Pergamon

Tetrahedron Letters 42 (2001) 4263–4265

TETRAHEDRON
LETTERS

The *N*,*O*-bridged sesquinorbornadienes: a testing ground for establishing the superiority of *N*-Z pyrrole over furan as a dienofuge in retro-Diels–Alder reactions

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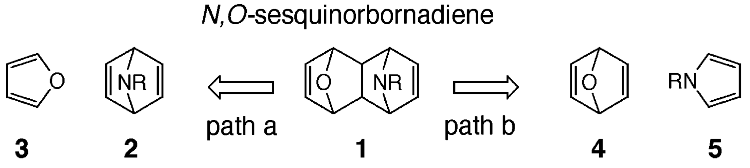
Received 19 October 2000; accepted 19 April 2001

Abstract—*N*-R pyrroles (R = H, Z, COPh but not Bn, TMS) **6** add selectively at rt to the substituted π-bond of 2,3-bis(trifluoromethyl)-7-oxanorbornadiene **7** under high pressure (14 kbar) to form exclusively the *syn*-facial *N*,*O*-sesquinorbornadienes **8**; at higher temperatures the thermodynamic stereoisomers **10**,**11** are produced by cycloreversion and reaction at the unsubstituted π-bond. The exclusive loss of *N*-Z pyrrole from the *N*-Z derivative of **8** demonstrated the superior dienofugacity of *N*-Z pyrrole over furan; kinetic studies showed that the activation energy for this fragmentation was 34.7 kcal mol^{-1}. This selectivity is in accord with theory (AM1, ab initio). © 2001 Elsevier Science Ltd. All rights reserved.

Retro-Diels–Alder (RDA) reactions are an important part of the armory of the synthetic chemist seeking to make alkenes or 1,3-dienes.[1] One strategy based on RDAs involves the protection of the incipient π-bond(s) as the Diels–Alder adduct while other chemistry is conducted on the molecule and removing it thermally to reconstitute the π-centre. While cyclopentadiene adducts have been used in this role for alkene protection it has become accepted folklore in cycloaddition chemistry that furan adducts are superior since they can be removed at lower temperatures, e.g. in the use of *O*-bridged rather than *C*-bridged transfer reagents for delivering dimethyl cyclobutadiene-1,2-dicarboxylate.[2] There is no shortage of examples where furan has been used as a trapping agent for active alkenes and removed by controlled RDA fragmentation to generate the alkene.[3] Indeed, the mild conditions required to effect RDA cycloaddition are highlighted by the fact that some furan and pyrrole adducts prepared at high-pressure spontaneously undergo RDA reaction upon return to ambient pressure.[4] While less common, pyrrole has also been used as a trapping agent for highly dienophilic π-bonds, e.g. for trapping tetra(trifluoromethyl) Dewar thiophene and protecting the π-bond during chemical exchange of the sulphur for oxygen and generating tetra(trifluoromethyl) Dewar furan by RDA.[5] In another study,[6] George and Isaacs demonstrated that the *endo*-adduct from the addition of *N*-benzoylpyrrole with *N*-phenylmaleimide underwent RDA at 30.7°C with a rate constant of 7.9×10^{-5} sec^{-1}, whereas the corresponding furan adduct required warming to 43°C to achieve fragmentation and the rate constant was still only 2.72×10^{-5} sec^{-1}, figures which clearly supported the superior dienofugacity of *N*-benzoylpyrrole over furan. The questions we set out to answer in this study were about the ability to form *syn*-facial *N*,*O*-bridged sesquinorbornadienes and whether their fragmentation could be used to confirm the superiority of pyrroles over furan as a dienofuge when they were part of the same molecule. A longer-



Scheme 1.

Keywords: retro-Diels–Alder; synthesis; high-pressure; pyrroles; 7-azanorbornanes.

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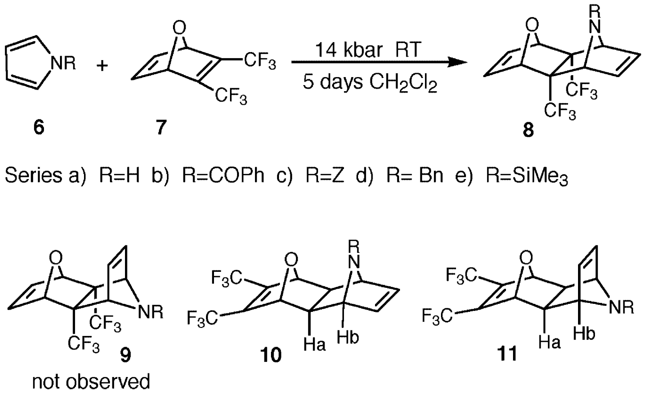
PII: S0040-4039(01)00665-7

term goal was to evaluate experimentally, the contribution made by the R-group of the incipient *N*-substituted pyrrole on the efficiency of the process.

