Intramolecular 1,3-dipolar cycloadditions of 2-substituted norbornadiene-tethered nitrones

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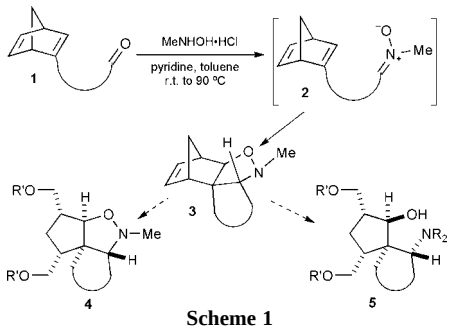
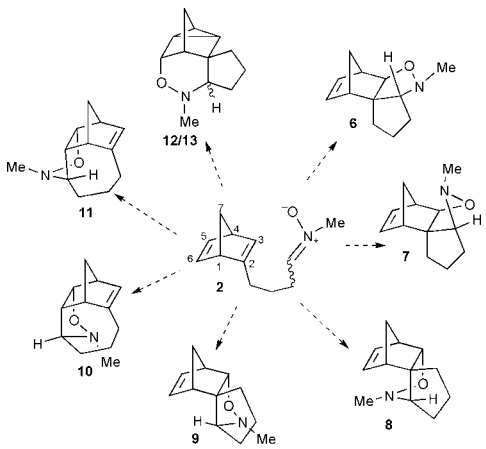
Efficient routes for the synthesis of norbornadiene-tethered nitrones have been developed and their intramolecular 1,3-dipolar cycloadditions were found to be highly regio- and stereo-selective.

Intramolecular cycloadditions with high regio- and stereo-control are important tools for the efficient assembly of complex molecular structures. We have recently initiated a program on the study of various types of intramolecular cycloadditions of substituted norbornadienes.[1] Our long-term goal is to develop an efficient route for the construction of angular fused tricyclic frameworks and spirocyclic frameworks with high regio- and stereo-control. 1,3-Dipolar cycloadditions offer a convenient one-step route for the construction of a variety of complex five-membered heterocycles.[2,3] Here we report our initial result on the intramolecular 1,3-dipolar cycloadditions of 2-substituted norbornadiene-tethered nitrones (Scheme 1).



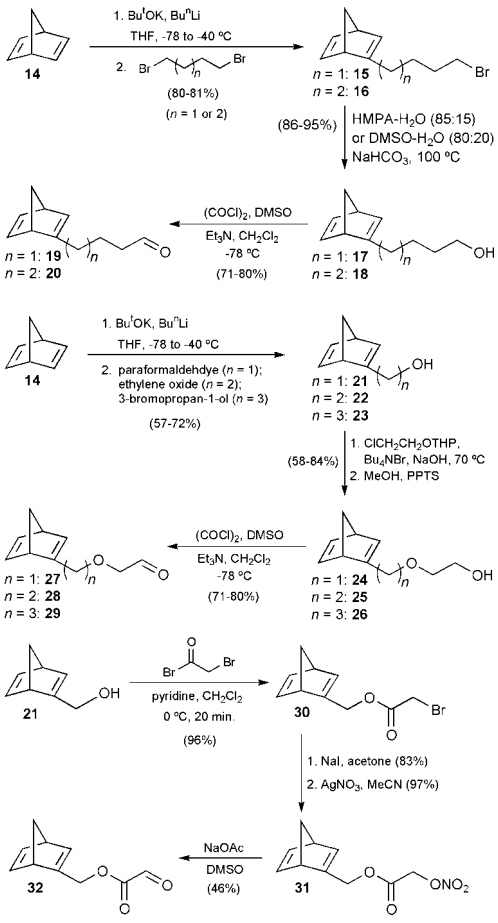
Scheme 1

Three different types of regioisomers could be formed from the intramolecular 1,3-dipolar cycloaddition of the norbornadiene-tethered nitrone **2** (Scheme 2). Cycloaddition on the C_2–C_3 double bond would give cycloadducts **6**–**9**; cycloaddition on the C_5–C_6 double bond would give **10** or **11**, and a [3 + 2 + 2] cycloaddition with both of the double bonds would give cycloadducts **12** or **13**. Other than regiochemistry problems, different stereoisomers are also possible. Thus, a total of eight possible cycloadducts (**6**–**13**) could be formed in the cycloaddition of norbornadiene-tethered nitrone **2**.



