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Investigation of the Montmorillonite clay-catalyzed [1,3] shift reaction of 3-methyl-2-butenyl phenyl ether

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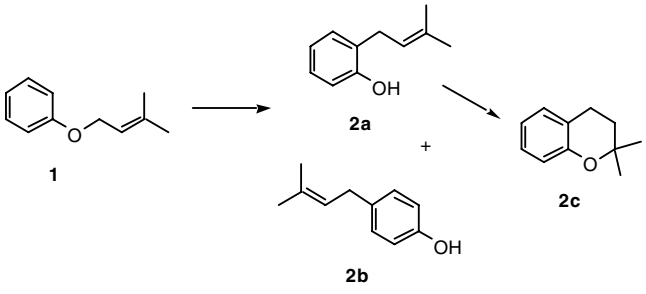
Abstract—The [1,3] shift reaction of 3-methyl-2-butenyl phenyl ether was catalyzed more effectively by Montmorillonite K10 clay than Montmorillonite KSF clay, and proceeded with greatest *ortho*-selectivity in carbon tetrachloride at room temperature.

ortho-Prenylated phenols exhibit a broad range of pharmacological activity, including anti-inflammatory,[1] anti-fungal,[2] anti-bacterial,[3] and anti-tumor.[4] In addition, this ubiquitous pharmacophore has been implicated in the treatment of HIV[5] and Alzheimer's disease.[6] Numerous strategies have been developed for the preparation of *ortho*-prenylated phenols, a survey of which was included in a recent report by Hoarau and Pettus.[7] In conjunction with a related synthesis project,[8] we had occasion to study one such methodology: the Montmorillonite clay-catalyzed [1,3] shift[9] reaction of allyl phenyl ether **1**, which was originally reported by Dauben et al. in 1990.[10] According to Dauben the reaction proceeded over 9 h (room temperature, benzene) in the presence of 1 equiv (by weight) of Montmorillonite KSF clay to give a 34% yield of *ortho*-prenyl phenol **2a**, along with small amounts of starting material, *para*-isomer **2b**, and coumaran **2c** (Scheme 1). Herein we present a more detailed investigation of this reaction and optimal conditions for the conversion of **1** to **2a**.



Scheme 1. Montmorillonite clay-catalyzed [1,3] shift of **1**.

Reproducing Dauben's results with Montmorillonite KSF clay was straightforward, though we observed about a 30% conversion of **1** to **2a** within 2 h along with significant amounts of **2b** (20%) and other products (phenol and bis-prenylated material, 12%) also present in the reaction mixture (Table 1, entry 3). Product distribution was determined by periodic GC–MS analysis during the course of the reaction. After 15 h, the starting material was completely consumed with a 1:1.3:1.1 distribution of **2a**:**2b**:**2c** (Table 1, entry 4). Presumably **2a** cyclizes to give **2c** upon prolonged exposure to the acidic clay.

We repeated this reaction using Montmorillonite K10 clay and observed a significant enhancement in the rate of conversion of **1** to **2a**–**c** (Table 2). The starting material was completely consumed after 0.5 h, with a 1:0.7:0.1 distribution of **2a**:**2b**:**2c**. The K10 clay in benzene also promotes formation of a greater quantity of

Table 1. KSF-catalyzed [1,3] shift of **1** in benzene

Entry	*t* (h)	Product distribution (%)				
		1	**2a**	**2b**	**2c**	Other
1	0.5	73	9	6	0	12
2	1	57	16	13	0	14
3	2	42	26	20	0	12
4	15	0	22	28	24	26

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Table 2. K10-catalyzed [1,3] shift of **1** in benzene

Entry	t (h)	Product distribution (%)				
		1	**2a**	**2b**	**2c**	Other
1	0.5	0	30	20	4	46
2	1	0	30	19	5	46
3	2	0	27	18	10	45
4	15	0	19	14	23	56

