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LETTERS

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

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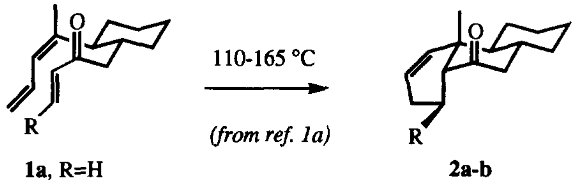
Abstract: β-arylsulfonyl vinylketones have been shown to react, both inter and intramolecularly, with 1,1-disubstituted dienes to afford, depending on the used *-i.e.* thermal or Lewis-acid catalysed-conditions, either [4+2] or [2+2] cycloadducts, respectively. © 1999 Elsevier Science Ltd. All rights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



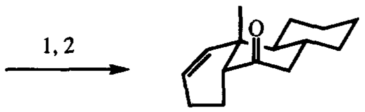
1a, R=H
1b, R=SO$_2$Ph

2a-b

Earlier attempt to catalyse these intramolecular Diels-Alder (IMDA) reactions by using BF$_3$.Et$_2$O, 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 CH$_2$Cl$_2$ had resulted in either no reaction (- 78 °C) or decomposition (r.t.) of the starting material.[1c]

This experiment with BF$_3$.Et$_2$O 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 work-up, the tricyclic ketone **2a** could be isolated in fairly good yield.

1a



2a (57%)

Reagents and conditions: BF$_3$.Et$_2$O (0.9 eq.), CH$_2$Cl$_2$ (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 BF$_3$.Et$_2$O as precedently was detrimental, the only observed reaction being the decomposition of the starting sulfone.

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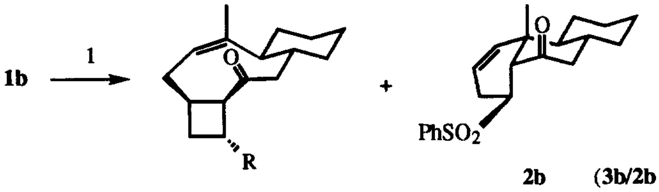
A more interesting result was obtained by using Et_2AlCl. Hence, stirring **1b** with excess Et_2AlCl in toluene, at r.t., for 18 hours led to the formation of two isomeric ketones: *i*) a minor one (ca 15% of the crude reaction product), that proved strictly identical (m.p., NMR) to the sulfo-ketone **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]



3b, R=SO_2Ph

2b (**3b**/**2b** = 85:15)

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

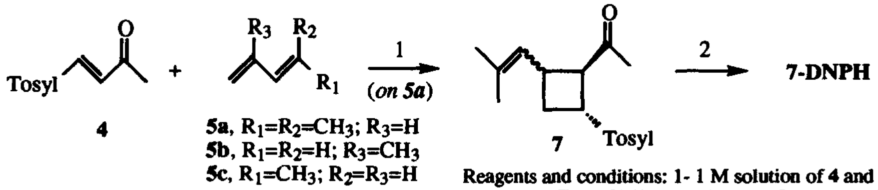
In search for a rationale for this unexpected process, we found in the literature that a few 1,1-disubstituted butadiene derivatives have already been mentioned as giving, besides normal Diels-Alder products, [2+2] cycloadducts when reacted at r.t. with the strongly-electrophilic TCNE, which was attributed 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 $BF_3 \cdot Et_2O$-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 CH_2Cl_2, preferred to toluene owing to the low solubility of **4** in the later solvent, and in presence of Et_2AlCl (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).

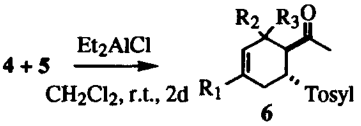
An X-ray analysis of this crystal was attempted however. The crystal data thus collected[6] furnished the Chemdraw® structure shown, which suggested to an eminent colleague, to whom this puzzling drawing was submitted, the following comment: "It seems more likely to me that the computer programme of 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.

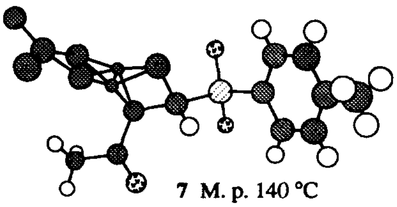


Reagents and conditions: 1- 1 M solution of **4** and **5** in toluene, Et_2AlCl (1 M, in hexane; 2 eq.); r.t., 2 days; 2- 2,4-dinitrophenylhydrazine (3 eq.), 1/100 25% HCl/MeOH; 45 °C, 15 min (100%).

Table:[8]



Diene	Products (Yield, %), m. p.
5b	**6b** (75), 101°C
5c	**6c** (85), oil



7 M. p. 140 °C

For the sake of comparison, the keto sulfone **4** was reacted with isoprene **5b** and piperylene **5c** in presence of Et_2AlCl 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] β-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 Et_2AlCl. 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 Et_2AlCl, 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-complexed[12] and, though activated by the used Lewis acid (**1a** undergoes indeed an IMDA process at ca -35°C in presence of $BF_3.Et_2O$), it will be not rendered sufficiently electrophilic so as to make the [2+2] process competitive, on a kinetic ground, with the *transoid-cisoid* change of the diene moiety: the Diels-Alder 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.

Acknowledgements: Thanks are due to the "Région Alsace" for a grant (to T. Z.) and to Dr. Serge Sablé (Rhône-Poulenc Rorer, Vitry-sur-Seine) for the high-field NMR experiments.

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).

3- a) Stewart, C. A. *J. Org. Chem.* **1963**, *28*, 3320-3321; b) Kataoka, F.; Shimizu, N.; Nishida, S. *J. Am. Chem. Soc.* **1980**, *102*, 711-716; c) Josey, A. D *Angew. Chem. Inter. Ed.* **1981**, *20*, 686; d) Brückner, R.; Huisgen, R. *Tetrahedron Lett.* **1994**, *35*, 3285-3288; e) Ruf, S.; Otto, H.-H. *Helv. Chim. Acta* **1995**, *78*, 629-635; f) Sustmann, R.; Tappanchai, S.; Bandmann, H. *J. Am. Chem. Soc.* **1996**, *118*, 12555-12561. See, however: Zutterman, F.; Krief, A. *J. Org. Chem.* **1983**, *48*, 1135-1137; Shimizu, N.; Nishida, S. *J. Chem. Soc. Chem. Commun.* **1978**, 931-932.

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 Et_2AlCl 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**: $C_{17}H_{22}O_3S$, mol. weight = 306.43, triclinic, space group P-1, a =8.2169(4), b = 10.1433(8), c = 11.2382(9) Å, α = 104.847(9), β = 106.778(9), γ = 104.175(9) deg, V = 813(3) $Å^3$, Z = 2, dcalc = 1.25 gcm^{-3}, μ= 0.173 mm^{-1}. Data were collected using a Nonius KappaCCD diffractometer, graphite monochromated MoKα radiation (λ = 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 $eÅ^{-3}$.

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

8- Same conditions as for the **4-5a** condensation excepted that CH_2Cl_2 was used as solvent.

9- Selected ^{13}C NMR data ($CDCl_3$): **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 cyclohexene 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.