Scheme 2 Possible cycloadducts

Efficient routes to the synthesis of norbornadiene-tethered aldehydes **19**, **20**, **27**–**29** and **32** were developed (Scheme 3) and these aldehydes served as precursors of the required nitrones for the cycloadditions. Deprotonation of norbornadiene **14** with Schlosser's base (Bu^tOK/Bu^nLi)[4] in THF at −78 °C, followed by addition of the resulting norbornadienyl anion to an excess of 1,4-dibromobutane or 1,5-dibromopentane provided the norbornadiene-tethered bromide **15** and **16**.[1] Conversion of these bromides to the corresponding alcohols followed by Swern oxidation provided the required aldehydes **19** and **20**. Norbornadiene-tethered aldehydes with an oxygen atom within the tether were prepared using a similar protocol. Trapping the norbornadienyl anion with paraformaldehyde, ethylene oxide and 3-bromopropan-1-ol provided norbornadiene-tethered alcohols **21**–**23**. A two-carbon homologation to the alcohols **24**–**26** was achieved by a two-step sequence[5] and Swern oxidation provided the required aldehydes **27**–**29**. An ester functionality



Scheme 3

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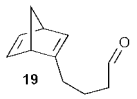
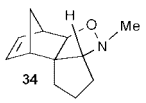
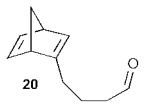
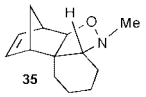
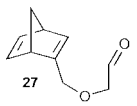
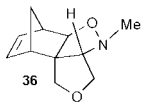
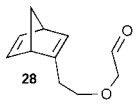
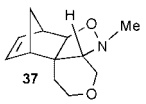
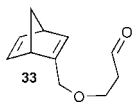
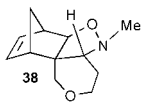
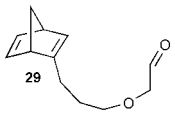
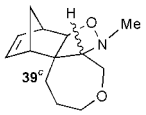
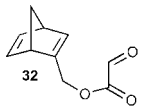
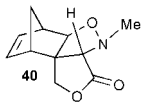
Table 1 1,3-Dipolar cycloaddition of norbornadiene-tethered nitrones

Entry	Starting aldehyde	Cycloadduct[a,b]	Yield[d](%)
1	 **19**	 **34**	51
2	 **20**	 **35**	19
3	 **27**	 **36**	71
4	 **28**	 **37**	60
5	 **33**	 **38**	47
6	 **29**	 **39**[c]	52
7	 **32**	 **40**	43

[a] *Reaction conditions*: MeNHOH·HCl (1.2–2 eq.), pyridine (3–5 eq.), 4 Å molecular sieves, toluene, r.t., 12–24 h then 60 to 90 °C 12–48 h. [b] Except in entry 6, the cycloadducts shown were the only regio- and stereo-isomers isolated in the cycloadditions. [c] An inseparable mixture of three isomers was obtained. [d] Isolated yields after column chromatography.

within the tether was prepared from alcohol **21**. Reaction of **21** with bromoacetyl bromide gave the a-bromo ester **30** which was converted to the nitrate ester **31** in two steps.[6,7] Treatment of the nitrate ester **31** with sodium acetate in DMSO provided the required aldehyde **32**.[6,7]

