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## REGIO- AND DIASTEREOSELECTIVE ALKYLATION OF (1<u>R</u>,5<u>S</u>)-4-ETHYL-6,6-DIMETYL-3-(PHENYLSULFONYL)BICYCLO[3.1.1]HEPT-3-EN-2-ONE

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Abstract: Alkylation of  $(1\underline{R},5\underline{S})-4-ethyl-6,6-dimethyl-3-(phenylsulfonyl) bicyclo[3.1.1]hept-3-en-2-one (3) with allyl bromide proceeded at the <math>\gamma$  position to the conjugated enone system in regio- and diastereoselective fashion, providing  $(1\underline{R},5\underline{S})-4-((1\underline{R})-1-methyl-3-butenyl)-6,6-dimethyl-3-(phenylsulfonyl)bicyclo[3.1.1]hept-3-en-2-one (9a) in good yield. An analogous trend was observed in alkylation of 3 with other representative alkyl halides.$ 

We have been studying natural product synthesis starting with (+)nopinone (1) as a chiral source,<sup>1,2</sup> and recently reported that the sulfone 2 obtainable in five steps and 70% overall yield from 1 is a reactive Michael acceptor, giving 4,4-disubstituted nopinones when reacted with some representative carbon nucleophiles.<sup>2,3</sup> In connection with our program dealing with the chemistry of reactive nopinone derivatives, we wish to report here that alkylation of the title compound 3, a homolog of 2, with a variety of alkyl halides provided  $\gamma$ -alkylation products 9 in an extracyclic stereocontrolled fashion.<sup>4,5</sup>



The sulfone 3 was readily prepared from 1 via phenylthic enone  $4^{2,3}$  by use of our standard synthetic route; (i) Michael addition (EtMgBr, CuI, THF) of 4, (ii) oxidation [mCPBA (1 equiv), CH<sub>2</sub>Cl<sub>2</sub>] of the adduct 5

followed by the Pummerer rearrangement (Ac<sub>2</sub>O, MsOH, CH<sub>2</sub>Cl<sub>2</sub>) of the resulting sulfoxide, and (iii) oxidation [mCPBA (2 equiv),  $CH_2Cl_2$ ] of the resulting enone 6 with formation of sulfone 3 in 74% overall yield from 4.

In order to determine the optimum reaction conditions, allylation of 3 with allyl bromide was examined in some detail with changes of metal ions in the bases. No reaction occurred upon generation of the carbanion with LDA (THF, -78 °C - rt), whereas formation of deconjugated enone 7 was detected when NaH (THF, rt or refluxing) was employed. Then, potassium bases were testified to be effective for allylation of this type. Although use of KH (THF, rt) or KOBu<sup>t</sup> (THF-HMPA) led to a mixture of  $\alpha$ and  $\gamma$ -allylation product,<sup>4</sup> a problem of a few by-products formation was accompanied. After all, it was found that the conditions using K<sub>2</sub>CO<sub>3</sub> (10 mole equiv.) in MeCN at 50 °C resulted in allylation smoothly and cleanly to provide a mixture of 9a and 10a in which the former was predominant,<sup>6</sup> along with 11a as the minor product and a very small amount of 0-allylation product.<sup>7</sup> Consequently, we adopted the above reaction conditions in all of our subsequent studies.



The alkyl halides **8a-e** used in this study and the results thereby obtained are summarized in Table 1. As can be seen, alkylation of **3** with **8a-d** proceeded at the  $\gamma$  position in extracyclic stereocontrolled fashion to give  $\gamma$ -alkylation products **9a-d** in good to high yields (run 1 - 4). Methylation also provided isopropyl enone in good yield (run 5). Recently, as a reagent,  $K_2CO_3-CsCO_3$  (9:1 ratio) was reported to be suitable base for alkylation of pentane-2,4-dione,<sup>8</sup> we examined use of this reagent for our case: No change was observed in the products distribution including their yields when **8c**,d were reacted, however interestingly, increasing diastereoselection was detected on formation of **9a**,b when **8a**,b were employed (run 1,2).

