained **7a** underwent selective acidic solvolysis of the tertiary lactam group to give methyl *cis*-8-oxo-6-phenyldecahydro[1,7]naphthyridine-6-carboxylate **8**. An NMR analysis of **8** is presented. © 2001 Elsevier Science Ltd. All rights reserved.

Upon the discovery of a short and highly flexible synthesis for 2(1*H*)-pyrazinones,[1] our research group has focused on the use of these compounds in the synthesis of alkaloid-like compounds of biological interest. One important research area is the application of Diels–Alder reactions to this cyclic azadiene system, using both alkenes and alkynes as dienophiles. Until now intramolecular [4+2] cycloadditions were described only for alkynyl and alkenyl[2] groups anchored in the 3[3]- or 6[4]-position. In this work we envisaged the introduction of dienophilic groups at the 1-*N*-position. In this respect, reactions of 1-*N*-alkynyl pyrazinones seemed to be of little interest, since cycloreversion of the highly strained bridged intermediate inevitably would lead to preferential extrusion of the cyanate group generating pyridines (alternative loss of ClCN indeed would produce a pyrazinone retaining a bridgehead double bond). On the other hand, cycloaddition of *N*-alkenyl pyrazinones might lead to more stable tricyclic adducts exhibiting a distorted amide function (Scheme 1). This non-planar tertiary amide in turn could be subject to selective solvolysis—in preference to the non-strained secondary amide produced by hydrolysis of the imidoyl chloride—to generate the corresponding *cis*-fused bicyclic ring system.

While different *N*-alkenyl side chains and pyrazinone substituents are conceivable, we first wanted to investigate the reaction of simple *N*-(ω-alkenyl)-2(1*H*)-pyrazinones **5** (Scheme 1, $n=0$–2). Among these, **5a** ($n=1$) was most promising on basis of the unique reactivity expected for both the cycloaddition reaction and subsequent solvolysis. Indeed, a balance of entropy and enthalpy factors should favour the formation of a six-membered piperidine relative to an azepane ($n=2$) or pyrrolidine ($n=0$) ring moiety as part of the tricyclic ring system. At the same time this ring size still could induce sufficient distortion of the tertiary amide to permit easy solvolysis via protonation of the basic N-atom.

As the *NH*- and *N*-alkenylpyrazinones are not directly accessible via reaction of α-aminonitriles and oxalyl chloride, the synthesis of **5a**–**c** had to proceed via a deprotection–coupling sequence starting from *N*-(*p*-methoxybenzyl)pyrazinone **2** (Scheme 2).[5] This was prepared from 2-[*N*-(4-methoxybenzyl)amino]acetonitrile (HCl salt) **1** according to the above-mentioned



5 **7** **8**

Scheme 1.

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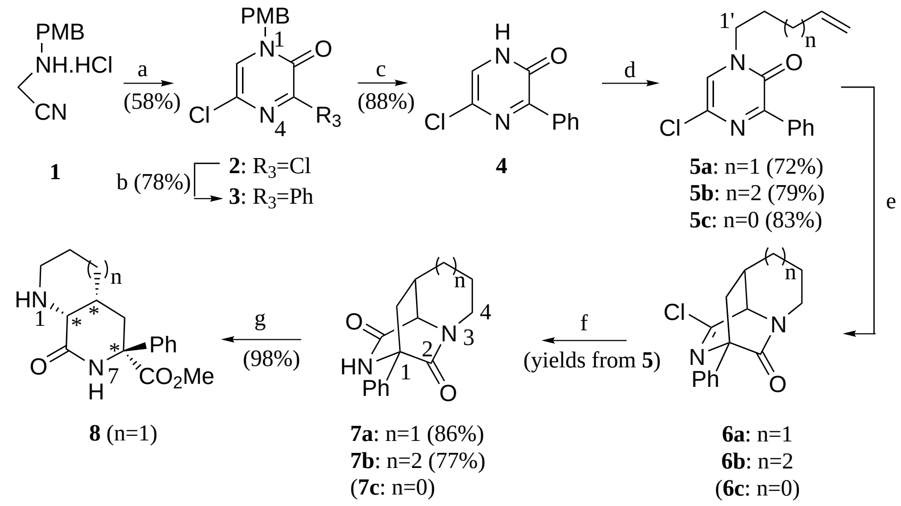
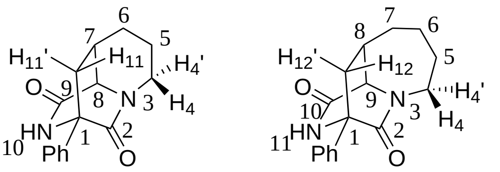


