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Fine Tuning of the [2+2] Vs [4+2] Selectivity of 1,1-Disubstituted Dienes in Cycloaddition Reactions

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Abstract: β -arylsulfonyl vinylketones have been shown to react, both inter and intramolecularly, with 1,1-disubstituted dienes to afford, depending on the used -*i.e.* thermal or Lewis-acid catalysed-conditions, either [4+2] or [2+2] cycloadducts, respectively. © 1999 Elsevier Science Ltd. All rights reserved.

Previously, we have shown that, irrespective of the substitution pattern of both their diene and dienophile residues, compounds with structure 1 cyclised upon heating to afford exclusively hydrophenanthrenones 2.1a



Earlier attempt to catalyse these intramolecular Diels-Alder (IMDA) reactions by using BF3.Et₂O, that induces effectively the related cyclisation of the *E* isomer of 1a, ^{1b} had proved unsatisfactory. Thus, addition of this catalyst to a solution of 1a in CH₂Cl₂ had resulted in either no reaction (- 78 °C) or decomposition (r.t.) of the starting material.^{1c}

This experiment with BF3.Et2O has been carefully re-examined. Contrary to which was previously observed, we found that by maintaining the temperature of the reaction mixture at -35 °C for a few hours, the used Lewis acid being neutralised with triethylamine under strictly anhydrous conditions before to apply an aqueous workup, the tricyclic ketone 2a could be isolated in fairly good yield.



Reagents and conditions: $BF_3.Et_2O$ (0.9 eq.), CH_2Cl_2 (10 ml/mmol); - 78 °C, 1 hour, then -35 °C, 5 hours; 2- NEt_3 (0.9 eq.); - 78 °C, 0.5 hour, then aqueous work-up.

Encouraged by this result, we next tried to catalyse similarly the IMDA reaction of the keto sulfone 1b but the use of BF3.Et₂O as precedently was detrimental, the only observed reaction being the decomposition of the

starting sulfone. 0040-4039/99/\$ - see front matter © 1999 Elsevier Science Ltd. All rights reserved. *PII*: S0040-4039(99)01884-5 A more interesting result was obtained by using Et₂AlCl. Hence, stirring 1b with excess Et₂AlCl in toluene, at r.t., for 18 hours led to the formation of two isomeric ketones: i) a minor one (ca 15% of the crude reaction product), that proved strictly identical (m.p., NMR) to the sulfo-ketone 2b, obtained previously by thermal rearrangement of 1b; ii) a major one, to which the cyclobutanic structure 3b was assigned after extensive NMR analysis.²



Reagents and conditions: Et_2AlCl (2 eq.), toluene (50 ml/mmol); - 78 °C, 0.5 hour, then room t., 18 hours (66%).

In search for a rationale for this unexpected process, we found in the literature that a few 1,1-disubstituted butadiene derivatives have already been mentioned as giving, besides normal Diels-Alder products, [2+2] cycloadducts when reacted at r.t. with the strongly-electrophilic TCNE, which was attributed to the difficulty for these dienes to attain the sterically-disfavoured *cisoid* conformation, required for the normal Diels-Alder cycloaddition to take place.³

Though indisputable presently (both 1a and 1b have a gem-substituted 1,3-diene residue), this restriction of a *transoid-cisoid* conformational equilibria cannot explain alone this formation of 3b from 1b since any trace of the related cyclobutanic compound (*i. e.* 3a, R=H) failed to be detected in the preceding BF3·Et2O-catalysed IMDA reaction of 1a. Now it could be argued that, due to the presence of a phenylsulfonyl group in 1b, the energetic profile of this conformational interconversion is not exactly the same in both cases.⁴ To make clear this point, we decided to examine the *intermolecular* condensation of a β -sulfonyl vinylketone with a 1,1-disubstituted diene. In this case, no such perturbation of the conformational change of the diene could be advocated and formation of a related cyclobutane derivative would have been clearly indicative of a distinctive dienophilic behaviour of the β -sulfonylvinyl residue toward conformationally-biased dienes. This proved to be the case.

