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Short Enantioselective Approach to Substituted Triazolopyridazines from [(S)*R*]-1-(1E, 3E)-1-*p*-Tolylsulfinyl-1,3-Pentadiene

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Abstract: Enantiomerically pure hydroxy substituted triazolopyridazine **5a** was obtained in one pot under mild conditions by reaction of (+)-(*R*)-(1*E*,3*E*)-1-(*p*-tolylsulfinyl)-1,3-pentadiene and 4-methyl-1,2,4-triazoline-3,5-dione in the presence of $P(OMe)_3$. The process involved a tandem Diels-Alder cycloaddition/sulfoxide-sulfenate rearrangement and trapping of the intermediate sulfenate.

Asymmetric Diels-Alder reactions of sulfinyl derivatives have been widely studied both on sulfinyl dienophiles[1] and sulfinyl dienes.[2] In the latter, when the sulfoxide is situated at C-2 of the butadiene system, cycloadditions occur in a highly diastereoselective manner, but synthetic applications of the resulting adducts meet the drawback of a difficult elimination of the sulfoxide. In systems bearing the sulfoxide at C-1, the adducts resulting from the highly diastereoselective cycloadditions evolve through a sulfoxide-sulfenate rearrangement, allowing the ready elimination of the sulfinyl group, [3,4,5] giving easy access to highly functionalized compounds not accessible by other routes. In this case, the potential synthetic usefulness of these processes remained unexplored due to the low reactivity of these dienes, which require high pressures or very long reaction times to complete the cycloaddition. In order to overcome this limitation we thought of using highly reactive dienophiles. Among them, we chose 1,2,4-triazoline-3,5-dione **2a** (Cookson reagent)[6] as heterodienophile, which is known to be strongly reactive towards dienes in comparison with homodienophiles of similar structure such as *N*-methylmaleimide (NMM). Besides the synthetic interest, this reaction would provide a new example of hetero Diels-Alder reaction with a sulfinyl partner, a topic scarcely studied.[7] We report herein[8] the efficient one-pot formation of triazolopyridazine carbinol **5a** by reaction between [(S)*R*]-(1*E*,3*E*)-1-*p*-tolylsulfinyl-1,3-pentadiene **1**[9] and **2a** which occurred in the presence of a thiophilic agent $P(OMe)_3$[10] through a highly diastereoselective tandem Diels-Alder cycloaddition/[2,3]-sigmatropic rearrangement/sulfenate trapping.

The reaction between **1** and **2a** took place under very mild conditions (CH_2Cl_2, -10°C, 2 h) affording sulfenate **4a** which resulted from the cycloadduct **3a** (not detected), by a sulfoxide-sulfenate rearrangement of the allylic sulfoxide (Scheme 1). In similar conditions sulfinyldiene **1** did not react with NMM[4] **2b**, being necessary a high excess of dienophile and a very long reaction time (20 days at rt, Scheme 1) to complete the cycloaddition. The significantly higher reactivity of compound **2a** towards **1** was evidenced from these results.

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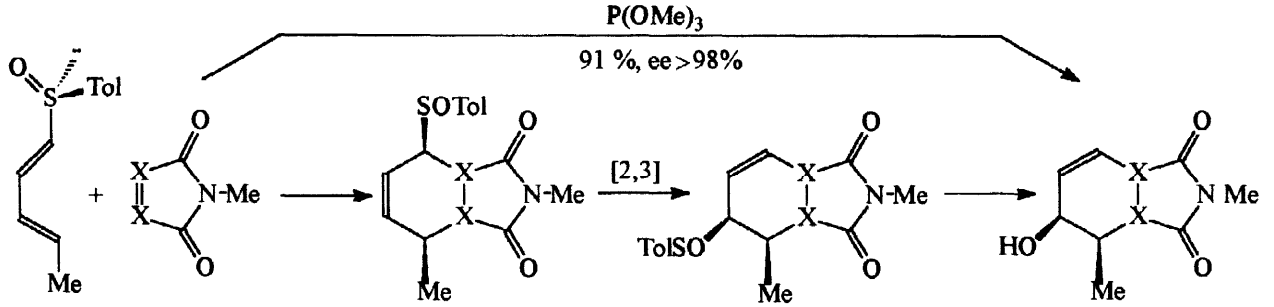
Moreover, the sulfoxide-sulfenate equilibrium in both cases is shifted to the opposite side. Only sulfenate **4a** was present in the reaction with heterodienophile **2a** whereas the initial sulfinyl cycloadduct **3b** could be isolated as the major component of the reaction mixture starting from **2b**. This could be due to the lower stability of the hemithioaminal S-oxide structure present in the hetero adduct **3a** compared to that of the sulfoxide **3b**.[11]

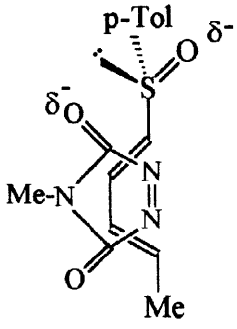


1	2	3	4	5
a: X= N (1 eq, -10 °C, 2h)		---	100	---
b: X=CH (10 eq, 30°C, 20 d)		60	---	40

Scheme 1

Sulfenate **4a** was not stable enough to be isolated but could be stored at -20°C for several days. On standing at room temperature we observed a slow evolution into a mixture of compounds.[12] The treatment of compound **4a** with the thiophilic agent $P(OMe)_3$ yielded cyclohexenol **5a** in high yield. When the cycloaddition between **1** and **2a** was carried out in the presence of $P(OMe)_3$, compound **5a** was directly formed and could be isolated in 91% overall yield.