Scheme 2. (a) $(COCl)_2$, $Et_3N{\cdot}HCl$, PhCl, rt, 2 days; (b) $SnPh_4$, $Pd(PPh_3)_4$, toluene, 120°C, 7 days; (c) CF_3CO_2H, reflux, 5 h; (d) $BrCH_2CH_2(CH_2)_nCH{=}CH_2$ ($n=0$–2), Cs_2CO_3, dioxane, 50°C, 5 days; (e) PhBr, reflux, 1 night (**5a**) or 7 days (**5b**); (f) EtOAc satd with H_2O, rt, 1 night; (g) MeOH, CH_3SO_3H, reflux, 1 night; PMB = *p*-methoxybenzyl.

method.[1,6] Subsequent *Stille* coupling using tetraphenyltin and $Pd(PPh_3)_4$ as a catalyst provided the corresponding 3-phenyl derivative **3**,[4] which was *N*-debenzylated by heating with trifluoroacetic acid. The resulting compound **4** was converted to the desired *N*-alkenylated pyrazinones **5** by heating with 5-bromo-1-pentene (**5a**), 6-bromo-1-hexene (**5b**) or 4-bromo-1-butene (**5c**) and Cs_2CO_3 in dioxane—the method of choice to minimise concurrent *O*-alkenylation.[7,8] *N*-substitution could be verified by the absorption of the $H_{1'}$-protons and $C_{1'}$ in the NMR spectrum ($CDCl_3$), for example **5a**: δ 3.93 and 50.1 (*N*-alkenyl) versus δ 4.35 and 66.8 (*O*-alkenyl).

Intramolecular cycloaddition of **5a** was found to proceed in refluxing chlorobenzene (4 days) or bromobenzene (1 night). These conditions are rather harsh compared to the intermolecular alkene additions,[9] which can be accounted for by the distortion imposed on the incipient tertiary amide function. The adduct **6a** easily underwent hydrolysis upon stirring in water-saturated ethyl acetate to give bis-lactam **7a** in good yield (86% from **5a**). A much slower cycloaddition reaction was observed for **5b** (7 days reflux in bromobenzene), which similarly provided bis-lactam **7b** upon hydrolysis (77% from **5b**). However, cycloaddition of **5c** failed to provide **6c** even under severe conditions (250°C, steel bomb). Fig. 1 shows the hydrolysed adducts with their corresponding numbering.



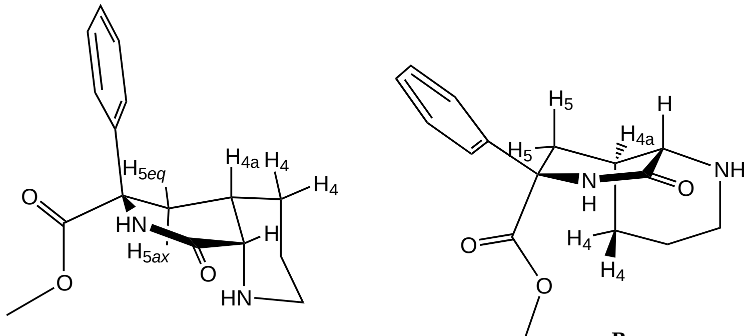
7a **7b**

Figure 1.

An optimised computer model of the cycloadducts **7a**–**c** (MM+ force field)[10] revealed that the energy content for **7a** and **7b** is similar, but increases dramatically for **7c**. In the latter case, the calculated $O{=}C{-}N{-}CH_2$ bond torsion of the tertiary amide strongly deviates from planarity (−63°). However, a significant distortion was also calculated for **7a** and **7b** (torsion angles −39 and −15.5°, respectively), which should lead to a higher sp^3 and basic character of the tertiary amide nitrogen. In the ^{13}C NMR spectrum of **7a** (100 MHz, DMSO-d_6), this was confirmed by two distinct absorptions in the carbonyl region corresponding to the secondary amide (170.1 ppm) and the tertiary amide (178.5 ppm) displaying increased ketone character. A similar difference in chemical shift values was not observed for the amide carbon signals of **7b** (171.1 and 171.8 ppm), indicating near-planarity of the tertiary amide. As argued above, the increased basic character implied for N-3 should permit selective solvolysis. Indeed, almost quantitative conversion (98%) of **7a** into *cis*-1,7-naphthyridine **8** was effected by refluxing for one night in methanol in the presence of 2.5 equiv. of methanesulfonic acid. However, no solvolysis could be effected for **7b**, even at 150°C in a steel bomb, in accordance with the less strained character of the tertiary amide moiety.

Molecular modelling of the *cis*-fused bicyclic system **8** (AM1 geometry optimisation) revealed two minimum energy conformations ***A*** and ***B***, of which ***A*** was favoured by ca. 3 kcal/mol (Fig. 2). To verify this, the solution conformation of **8** was determined by NMR spectroscopy. The results summarised in Table 1 confirm that **8** adopts conformation *A*, as shown by relevant coupling constants, i.e. a large ^3J-*trans* between H-4a and H-5*ax* and a small ^3J-*gauche* between H-4a and both H-4 protons.