The sulfone 4, which was prepared from methyl vinylketone by an improved procedure,⁵ was reacted with 1,1-dimethylbutadiene 5a in CH₂Cl₂, preferred to toluene owing to the low solubility of 4 in the later solvent, and in presence of Et₂AlCl (excess) as precedently. Though the reaction proceeded very slowly, a new product was detected by TLC after two days at r.t.. Subsequent column chromatography of the crude reaction product permitted to isolate, besides unidentified compounds and unreacted 4, a major constituent that seemed to be a 1/1 mixture (NMR) of the indicated syn and anti isomers of the cyclobutanic ketosulfone 7. Though these diastereomers failed to be separated by chromatography, slow crystallisation of this product from diisopropylether provided a single crystal. Unfortunately, subsequent NMR analysis indicated it was still constituted of these two isomeric sulfones (same ratio).

An X-ray analysis of this crystal was attempted however. The crystal data thus collected⁶ furnished the Chemdraw[®] structure shown, which suggested to an eminent colleague, to whom this puzzling drawing was submitted, the following comment: "It seems more likely to me that the computer programme of the X-ray machine has done the best it could from confused data, and that you really have a mixture of two epimers with different orientations, one *cis-trans* and the other *trans-trans*".⁷

This was confirmed by reacting 7 with 2,4-dinitrophenylhydrazine to form the corresponding DNPH derivative (*i.e.* 7-DNPH) as a 1:1 mixture of diastereomers, which could be separated by chromatography and characterised unambiguously by NMR.



For the sake of comparison, the keto sulfone 4 was reacted with isoprene 5b and piperylene 5c in presence of Et2AlCl as above (Table). At r.t. the sulfone 4 condensed with these unrestricted dienes to afford exclusively the cyclohexene derivatives 6b and 6c, respectively.⁹

In summary, whereas condensing intermolecularly with not-sterically-demanding dienes to give Diels-Alder products whatever the conditions used, $^{10}\beta$ -sulfonyl vinylketones react with conformationally restricted dienes, both in the *intra* and the *intermolecular* mode, to give either [2+2] or [4+2] cycloadducts, the former ones being preferred when the reaction is conducted in presence of excess Et₂AlCl. Noteworthy, such a dichotomy in reactivity was not noticed with the vinylic ketone 1a.

To explain these results, we suggest tentatively that, in presence of excess Et₂AlCl, the β -sulfonylvinyl keto residue is twice-coordinated and thus rendered electronically equivalent to a superdienophilic species such as TCNE. In the event, the [2+2] process would become so fast that it could compete, when the diene is particularly sterically-demanding (e. g. **5a**), with the *transoid-cisoid* change, hence with the [4+2] process.¹¹ The later pathway would be favoured, however, when this *transoid-cisoid* equilibrium will be not sufficiently slow down, as it is the case with **5b** (or **5c**). By contrast, the vinylic ketone residue should be only single-complexed¹² and, though activated by the used Lewis acid (1a undergoes indeed an IMDA process at ca -35°C in presence of BF3.Et₂O), it will be not rendered sufficiently electrophilic so as to make the [2+2] process will take place, as observed. Should these hypotheses be correct, this fine tuning of the [2+2] vs [4+2] selectivity of 1,1-disubstituted dienes in their reaction with β -sulfonyl vinylketones will be applicable to other, related, doubly-activated dienophilic species such as, for instance, 1,2-bis-keto (or bis-sulfonyl) ethylene derivatives. Experiments in this way are in progress and will be reported in due course.

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Notes and References

1- a) Zoller, T.; Uguen, D. Tetrahedron Lett. 1999, 40, 6249-6252; b) Thari, A.; Uguen, D. Tetrahedron Lett., 1994, 35, 3945-3948; c) Zoller, T.; Uguen, D.; De Cian, A.; Fisher, J. Tetrahedron Lett. 1997, 38, 3409-3412.

2- All new compounds have been fully characterised by high-field NMR experiments and elemental analysis (C, H).