The above regio- and diastereoselection can be explained as follows (Scheme 1). First, a potassium extend enolate anion 12 generated from 3 is alkylated preferentially at the  $\gamma$  site to give 9 and 10, because development of the transition state for the  $\alpha$ -alkylation process is unfavorable from a non-bonded interaction between a phenylsulfonyl group and <u>gem</u>-dimethyl face, as seen in 11. Second, the nucleophiles approach to the  $\gamma$  position of 12 from the less hindered  $\alpha$  side away from the <u>gem</u>-dimethyl face, according to the well-known reactivity<sup>2</sup>,<sup>9</sup> of pinane-type

			product <sup>a</sup>		
run	alkyl halide (RBr) <b>8</b> R		PhO <sub>2</sub> S R 9b yield (%) <sup>d,e</sup>	$\frac{PhO_2S}{R}$	PhO <sub>2</sub> S O R 11 <sup>C</sup> yield (%) <sup>e</sup>
1	a	CH <sub>2</sub> CH=CH <sub>2</sub>	68	10:1 (20:1)9	20
2	b	CH <sub>2</sub> CH=CMe <sub>2</sub>	62	7:1 (12:1)g	16
3	с	CH2C≡CH	60	13:1	20
4	đ	CH <sub>2</sub> Ph	87	18:1	3
5	е	Meh	70	-	27

Table 1. Regio- and diasterecselective alkylation of 3

a A small amount of O-alkylation product was detected in each case.

b [α]<sub>D</sub> in CHCl<sub>3</sub>: 9a, +157.9°; 9b, +123.0°; 9c, +120.5°; 9d, +65.3°.

c A single isomer with respect to the double bond geometry.

- d Combined yield of 9 and 10.
- e Isolated yield.

f Ratio obtained from the  $^{1}\mbox{H}$  NMR (600 MHz) analysis.

- g Ratio obtained when alkylated under the conditions of  $K_2CO_3$ -CsCO<sub>3</sub> (9:1) in MeCN at room temperature.
- h MeT was employed.

compounds, providing 9 stereoselectively. Third, a severe non-bonded interaction between a phenylsulfonyl group and a cisoid substituent ( $R^1$ , probably Me) shown in 13 prevents enolization of 9 under the basic conditions used here, leading to the integrity of the newly formed asymmetric carbon in the side chain of 9.10



The regioisomers produced were readily separated by column chromato-

graphy on silica gel, whereas separation of 9 and 10 was carried out by high-pressure liquid chromatography. Fortunately, the sulfones 9 and 10 are highly crystalline, so that the major 9 were practically obtained as pure crystals by a simple recrystallization of a mixture of the two.

When heating in xylene at 50  $^{\circ}$ C, 11a was recovered unchanged, whereas under refluxing, 9a was produced albeit in low yield (20%). The findings indicated that 9a is a direct alkylation product and not one arisen from Cope rearrangement of 11a.

Considering that the sulfones 9 obtained can be utilized as reactive Michael acceptors for preparation of 4,4-disubstituted nopinones, and that their cyclobutane rings can be cleaved without loss of optical purity, affording 5,5-disubstituted 1-acetoxy cyclohexenes,<sup>11</sup> the sulfones 9 would serve as promising intermediates for asymmetric synthesis of natural products.

## References and Notes

- 1 Kato, M.; Watanabe, M.; Vogler, B.; Tooyama, Y.; Yoshikoshi, A. J. Chem. Soc., Chem. Commun. 1990, 1706.
- 2 Kato, M.; Vogler, B.; Tooyama, Y.; Yoshikoshi, A. <u>Chem. Lett.</u> 1990, 151.
- 3 Kato, M.; Watanabe, M.; Awen, B. Z.; Vogler, B.; Masuda, Y.; Tooyama, Y.; Yoshikoshi, A. <u>J. Org. Chem</u>. accepted for publication (1991).
- 4 Positioning  $\alpha$  and  $\gamma$  are given to the conjugated enone system in 3.
- 5 Bartlett, P. Tetrahedron, 1980, 36, 61.
- 6 Stereochemistry of 9a and 10a was not only deduced from the study on reaction mechanism (vide post), but also chemically verified by the synthesis of (-)-kanshon A whose absolute configuration has been determined, starting from 9a, as shown in the succeeding paper.
- 7 The O-alkylation product was unstable and gradually transformed to 3 during chromatographic separation on silica gel.
- 8 Shrout, D. P.; Lightner, D. A. Synth. Commun. 1990, 2075.
- 9 For examples, Pellegata, R.; Ventura, P.; Villa, M. Synth. Commun. 1985, <u>15</u>. 165; Yanami, T.; Miyashita, M.; Yoshikoshi, A. J. Org. Chem. 1980, <u>45</u>, 607.
- 10 Similarly, no racemization occurs in 10.
- 11 For BF<sub>3</sub>·OEt<sub>2</sub>-catalyzed cyclobutane-opening reaction, see Kato. M.; Kamat, V. P.; Tooyama, Y.; Yoshikoshi, A. J. Org. Chem. 1989, 54, 1536.

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