As we embarked on a program to prepare hetero-bridged sesquinorbornadienes,[7] it soon became apparent that *N*,*O*-bridged sesquinorbornadienes could be retrosynthesised in two ways (parity reversal),[8] one of which involved furan cycloaddition to an *N*-R 7-aza norbornadiene (Scheme 1, path a) while the other required the addition of *N*-R pyrrole to a 7-oxanorbornadiene (Scheme 1, path b). However, the alternative pathways in Scheme 1 could be interpreted in terms of RDA reactions of **1**, and indeed represented a perfect substrate to test the relative dienofugacity of the two 5-membered cyclic dienes (*N*-R pyrrole versus furan). For this comparison to be valid, the steric environments must be identical and this was satisfied by having both bridges *syn*-related, and any substitutents on the alicyclic frame symmetrically disposed.

Our initial approach studied the reaction of *N*-substituted pyrroles **6a**–**e** with 2,3-bis(trifluoromethyl)-7-oxanorbornadiene **7**[9] under high pressure (14 kbar, rt, 3–5 days) (no reaction occurred thermally, e.g. toluene at reflux) as a route to *N*,*O*-bridged sesquinorbornadienes **8**–**11** and to evaluate the stereoselectivity of the process. We found that addition occurred site selectively at the trifluoromethyl-substituted π-bond of **7** under these conditions to form the *syn*-facial adducts **8a**–**8c** exclusively with pyrrole **6a** (58%), *N*-benzoyl pyrrole **6b** (100%) and *N*-Z pyrrole **6c** (100%), respectively, but failed with *N*-benzyl pyrrole and *N*-TMS pyrrole (Scheme 2). The fact that other isomers **10**,**11** appeared when the reaction temperature was increased, was a useful synthetic adjunct for isomer production and represented thermodynamic dominance for the production of *syn*-facial adduct **10c** over bent-frame isomer **11c**, a feature which had precedent in the reaction of furan with 2,3-bis(trifluoromethyl)-7-oxanorbornadiene **7**.[2,10] The results of the reaction of *N*-Z pyrrole **6c** with **7** are reported in Table 1.



Scheme 2.

The other noteworthy feature of isomer production in the reaction of **6** and **7** at higher temperature was that the mechanism for interconversion required the loss of *N*-Z pyrrole from **8c** by RDA and subsequent attack by *N*-Z pyrrole at the unsubstituted π-bond of 7-oxanorbornadiene **7**.[11] As the reaction proceeds in good yield, this ruled out competing loss of furan. We confirmed this premise by a study of the RDA of isolated *N*,*O*-bridged sesquinorbornadiene **8c** in which we determined that **6c** and **7** were formed exclusively and that the process had an activation energy of 34.7 kcal mol^{-1}. This experiment convincingly showed that *N*-Z pyrrole was a superior dienofuge than furan.

We have also conducted computational studies on the thermal decomposition of the *N*-Z bis(trifluoromethyl) *N*,*O*-bridged sesquinorbornadiene **8c** and find that loss of *N*-Z pyrrole is favoured by 9.8 kcal mol^{-1} (AM1), whereas higher order calculations were conducted on the parent system **8a** (R=H) and all predicted preferential loss of pyrrole by 12.4–23.3 kcal mol^{-1} (see Table 2).

Table 2. Calculated transition state energies for the RDA loss of pyrrole and furan from *N*,*O*-sesquinorbornadiene **8a** (R=H)

Method	E_{TSp} (pyrrole)	E_{TSf} (furan)	E_{TSp}–E_{TSf}
AM1	24.3	41.6	17.3
6-31G	34.9	47.8	12.9
B3LYP/6-31G*//AM1	14.3	37.6	23.3
B3LYP/6-31G*//6-31G	13.3	25.7	12.4

Table 1. Product ratios for the addition of *N*-Z pyrrole **6c** with 2,3-bis(trifluoromethyl)-7-oxanorbornadiene **7** under different conditions

Entry	Conditions	Yields[a] of adducts			
		8c	**9c**	**10c**	**11c**
1	14 kbar, rt, 5 days	100	0	0	0
2	14 kbar, 55°C, 4 days	94	0	4	0
3	14 kbar, 90°C, 2 days	28	0	57	7
4	100°C, toluene	0	0	0	0
5	130°C CH_2Cl_2 sealed tube, 2 days	0	0	62[b]	3[b]

[a] Conversion yield by NMR.

[b] Isolated yield.

Pyrroles with electron-withdrawing *N*-substituents are shown to react with 2,3-bis(trifluoromethyl)-7-oxanorbornadiene **8** under high-pressure to produce *syn*-facial *N*,*O*-sesquinorbornadienes at room temperature and that these can be isomerised at higher temperature. FVP of the *syn*-facial adducts all eject the pyrrole in preference to furan thereby confirming the superiority of *N*-(EWG) pyrroles as dienofuges and this preference is in full accord with theory.

Acknowledgements

This work was supported by the Central Queensland University Research Centre program and by a PhD scholarship award to G.S.

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11. A referee has suggested that a trimeric adduct might be involved in this reaction and this cannot be rejected or confirmed on current evidence; however, no trimer was detected in the reaction mixture.