The structure of **4a** and **5a** was established on the base of their NMR parameters.[13] The *cis*-arrangement of the methyl group and the OH (in **5a**) or the OSTol (in **4a**) was deduced from the value of the vicinal coupling constant $J_{5,6}$ (≈ 6.2 Hz). The absolute configuration at C-6 was established as *S* by ^{1}H-NMR studies of its (*R*)- and (*S*)-MTPA esters.[14] Taking into account the suprafacial course of the sulfoxide-sulfenate rearrangement we can conclude that the absolute configuration of the non detectable cycloadduct **3a** is that depicted in Scheme 1. In order to explain the high stereoselectivity of the reaction we assume that the sulfinyl oxygen must adopt the s-*trans* conformation with respect to the dienic system in order to minimize the electrostatic repulsion with the carbonyl oxygen of the attacking heterodienophile in the transition state corresponding to its *endo* approach from the less hindered face of diene (that supporting the lone electron pair at sulfur).[4] The high optical purity of **5a** (ee > 98%) revealed that both the hetero Diels-Alder reaction and the sulfoxide-sulfenate rearrangement were completely π-facial diastereoselective.



Although the *endo* character of cycloaddition can not be established directly from the structure of **5a**, previous results on related systems[4] suggested such a favored approach. Moreover in accordance with our model, the *exo* approach would give the enantiomer of **5a** , decreasing its enantiomeric excess.

Studies directed towards the transformation of the resulting substituted [1,2,4]triazolo [1,2a]pyridazine-3,5-dione into optically pure β-hydroxy, γ-aminoacids are being carried out in our laboratory and they will be published in the due course.

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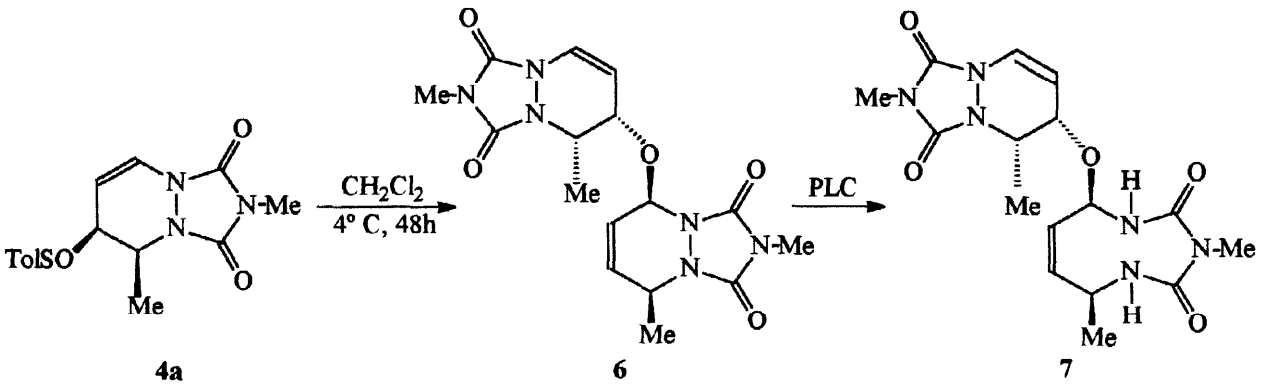
11. The absence of carbinol **5a** in the crude mixture resulting from **2a** contrasted with the significant

amount of carbinol **5b** (40 %) formed in the reaction with NMM. This suggested a certain thiophilic character for NMM[4a,5] which must be absent in the analogue triazoline derivative **2a**.

12. Compound **6** was the main component of this mixture. All the efforts made to purify it by PLC produced its transformation into 7 which could be isolated pure with 45% yield from starting diene.



4a **6** **7**

45 % yield from **1**

Formally the formation of compound **6** must be a consequence of a S_N2' type reaction between carbinol **5a**, acting as nucleophile and the sulfenate **4a**.

13. All new compounds were characterized on the basis of their IR, ^{1}H-NMR and ^{13}C-NMR (200 MHz, $CDCl_3$) spectral data and elemental analysis and/or MS. **4a** : ^{1}H-NMR δ 7.33-7.16 (AA'BB'system, 4H, p-Tol), 6.70 (dd, 1H ; J=8.2 and 2.0 Hz, H-8), 4.99 (dd, 1H, J= 8.2 and 1.1 Hz, H-7), 4.60 (dc, 1H, J= 6.5 and 5.8 Hz, H-5), 4.40 (ddd, 1H, J= 1.1, 2.0 Hz, H-6), 3.00 (s, 3H, CH_3-N), 2.30 (s, 3H, CH_3-p-Tol), 1.06 (d, 3H, J= 6.5, CH_3-C-5). **5a** : mp 187-188°C (CH_2Cl_2 :Hexane) ; $[\alpha]_D^{20}$ = -108 (c= 0.36, $CHCl_3$) ^{1}H-NMR δ 6.83 (dd, 1H, J=8.2 and 1.7 Hz, H-8) , 5.09 (dd, 1H, J=8.2 and 2.3 Hz, H-6), 4.63 (dddd, 1H, J= 6.2, 2.3, 1.7 and 7.3, H-6), 4.43 (dc, 1H, J= 6.5 and 6.2, H-5), 3.11 (s, 3H, CH_3-N), 2.04 (d, 1H, J= 7.3, OH), 1.28 (d, 3H, J=6.5, CH_3-C-5). ^{13}C-NMR : 151.5 (2C), 117.6, 106.9, 64.5, 51.7, 25.2, 11.2.

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