Table 3. K10-catalyzed [1,3] shift of **1** in various solvents

Entry	Solvent	t (h)	Product distribution (%)				
			1	**2a**	**2b**	**2c**	Other
1	Hexane	8	10	56	8	8	18
2	Pentane	8	11	26	3	5	56
3	CH_2Cl_2	0.25	0	49	18	5	28
4	$CHCl_3$	50	48	35	0	17	0
5	CCl_4	8	9	66	0	9	8

byproducts, including phenol and higher molecular weight compounds (Tables 1–3, 'other'). As with the KSF clay, prolonged exposure of **2a** to Montmorillonite K10 promoted significant cyclization to **2c** (Table 2, entry 4). Given the considerable difference in surface area between K10 (220–270 m^2/g) and KSF (20–40 m^2/g), the observed rate difference is not surprising and lends further support to Dauben's suggestion that catalysis occurs on the outer surface of the clay, rather than in the interlamellar regions.[10]

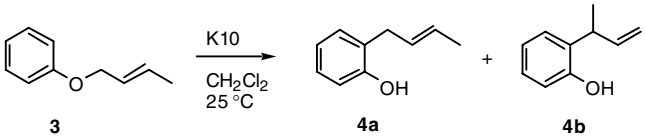
The presence of phenol and bis-prenylated material ($M^+ = 230$) in the product mixture suggests the reaction is not exclusively intramolecular. It is likely that the clay promotes formation of a discrete, delocalized prenyl carbocation and phenoxide ion, which in time recombine to give the desired product (**2a**) along with **2b** and other higher molecular weight compounds.

We next studied the [1,3] shift of **1** using Montmorillonite K10 in a variety of solvents, and observed notable differences in both reaction rate and product distribution (Table 3). The reaction proceeded most rapidly in dichloromethane (entry 3), with complete consumption of **1** within 0.25 h. While the reaction proceeded much more slowly in hexane, it was more regio-selective in this solvent, giving primarily the *ortho*-isomer (**2a**). The reaction was less selective in pentane, yielding a mixture of products, including phenol and bis-prenylated material. The reaction proceeded very slowly and never to completion in chloroform, while in carbon tetrachloride both yield and regio-selectivity were optimized in a reasonable period of time (66% **2a** in 8 h).

In an effort to better control regio-selectivity in dichloromethane, we ran the reaction at lower temperatures, 0 and −20 °C (Table 4). We observed a dramatic decrease in the rate of the reaction at 0 °C with only a modest increase in the ratio of **2a**:**2b** (4.3:1). A more significant increase in the ratio of **2a**:**2b** was observed at −20 °C (5.2:1), but only after a much longer reaction period (96 h).

Table 4. K10-catalyzed [1,3] shift of **1** in CH_2Cl_2 at low temperature

Entry	T (°C)	t (h)	Product distribution (%)				
			1	**2a**	**2b**	**2c**	Other
1	0	18	0	52	12	5	31
2	−20	96	0	62	12	5	21



3 **4a** **4b**

Scheme 2. [1,3] vs [3,3] rearrangement of **3**.

Dauben noted competing [1,3] and [3,3] rearrangements with crotyl phenyl ethers in the presence of the KSF clay, where the [3,3] product was favored.[10] We observed a similar effect upon treatment of **3** with Montmorillonite K10 clay in dichloromethane at room temperature, with about a 40% conversion of **3** to **4a** and **4b** after 96 h (1:2.5, respectively, Scheme 2).

In a typical experiment, a slurry of the clay (1 equiv by weight) and solvent was treated with **1** and the resulting mixture stirred vigorously at room temperature. At periodic intervals, aliquots of the reaction mixture were removed, filtered, diluted with dichloromethane and analyzed by GC–MS. On a preparative scale, the reaction mixture was filtered, and the filtrate concentrated. The crude product mixture was purified by column chromatography with silica gel, eluting with 90:10 hexane–ethyl acetate. Spectral data for compounds **1**, **2a** and **2b** are provided in Ref. 11.

Finally, we examined the turnover of the K10 clay in carbon tetrachloride as a function of percent conversion of **1** to **2a** in 2 h intervals (Fig. 1). In this experiment a slurry of the clay in carbon tetrachloride was treated with **1** and the resulting mixture stirred vigorously for 2 h. The clay was removed by vacuum filtration and the filtrate analyzed by GC–MS. The clay was then re-used in the next 2-h trial. The clay was considerably less active after the first use and completely inactive after the third use (0% conversion of **1** to **2a** in trial 4). Apparently small amounts of higher molecular weight by-

