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Stereoselective intramolecular Diels–Alder reactions of 3-alkenyl(oxy)-2(1*H*)-pyrazinones

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Abstract—Dichloropyrazinones are reacted with alkenolates or a Grignard reagent in order to tether a dienophilic side-chain at the 3-position. The compounds smoothly undergo intramolecular Diels–Alder reaction forming tricyclic ring systems. The reactions proceed completely stereoselective yielding only *endo* adducts. In the case of the alkenylpyrazinone, the core skeleton of the breviamides is obtained. © 2002 Elsevier Science Ltd. All rights reserved.

We previously reported on the intramolecular Diels–Alder reaction of pyrazinones with an alkene tethered via the 1-position (Fig. 1).[1] These structures smoothly underwent cycloaddition upon heating and (in contrast with the intermolecular variant)[2] showed a remarkable regioselectivity. In a continuous effort to explore the intramolecular Diels–Alder reaction of alkenyltethered pyrazinone systems we now focused on the cycloaddition from the 3-position (Fig. 1).

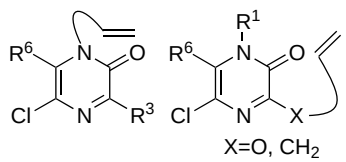
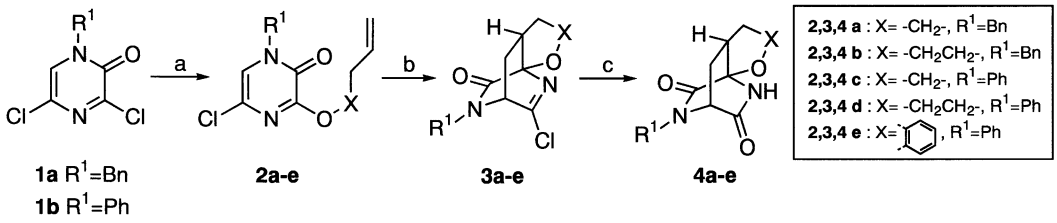


Figure 1. Tethering via the 1- and 3-position of the pyrazinone.

Based on experience with intramolecular alkyne reactions, introduction of the dienophilic side-chain in the 3-position of the pyrazinone system seemed to be most viable via an oxygen atom.[3] Indeed this strategy allows variation of the dienophilic side-chain by choosing the appropriate (commercially available) alkenol. The stereochemistry of the adducts was carefully analyzed and some calculations were done to gain a better insight into the obtained stereochemistry of these tricyclic compounds (*endo*/*exo* ratio of compounds formed).

Pyrazinones **1a** and **1b** (Scheme 1) are easily synthesized starting from the appropriate α-aminonitrile and oxalyl chloride.[4] The dienophilic side-chain is introduced by reacting the imidoyl chloride moiety of the pyrazinones **1** with the suitable deprotonated alkenol (2 equiv.) in THF under reflux conditions (Scheme 1, Table 1). Upon completion of the reaction (TLC monitoring), the solvent is evaporated and the crude oil is dissolved



Scheme 1. (a) Alkenol, NaH, THF, reflux; (b) chlorobenzene, reflux; (c) chloroform, air moisture.

Keywords: pyrazinone; cycloaddition; Diels–Alder reaction; brevianamide.

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Table 1. Substitution of the 3-position of **1** with alkenolates and subsequent cycloaddition/hydrolysis

Starting compound **1**	Alkenol	Substitution product **2** (yield in %)	Cycloadduct **4** (yield from **2** in %)
1a	3-Buten-1-ol	**2a** (69)	**4a** (74)
1a	4-Penten-1-ol	**2b** (78)	**4b** (63)
1b	3-Buten-1-ol	**2c** (65)	**4c** (70)
1b	4-Penten-1-ol	**2d** (82)	**4d** (60)
1b	2-Allylphenol	**2e** (79[a])	**4e** (63)

[a] About 5% of cycloaddition product was also isolated.

in dichloromethane and washed with water. The organic phase is dried ($MgSO_4$) and evaporated. Column chromatography (silica gel, CH_2Cl_2) yields the compounds **2a–e** as transparent viscous oils, which slowly crystallize upon standing. They are subsequently recrystallized from dichloromethane/hexane.[5] In the case of compound **2e**, about 5% of cycloadduct **3e** was already formed under the reaction conditions used.

Intramolecular cycloaddition reaction proceeded in 1–2 days by heating the alkenyloxypyrazinones **2a–e** under reflux conditions in chlorobenzene (Scheme 1, Table 1). The imidoyl chlorides **3a–e** are converted into the more stable bislactams **4a–e** upon stirring in $CHCl_3$ open to the air. Column chromatography (silica gel, EtOAc) provides the pure tricyclic compounds **4a–e** in good yields.[6]

As mentioned in the introduction, the stereochemistry of the products formed was to be examined (*endo*/*exo* ratio). To our surprise, ^{1}H NMR analysis of the purified cycloadducts revealed only the presence of the *endo* compounds.[7] The characteristic coupling constants observed for these bridged adducts are presented in Fig. 2.[8] Also, in the spectrum of the crude hydrolysates, no traces of the *exo* products were detected. In order to account for these results, we performed semi-empirical calculations (PM3) on compounds **3a–e**. Transition state structures[9] were computed for both *endo* and *exo* forms. In each case the energy of the *endo* transition state is lower than the energy of the *exo* transition state. This is probably due to sterical repulsions between the tether and the lactam carbonyl in the *exo* mode of attack. The lone pair on nitrogen apparently causes less hindrance promoting the exclusive formation of the *endo* adducts. The *endo* compounds are also somewhat lower in energy than the *exo* compounds hence more stable (PM3 calculations).

