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A regioselective and a practical synthesis of 2,5-di(methylsufonyl)phenol is described on the basis of the reactivity analysis of 2,4-dichloro-methylsulfonylbenzene by use of the HSAB principle.

We have recently developed one of the intramolecular CT type dichroic functional azo dyes<sup>1)</sup> exhibiting both an extreme narrow absorption band with a high intensity and a considerable stability.<sup>2)</sup> These remarkable properties may be induced by both the methylsulfonyl substituents and their relative positions in the phenolic coupling component of <u>lb</u>. In the practical preparation of <u>la</u>, however, a variety of functionalization methods established in the chemistry of aromatic compounds gave unsuccessful results,<sup>3)</sup> owing to the unfavorable orientation of the methylsulfonyl substituents against the hydroxyl group. In our previous publication,<sup>4)</sup> we have reported an efficient method for the preparation of <u>2</u>. In this paper, we wish to describe a regioselective synthesis of <u>la</u> from <u>2</u> on the basis of the reactivity analysis of two possible sites of <u>2</u> (C<sub>2</sub> and C<sub>4</sub>) susceptible of undergoing nucleophilic attack by use of the HSAB principle.<sup>5)</sup>



A STO-3G *ab initio* calculation programmed by GAUSIAN 80 on  $\underline{2}$  was carried out<sup>6)</sup> in order to estimate the relative reactivity between the C<sub>2</sub> and the C<sub>4</sub>. Both the frontier electron densities and the total charge densities in Fig. 1 suggest that the relative affinity between the C<sub>2</sub> and the C<sub>4</sub> toward a hard nucleophile would be similar, whereas that toward a soft one would be favoured on the C<sub>4</sub>.

The preliminary results obtained in the hydroxylation reactions were in good accordance with these predictions. That is, treatment of 2 with KOH (1.1 equiv.) in DMSO/H<sub>2</sub>O (3:1)<sup>7)</sup> at 100 °C for 3 h led to a nonselective hydroxylation, giving an unseparable mixture of <u>3a</u> and <u>3b</u>(1:1; 96%). In surprising contrast, treatment of <u>2</u> with CH<sub>3</sub>CO<sub>2</sub>K (2.0 equiv.) in the same solvents afforded <u>3b</u> (mp 104-106 °C),



Fig. 1. coefficients total charge in LUMO. densities.

exclusively in 73% yield with 4 (mp 142-143 °C; 8%). By regarding CH<sub>3</sub>CO<sub>2</sub>K as a soft

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reagent relative to KOH, the present regioselectivity would be explained in terms of an orbital controlled reaction.<sup>8)</sup> These findings also indicate that the transformation of 2 into la should be started by the introduction of an appropriate soft nucleophile on the C<sub>4</sub> of  $\underline{2}$ . Treatment of  $\underline{2}$  with  $\underline{5}$  as a soft synthon of methylsulfonyl group, in DMF/H2O (1:2) at 120 °C for 3 h, gave 6 (mp 124-126 °C) in 81% yield in a regioselective manner:<sup>9)</sup> FD-MS m/z 280 (M<sup>+</sup>); IR (Nujol) 3600-2550(broad), 1720, 1600 cm<sup>-1</sup>; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>)  $\delta$  3.26 (s, 3H, CH<sub>3</sub>), 3.85 (s, 2H, -CH<sub>2</sub>-), 7.44 (dd, lH, J=1 and 8 Hz,  $C_5$ -H), 7.51 (d, lH, J=1 Hz,  $C_3$ -H), and 7.96 (d, lH, J=8 Hz,  $C_6$ -H). <u>6</u> Was treated with KOH (4.0 equiv.) in DMSO/H<sub>2</sub>O (3:1)<sup>7)</sup> at 110 °C for 6 h to give 7 (mp 202-204 °C; 72%). Transformation of 7 into la was accomplished by oxidation of 7 with CH<sub>3</sub>CO<sub>3</sub>H (3.0 equiv.) in AcOH at 80 °C for 2 h and the subsequent decarboxylation of 8 with NaOH (1.1 equiv.) at 100 °C for 6 h. The reactions proceeded as expected to afford la (mp 224 °C) in 60% yield. Thus, a regioselective and a practical route of the preparation of <u>la</u> was achieved by the reactivity analysis based on the HSAB principle. The overall yield was 35% from 2. The present results also provide a successful example of the prediction of the reactivity toward aromatic compounds containing two electrophilic centers.<sup>10)</sup>



## References

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