Addition of *N*-methylhydroxylamine to a solution containing aldehyde **19**, pyridine and 4 Å molecular sieves in toluene at room temperature lead to the formation of the corresponding norbornadiene-tethered nitrone which underwent spontaneous intramolecular 1,3-dipolar cycloaddition at 80 ºC to provide a single cycloadduct **34** in 51% isolated yield (Table 1, entry 1). Very little reaction was observed at a lower temperature and prolonged heating led to decomposition of the cycloadduct. Although as many as eight different cycloadducts could be formed in the reaction, only cycloadduct **34** was isolated. With one more carbon in the tether (entry 2), the only cycloadduct isolated was **35** but the yield was only 19%. For aldehydes with an oxygen atom within the tether (entries 3–5), the yields of the cycloadditions were generally much better than the all-carbon tethered substrates. Aldehyde **27** provided the 5-membered ring cycloadduct **36** in 71% yield while aldehydes **28** and **33** gave the corresponding 6-membered ring cycloadducts **37** and **38** in 60 and 47% yield. In all these reactions, cycloadducts **36**–**38** were the only cycloadducts isolated. Formation of a 7-membered ring cycloadduct **39** was also possible starting from aldehyde **29** (entry 6). In this case, 54% of an inseparable mixture of three isomers was obtained. Although some literature examples have shown that as the tether length increases, an alternative regioisomer (with oxygen attached to C_2 and carbon attached to C_3) could be formed as the major regioisomer,[8] we are certain that the two major isomers in this mixture have the same regiochemistry as in other cases (with oxygen attached to C_3 and carbon attached to C_2), since ^{1}H NMR showed that both of these two isomers have two vinylic protons and one proton next to an oxygen (regioisomers with oxygen attached to C_2 and carbon attached to C_3 will not have such a proton peak since the oxygen is attached to a quaternary carbon center). However, we are not certain about the regiochemistry of the third minor isomer in the mixture. Cycloaddition of the substrate with an ester functionality within the tether (entry 7) gave a single cycloadduct **40** in 43% yield. As we noticed that most of the cycloadducts were thermally unstable and they decomposed on prolonged heating, we attempted the reactions at a lower temperature with the use of Lewis acid catalysts. Unfortunately the isolated yields were even lower than the thermal reactions. The regio- and stereo-chemistry of the cycloadducts were confirmed by NMR experiments (HCOSY, HSQC and NOESY experiments). These assignments were also supported by X-ray crystallography.[9]

Several factors could control the regio- and stereo-selectivity of the cycloadditions. Those factors include: the *E/Z* ratio of the nitrones generated from the corresponding aldehydes, the distance and the flexibility of the tether to reach the double bonds, the *exo/endo* selectivity of the double bond (C_2–C_3) in the norbornadiene in the cycloadditions, and the strain and the stability of the cycloadducts formed. At this stage, we are not sure the reasons for the formation of single cycloadducts in the cycloadditions. Either the *E/Z* selectivity of the formation of nitrones was very high and the cycloadditions were highly regio- and stereo-selective, or other cycloadducts were formed but were too unstable and decomposed under the reaction conditions. The cycloadditions can also be reversible and thus giving rise to the most stable cycloadducts. Nevertheless, although up to eight possible cycloadducts could be formed in the cycloadditions, we were able to generate and to isolate single regio- and stereo-isomers in the cycloadditions.

In conclusion, we have demonstrated the first examples of the intramolecular 1,3-dipolar cycloadditions of norbornadiene-tethered nitrones. Single regio- and stereo-isomers were obtained in moderate to good yields. Further investigation on the effect of a substitutent at C_3 on the norbornadiene in the cycloaddition (*e.g.* electron-withdrawing groups on the norbornadiene may activate the alkene component in the cycloaddition and thus a lower reaction temperature may be possible), as well as subsequent cleavage reactions of the cycloadducts (Scheme 1) for the construction of angular-fused tricyclic and spirocyclic frameworks, are ongoing in our laboratory.

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Notes and references

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9 Recrystallization of cycloadduct **40** in 20% EtOAc–hexanes provided suitable crystals for X-ray analysis. Details of the X-ray analysis will be submitted for publication in *Acta Crystallogr., Sect. C.*