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4- Another possibility could have been that the [2+2] cycloadduct 3b (res 3a (R=H)) was first formed, and then isomerised into the corresponding IMDA product 2b (res 2a), this final isomerisation being faster for 3b than for 3a. However, prolonged heating of 3b at ca 160 °C (in xylene) or its treatment by Et2AlCl at r.t. failed to induce any 3b-2b interconversion, which indicates that 2b and 3b were formed from 1b under kinetic control by two different pathways.

5- This crystalline sulfone (M. p. 90 °C) was efficiently obtained (70% Yield, overall) by reacting sequentially 4-tosyl-2-butanone (obtained by addition of *p*-toluenesulfinic acid to methyl vinylketone according to: Gibson, S. E.; Justin, G. J. J. Chem. Soc. Perkin I 1995, 2429) with bromine and triethylamine.

6- Crystal data of 7: C17H22O3S, mol. weight = 306.43, triclinic, space group P-1, a =8.2169(4), b = 10.1433(8), c = 11.2382(9) Å, $\alpha = 104.847(9)$, $\beta = 106.778(9)$, $\gamma = 104.175(9)$ deg, V = 813(3) Å³, Z = 2, dcalc = 1.25 gcm⁻³, μ = 0.173 mm⁻¹. Data were collected using a Nonius KappaCCD diffractometer, graphite monochromated MoK α radiation ($\lambda = 0.71073$ Å) at 173K. 7103 reflexions were collected using a crystal of dimensions 0.19*0.13*0.10 mm. The structure was solved using direct methods and refined with 2114 reflections having I > 3s(I). Hydrogen atoms were introduced as fixed contributors to structure factors at their computed coordinates (d(C-H) = 0.95 Å, B(H) = 1.3 Beqv(C). Full matrix least squares against F. Final results: R = 0.078, Rw = 0.107, GOF = 1.304, largest peak in final difference = 0.651 e λ^{-3} .

7- Pr. Sir John Comforth (Sussex University; U.K.) is deeply acknowledged for his interest.

8- Same conditions as for the 4-5a condensation excepted that CH2Cl2 was used as solvent.

9- Selected ¹³C NMR data (CDCl₃): **3b** (125 MHz): 19.6; 21.7; 26, 26.1, 26.6, 31, 32.1, 35.3, 35.5, 44.8, 45.8, 53.4, 58.6, 125.7, 128, 129.9, 135.3, 141, 144.7, 204.9; **6b** (50 MHz): 17, 21.4, 25.7, 30, 30.3, 48.5, 57.7, 122.3, 128.8, 129.8, 131, 136.5, 144.7, 206; **6c** (50 MHz): 21.7, 23.1, 27.6, 28.6, 29.2, 44.9, 61.2, 118.4, 128.8, 130, 131.1, 135.2, 145, 209.

10- The thermal condensation of the sulfone 4 with butadiene has previously been shown to produce the normal Diels-Alder cycloadduct (Leon, F. M.; Carretero, J. C. Tetrahedron Lett. 1990, 31, 2487-2490).

11- Obviously, unrestricted dienes can also react with strongly-dienophilic species via a [2+2] process. For instance, butadiene condenses with dichloro-difluoroethylene to afford cyclobutane and cyclobexene derivatives in a ratio linearly correlated to the *cisoid-transoid* equilibria constant of the used diene (Bartlett, P. D. J. Am. Chem. Soc. 1973, 95, 146 and 150. Swenton, J. S.; Bartlett, P. D. J. Am. Chem. Soc. 1968, 90, 2056-2058). For a general discussion, see: *i*) Bartlett, P. D. Q. Rev. Chem. Soc. 1970, 24, 473, and ref. quoted therein; *ii*) Baldwin J. E. Thermal Cyclobutane Ring Formation; In Comprehensive Organic Synthesis Trost B. M., Fleming I. Editors; Pergamon Press: Oxford, New-York, Seoul, Tokyo 1991 vol. 5; pp 63-84. 12- Wuest, J. D. Acc. Chem. Res. 1999, 32, 81-89.