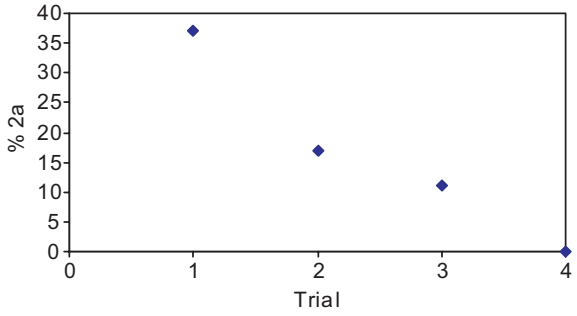


Figure 1. Percent conversion of **1** to **2a** in four consecutive reactions (2 h, CCl_4) with the same clay.

products, bis- and tris-prenylated material ($M^+ = 230$ and 298, respectively), become trapped in the interstitial layers of the clay and eventually render it inactive. However, activity can be completely restored by washing the clay with methanol and pumping on it to remove residual solvent.

As 'green chemistry' becomes more prevalent in organic synthesis,[12–18] environmentally benign clays are becoming attractive alternatives to more toxic Lewis acid catalysts for an array of reactions,[19,20] and optimization of conditions for their use is necessary. We found that the conversion of **1** to **2a** is catalyzed more effectively by Montmorillonite K10 than KSF clay, and proceeds fastest in dichloromethane at room temperature, but most selectively in carbon tetrachloride at room temperature. At lower temperatures, the regio-selectivity (ratio of **2a**:**2b**) in dichlormethane increases, but reaction rate drops off dramatically. In general, prolonged exposure of **2a** to Montmorillonite clay at ambient temperature results in its cyclization to coumaran **2c**. The clay can be recycled as long as higher molecular weight compounds are completely removed by washing with methanol. The work reported here has proved important in our ongoing efforts to demonstrate the utility of Montmorillonite clays in organic synthesis, and may prove useful for others as well. We are currently applying this methodology to the synthesis of a variety of biologically active natural products.

Acknowledgements

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11. (**1**): IR 3062, 3029, 2975, 2861, 1677, 1599, 1495, 1383, 1333, 1299, 1239, 1172, 1154, 1111, 1078, 1029, 1008 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33–7.27 (m, 3H), 6.99–6.94 (m, 2H), 5.53 (t, $J = 6.8$ Hz, 1H), 4.51 (d, $J = 6.8$ Hz, 2H), 1.83 (s, 3H), 1.77 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 159.24, 138.61, 129.83, 120.99, 120.11, 115.03, 65.02, 26.28, 18.61; GC–MS (70 eV), $t_R = 9.076$ min, m/z 162, M^+ (3%); 94, $[M-68]^+$ (100%); 69, $[M-93]^+$ (28%); (**2a**): IR 3445, 3031, 2969, 2917, 2857, 1591, 1493, 1453, 1377, 1341, 1218, 1171, 1092, 1042, 981, 920, 839, 752 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.16–7.12 (m, 1H), 6.91–6.76 (m, 3H), 5.37–5.30 (m, 1H), 3.40 (d, $J = 7/2$ Hz, 2H), 1.81 (s, 3H), 1.80 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 154.71, 135.24, 130.38, 127.95, 121.16, 116.11, 38.03, 30.24, 26.22; GC–MS (70 eV), $t_R = 9.822$ min, m/z 162, M^+ (50%); 147, $[M-15]^+$ (39%); 107, $[M-55]^+$ (100%); 91, $[M-71]^+$ (25%); 77, $[M-85]^+$ (22%); (**2b**): IR ($CHCl_3$) 3334, 2967, 2916, 1597, 1512, 1473, 1447, 1375, 1232, 1101, 820, 753, 691 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.06 (d, $J = 8.5$ Hz, 2H), 6.78 (d, $J = 8.5$ Hz, 2H), 5.32 (t, $J = 7.4$ Hz, 1H), 3.29 (d, $J = 7.3$ Hz, 2H), 1.76 (s, 3H), 1.73 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 153.91, 134.46, 132.68, 130.09, 129.78, 123.95, 115.56, 33.83, 26.19, 18.20; GC–MS (70 eV), $t_R = 10.278$ min, m/z 162, M^+ (57%); 147, $[M-15]^+$ (100%); 107, $[M-55]^+$ (35%); 91, $[M-71]^+$ (19%); 77, $[M-85]^+$ (16%).
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