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Montmorillonite Clays in Organic Synthesis: A One-Pot Conversion of Phenols to 2,2-Dimethylbenzopyrans

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Received 26 January 2004

Abstract: 2,2-Dimethylbenzopyran derivatives were generated through a one-pot Montmorillonite K10 clay-catalyzed condensation of substituted phenols with prenyl bromide.

Key words: heterogenous catalysis, heterocycles, phenols, natural products

A multitude of natural products, including coumarins, chromenes, and flavanoids, contain the 2,2-dimethylbenzopyran moiety as part of their carbon framework.[1] Many of these compounds exhibit significant biological activity which has made them of interest to the synthetic community and resulted in the development of an array of methodologies for their construction.[2] In particular, Nicolaou and coworkers recently reported a solid-phase combinatorial approach to 2,2-dimethylbenzopyrans as a template for demonstrating a novel strategy for the construction of natural and natural product-like libraries based on the principle of privileged structures.[3]

In conjunction with ongoing efforts in our laboratories aimed at the application of environmentally benign clays in organic synthesis, we have developed a convenient clay-catalyzed route to benzopyran derivatives that may be applied in the synthesis of benzopyran-containing natural products. Although clays have been shown to successfully catalyze a variety of organic reactions,[4] they are somewhat under-exploited in natural products synthesis,[5] perhaps because their specific modes of action are not entirely understood. Given their natural availability, low cost, and ease of use, however, application of clays in synthesis comprises an attractive topic for further investigation.

We recently reported[6] a detailed study of the intramolecular clay-catalyzed [1,3] shift reaction of 3-methyl-2-butenyl phenyl ether (Figure 1), which was originally observed by Dauben and coworkers in 1990.[7] Under optimal conditions, the major product of this reaction was *o*-prenyl phenol (**1**, R = H), with minor amounts of *p*-prenyl phenol (**2**, R = H) and benzopyran **3a** (R = H) also generated. During the course of our investigation we observed that phenol (**4a**, R = H) could be directly condensed with prenyl bromide in the presence of Montmorillonite K10 clay to give **3a** as the major product.

SYNLETT 2004, No. 11, pp 2028–2030
Advanced online publication: 04.08.2004
DOI: 10.1055/s-2004-830865; Art ID: S00804ST

Although two separate approaches for the direct generation of benzopyrans from phenols under heterogeneous catalysis have been previously reported, neither proceeded with exceptional percent conversion or regioselectivity, and required either elevated temperature or long reaction times.[2d,e] We were encouraged, therefore, to have observed the clay-catalyzed generation of **3** from phenol in 2 hours at room temperature.

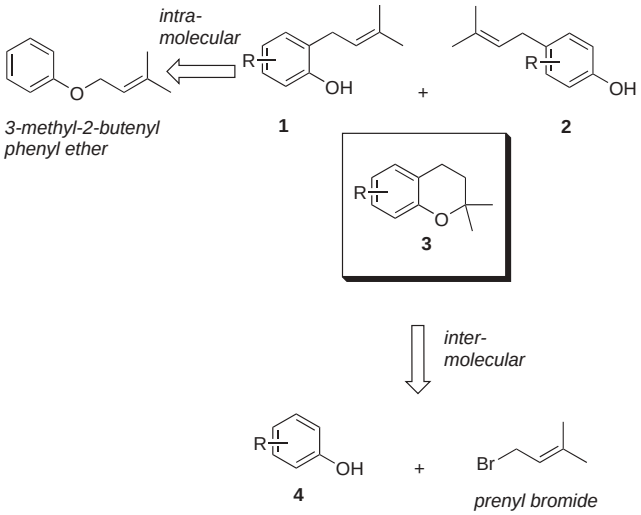


Figure 1 Intra-[6] and intermolecular clay-catalyzed generation of 2,2-dimethylbenzopyrans **3**

We set out to optimize the reaction conditions by varying the amount of the clay used (Table 1). It was clear that as the amount of clay was increased, so was the percent conversion of **4a** (R = H) to the desired 2,2-dimethylbenzopyran product (**3a**, R = H). In the presence of 20 equivalents by weight of the clay (relative to the phenol) we observed complete consumption of starting materials within two hours, with nearly 70% conversion to benzopyran **3a** (Table 1, entry 7). In all cases mixtures of *bis*-prenylated products (Table 1, 'other') were also obtained, but these by-products were separable from the desired benzopyran by column chromatography.

Once conditions were optimized for the reaction of prenyl bromide with phenol, we proceeded to investigate the scope of the reaction with a variety of substituted phenols (Table 2). For convenience, data are reported as percent conversions (directly from GC-MS analysis), though it should be noted that these values, based on crude product yield, correspond well with percent yields. With electron

Table 1 Product Distribution from Reaction of Phenol (**4**, R = H) with Prenyl Bromide with Increasing Equivalents of Montmorillonite K10 Clay (by Weight Relative to Phenol)