In summary, we have used a flexible intramolecular Diels–Alder strategy to generate two yet undescribed tricyclic bis-lactams, of which the most strained one



A **B**

Figure 2.

Table 1. Relevant couplings (Hz) for conformational analysis of **8**[a]

δ	H	$J_{4a,8a}$	$J_{4a,5eq}$	$J_{4a,5ax}$	$J_{4a,4ax}$	$J_{4a,4eq}$
3.17	8a	4				
2.93	5*ax*			10		
1.43	4*ax*				5[b]	
1.22	4*eq*					6[b]
2.02	5*eq*		3			
1.81	4a	4	3	10	5[b]	6[b]

[a] 400 MHz, $CDCl_3/C_6D_6$ (50:50).

[b] Difference in ΣJ upon homo-decoupling of H_{4a}.

was subject to selective solvolysis of the tertiary amide group furnishing a novel type of substituted *cis*-1,7-naphthyridine. Further research will be directed towards the conversion of **8** into compounds of biological interest.

Acknowledgements

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5. Compound **5a**: yellow oil, exact mass calculated for $C_{15}H_{15}ClN_2O$: 274.0873, found: 274.0873. Compound **5b**: yellow oil, exact mass calculated for $C_{16}H_{17}ClN_2O$: 288.1029, found: 288.1026. Compound **5c**: yellow crystals, mp 50°C, exact mass calculated for $C_{14}H_{13}ClN_2O$: 260.0716, found: 260.0710. Compound **7a**: white crystals; mp 285°C; IR (KBr) cm^{-1}: 3194 (NH stretching), 1694 (CO); ^1H NMR (DMSO-d_6, 400 MHz): 8.79 (s, 1H, H_{10}), 7.44–7.38 (m, 5H, arom.-H), 3.91 (m, 1H, H_8), 3.79 (dd, $J=13$, 5 Hz, 1H, H_4), 2.99 (dt, $J=13$, 3 Hz, $H_{4'}$), 2.5 (hidden m, 2H, $H_{11'}+H_7$), 1.95 (dd, $J=13$, 2 Hz, 1H, H_{11}), 1.93, 1.67 (m, 2H, H_6), 1.59, 1.29 (m, 2H, H_5); exact mass calculated for $C_{15}H_{16}N_2O_2$: 256.1212, found: 256.1208. Compound **7b**: white crystals; mp 254°C; IR (KBr) cm^{-1}: 3205 (NH stretching), 1691 (CO), 1679 (CO); ^1H NMR (400 MHz, $CDCl_3$): 7.42 (m, 5H, arom.-H), 6.18 (s, 1H, H_{11}), 4.20 (ddd, $J=13$, 12, 7 Hz, 1H, H_4), 4.00 (m, 1H, H_9), 3.03 (dd, $J=13$, 7 Hz, 1H, $H_{4'}$), 2.71 (m, 1H, H_8), 2.66 (dd, $J=12$, 10 Hz, 1H, $H_{12'}$), 1.94 (dd, $J=12$, 3 Hz, 1H, H_{12}), 2.06, 1.92, 1.68, 1.22 (m, 6H, $H_5+H_6+H_7$); exact mass calculated for $C_{16}H_{18}N_2O_2$: 270.1368, found: 270.1371. Compound **8**: white crystals; mp 122°C; IR (KBr) cm^{-1}: 1746 (COOMe), 1664 (CO); ^1H NMR (400 MHz, $CDCl_3$): 7.45–7.31 (m, 5H, arom.-H), 6.85 (s, 1H, H_7), 3.75 (s, 3H, CH_3), 3.31 (d, $J=4$ Hz, H_{8a}), 2.98 (dd, $J=14$, 10 Hz, 1H, H_{5ax}), 2.88 (m, 1H, H_2), 2.69 (ddd, $J=11$, 8, 3 Hz, 1H, H_2), 2.39 (s, 1H, H_1), 2.14 (dd, $J=14$, 3 Hz, 1H, H_{5eq}), 1.94 (m, 1H, H_{4a}), 1.67–1.33 (m, 4H, H_3+H_4); exact mass calculated for $C_{16}H_{20}N_2O_3$: 288.1474, found: 288.1461 (NMR analysis of all described compounds was carried out on a *Bruker AMX 400*; IR spectra were recorded on a *Perkin–Elmer 1600 FTIR Spectrometer*; exact mass measurements were run on a *Kratos MS50TC* instrument in the EI mode at a resolution of 10,000).
6. All pyrazinones were purified by column chromatography on silica gel with CH_2Cl_2 as eluent and, if necessary, EtOAc as co-eluent.
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10. Calculations were carried out with the *Hyperchem*™ package.