These results prompted us to introduce a dienophilic tether via a carbon atom. Provided the cycloadditions of these compounds proceed with comparable stereoselectivity, we would be able to synthesize analogs of brevianamides[10] (compare **6** in Scheme 2 with brevianamide **5** in Fig. 3). The aliphatic tether was introduced by reacting pyrazinone **1a** with pentenylmagnesium bromide (1.3 equiv.) in THF at −78°C. Under these conditions the lactam moiety was unaffected. Upon workup at −78°C (saturated NH_4Cl solution), extraction with CH_2Cl_2, subsequent drying ($MgSO_4$) and evaporation, TLC analysis and mass spectral analysis of the crude mixture revealed the presence of alkenylpyrazinone **2f**, cycloadduct **6** (also some of its unhydrolyzed imidoyl chloride precursor) and some starting material: during workup, partial cycloaddition had already occurred. In order to simplify the purification, the cycloaddition was driven to completion by refluxing the crude mixture in chloroform (open to the air to promote hydrolysis) for 12 h. The hydrolyzed adduct **6** was purified by column chromatography (silica gel, gradient heptane/EtOAc (50/50) –>EtOAc, yield: 52% from **1a** (if the recovered starting material is considered, the yield is increased to 84%)). The higher reactivity of **2f** compared to **2a–e** (reflux in $CHCl_3$ instead or reflux in chlorobenzene) is consistent with the results obtained above: when the azadiene is substituted with a less electron donating substituent (2-allylphenol) we also isolate about 5% of cycloadduct (reflux in THF). Product **6** also displayed the same *endo* selectivity as the products mentioned above (proven by ^{1}H NMR spectroscopy and NOESY experiments).

We can conclude that an alkenyl(oxy) substituent can be introduced at the 3-position of the pyrazinone. The subsequent intramolecular cycloaddition reactions are completely stereoselective and allow the introduction of five- and six-membered (substituted) rings annelated to the bicyclic system. An increase in reactivity is observed if the tether is less electron donating. Coupling via a carbon atom provides us with a synthetic method for brevianamide type compounds, a topic to be studied further.

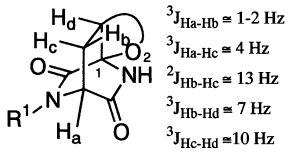

Figure 2. Relevant coupling constants observed in the ^{1}H NMR-spectrum of the cycloadducts (*endo* compound shown).

Acknowledgements

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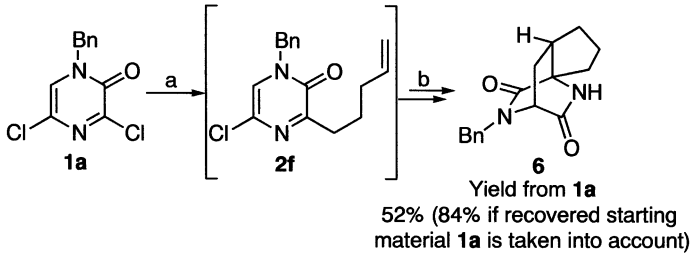

Scheme 2. (a) Pentenylmagnesiumbromide, THF, −78°C; (b) $CHCl_3$, reflux (open to the air to promote hydrolysis).

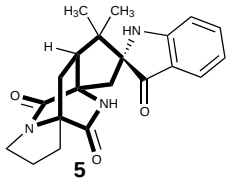

Figure 3. Brevianamide.

the use of the Spartan package. W.D.B. (Research assistant of the FWO-Flanders) thanks the F.W.O. and F.R. thanks the K.U. Leuven for the fellowships received.

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5. All compounds exhibit satisfactory spectral and analytical data. R_f values (CH_2Cl_2): **1a** (0.21), **1b** (0.23), **2a** (0.13), **2b** (0.16), **2c** (0.15), **2d** (0.16), **2e** (0.32).
6. Spectral data for 8-benzyl-2-oxa-8,10-diaza-tricyclo-[5.2.2.$0^{1,5}$] undecane-9,11-dione (**4a**) white crystals; mp 142°C; IR (KBr) cm^{-1}: 1704 (C=O×2); ^{1}H NMR (400 MHz, $CDCl_3$) 7.30 (m, 5H, arom. H), 6.68 (br s, 1H, NH), 4.92 (d, 1H, $J=14.9$ Hz, BnH), 4.38 (ddd, 1H, $J=9.0$, 8.9, 1.6 Hz, H3), 4.30 (ddd, 1H, $J=10.5$, 8.9, 6.2 Hz, H3), 4.27 (d, 1H, $J=14.9$ Hz, BnH), 3.88 (ddd, 1H, $J=4.7$, 2.4, 1.0 Hz, H7), 2.40 (m, 1H, H4), 2.24 (m, 1H, H4), 1.89 (m, 2H, H5-H6), 1.55 (ddd, 1H, $J=13.5$, 6.1, 1.0 Hz, H6); ^{13}C NMR (100 MHz, $CDCl_3$) 169.6 (CO), 168.7 (CO), 136.1 (*ipso*-C), 128.9–128.1 (3×ArCH), 91.4 (C1), 73.0 (C3), 60.1 (C7), 48.3 (BnC), 43.3 (C5), 28.5 (C6), 26.1 (C4); *m*/*z* (%): 273 (MH^+, 100). (NMR analysis was carried out on a *Bruker AMX 400*; IR spectra were recorded on a *Perkin–Elmer 1600 FTIR Spectrometer*).
7. In the *endo* adducts, the tether on the bridge is directed towards the imidoyl chloride moiety formed in the cycloaddition step.
8. A more elaborate discussion on the spectral analysis of bicyclic pyrazinone adducts is presented in Ref. 2.
9. Transition states were generated using the transition state search functionalities in the Spartan 5.1.3 package (PM3 calculations).
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