CHEMISTRY LETTERS, pp. 1393-1394, 1988.

A Regioselective Synthesis of 2,5-Di(methylsulfonyl)phenol

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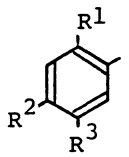
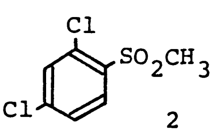
A regioselective and a practical synthesis of 2,5-di(methylsufonyl)phenol is described on the basis of the reactivity analysis of 2,4-dichloro-methylsulfonylbenzene by use of the HSAB principle.

We have recently developed one of the intramolecular CT type dichroic functional azo dyes[1)] exhibiting both an extreme narrow absorption band with a high intensity and a considerable stability.[2)] These remarkable properties may be induced by both the methylsulfonyl substituents and their relative positions in the phenolic coupling component of 1b. In the practical preparation of 1a, however, a variety of functionalization methods established in the chemistry of aromatic compounds gave unsuccessful results,[3)] owing to the unfavorable orientation of the methylsulfonyl substituents against the hydroxyl group. In our previous publication,[4)] we have reported an efficient method for the preparation of 2. In this paper, we wish to describe a regioselective synthesis of 1a from 2 on the basis of the reactivity analysis of two possible sites of 2 (C_2 and C_4) susceptible of undergoing nucleophilic attack by use of the HSAB principle.[5)]



1a: R^1=OH, R^2=$-SO_2CH_3$, R^3=H
1b: R^1=OH, R^2=$-SO_2CH_3$,
R^3=-N=N-Ar



2

A STO-3G *ab initio* calculation programmed by GAUSIAN 80 on 2 was carried out[6)] in order to estimate the relative reactivity between the C_2 and the C_4. Both the frontier electron densities and the total charge densities in Fig. 1 suggest that the relative affinity between the C_2 and the C_4 toward a hard nucleophile would be similar, whereas that toward a soft one would be favoured on the C_4.

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_2O (3:1)[7)] at 100 °C for 3 h led to a nonselective hydroxylation, giving an unseparable mixture of 3a and 3b(1:1; 96%). In surprising contrast, treatment of 2 with CH_3CO_2K (2.0 equiv.) in the same solvents afforded 3b (mp 104-106 °C), exclusively in 73% yield with 4 (mp 142-143 °C; 8%). By regarding CH_3CO_2K as a soft

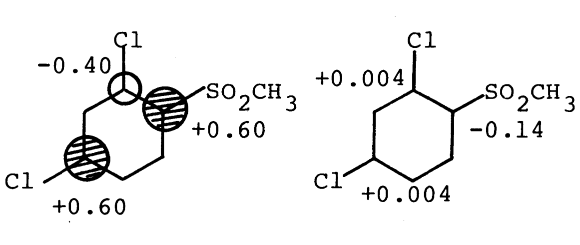
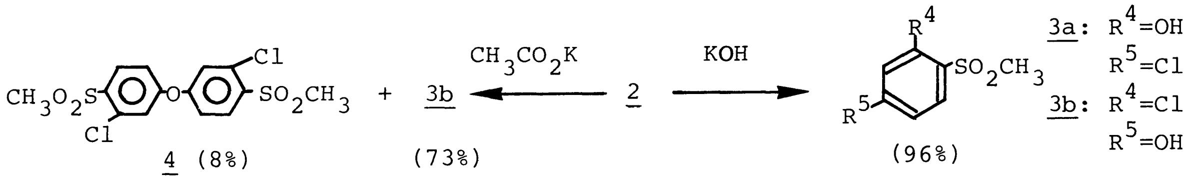
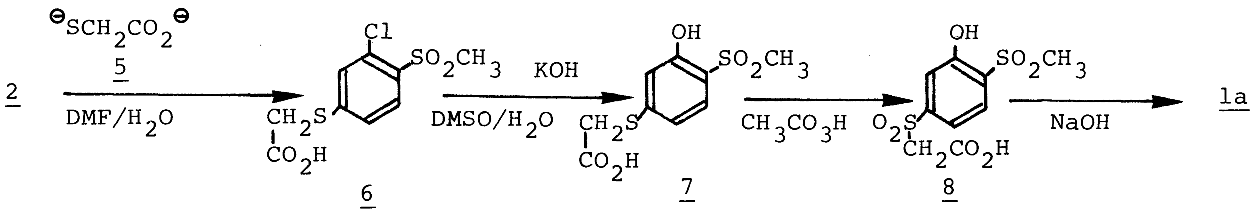


Fig. 1. coefficients in LUMO. total charge densities.



reagent relative to KOH, the present regioselectivity would be explained in terms of an orbital controlled reaction.[8)] These findings also indicate that the transformation of 2 into 1a should be started by the introduction of an appropriate soft nucleophile on the C_4 of 2. Treatment of 2 with 5 as a soft synthon of methylsulfonyl group, in DMF/H_2O (1:2) at 120 °C for 3 h, gave 6 (mp 124-126 °C) in 81% yield in a regioselective manner:[9)] FD-MS m/z 280 (M^+); IR (Nujol) 3600-2550(broad), 1720, 1600 cm^{-1}; ^1H-NMR (DMSO-d_6) δ 3.26 (s, 3H, CH_3), 3.85 (s, 2H, $-CH_2-$), 7.44 (dd, 1H, J=1 and 8 Hz, C_5-H), 7.51 (d, 1H, J=1 Hz, C_3-H), and 7.96 (d, 1H, J=8 Hz, C_6-H). 6 Was treated with KOH (4.0 equiv.) in DMSO/H_2O (3:1)[7)] at 110 °C for 6 h to give 7 (mp 202-204 °C; 72%). Transformation of 7 into 1a was accomplished by oxidation of 7 with CH_3CO_3H (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 1a (mp 224 °C) in 60% yield. Thus, a regioselective and a practical route of the preparation of 1a 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.[10)]



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(Received May 10, 1988)