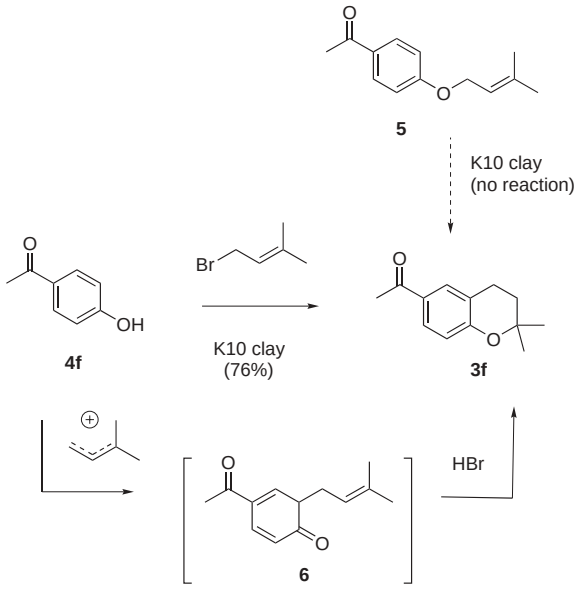
			Product distribution (%)				
Entry	Equiv clay by wt	Time (h)	**4**	**3**	**2**	**1**	Other
1	0.1	2	45	0	5	6	44
2	0.5	2	26	7	19	36	12
3	1	2	9	28	15	15	33
4	2	2	0	33	11	6	50
5	5	2	0	35	0	0	65
6	10	2	0	38	0	0	62
7	20	2	0	67	0	0	33

rich phenols (**4b**–**d**) the reaction proceeded rapidly and with excellent percent conversion to the corresponding benzopyrans (**3b**–**d**). Lower percent conversions were observed for electron deficient phenols (**4f** and **4g**) and the reaction was unsuccessful with 4-nitrophenol (**4h**). With phenol systems where regioisomeric benzopyran products were possible (**4b**,**c**,**i**,**j**), the reaction proceeded with good or complete regioselectivity. Treatment of resorcinol (**4j**) with prenyl bromide in the presence of K10 clay resulted in the generation of a considerable amount of *bis*-prenylated product in addition to a 5:1 mixture of regioisomeric benzopyrans.

Of particular interest from a mechanistic perspective is benzopyran **3f**, which was generated from 4′-hydroxyacetophenone (**4f**) upon treatment with prenyl bromide in the presence of Montmorillonite K10 clay (76% conversion with 24% unreacted phenol detected by GG-MS after 2 h). Previous attempts to generate **3f** from the corresponding allyl aryl ether **5** via clay-catalyzed [1,3] shift were unsuccessful, which suggests that **5** is not an intermediate in the conversion of **4f** to **3f**. We suggest that the benzopyran forms via acid-catalyzed cyclization of intermediate **6**, which results from electrophilic addition of a prenyl carbocation to the phenol at the *ortho*-position (Scheme 1).

Table 2 Scope of Reaction with 20 Equiv K10 Clay in CCl_4

Entry	Phenol (**4**)	Time (h)	Conversion (%) to **3a**–**j**
1	Phenol (**4a**)	2	67
2	3,4-Methylenedioxyphenol (**4b**)	1	91
3	3,4-Dimethoxyphenol (**4c**)	0.5	100
4	4-Methoxyphenol (**4d**)	1	84
5	4-Methylphenol (**4e**)	2	91
6	4′-Hydroxyacetophenone (**4f**)	2	76
7	4-Hydroxybenzaldehyde (**4g**)	2	41
8	4-Nitrophenol (**4h**)	–	–
9	3-Methylphenol (**4i**)	1	54 (2:1 mix of regioisomers)
10	Resorcinol (**4j**)	2	53 (5:1 mix of regioisomers)



Scheme 1 Possible mechanism for the clay-catalyzed reaction of phenols with prenyl bromide

We have demonstrated that 2,2-dimethyl-benzopyrans can be effectively generated from the Montmorillonite K10 clay-catalyzed condensation of prenyl bromide with the corresponding phenols. This methodology represents an attractive and environmentally friendly alternative to more demanding synthetic routes[2] to 2,2-dimethylbenzopyrans and further illustrates the potential of Montmorillonite K10 clay as a valuable resource for natural products synthesis. We are currently investigating other applications of Montmorillonite clays in the synthesis of biologically active natural products.

Proton nuclear magnetic resonance (^{1}H) spectra and carbon-13 (^{13}C) spectra were collected at 400 MHz and 100 MHz, respectively. The proton signal of residual, nondeuterated solvent (δ = 7.26 ppm for $CHCl_3$) was used as an internal reference for ^{1}H NMR spectra. For ^{13}C NMR spectra, chemical shifts are reported relative to the δ = 77.23 ppm resonance of $CDCl_3$. Coupling constants are reported in Hz. Infrared spectra were recorded as thin films on a Nicolet Avatar 360. Gas chromatographic analysis was performed on a Hewlett Packard 5890 Series II gas chromatograph with a 5971 Series mass selective detector. Column chromatography was performed using Selecto Scientific (70–150 mesh) silica gel. All reagents and solvents were used as purchased from the manufacturer, without further purification. In a typical experiment, a slurry of the clay in carbon tetrachloride (ca. 5 mL) was treated with the phenol (1 mmol), followed by addition of prenyl bromide (1 mmol). At periodic intervals, an aliquot (100 μL) of the reaction mixture was re-

moved, filtered, diluted with CH_2Cl_2, and analyzed by GC-MS. On a preparative scale, the reaction mixture was vacuum filtered, washing with CH_2Cl_2 and the filtrate concentrated under vacuum. The recovered clay was reactivated by washing with MeOH and could be reused at least 2 times with minimal decrease in activity. The crude product mixture was purified by column chromatography with silica gel, eluting with hexane–EtOAc. Spectral data for 2,2-dimethylbenzopyrans **3a–g** follow. **3,4-Dihydro-2,2-dimethyl-2*H*-1-benzopyran (3a):**[8] IR: 2928, 1595, 1489, 1455, 1369, 1219, 1157, 1122, 947, 883, 813, 754, 691 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.24 (m, 1 H), 7.08 (m, 1 H), 6.93 (m, 1 H), 6.84 (m, 1 H), 2.77 (t, *J* = 6.8 Hz, 2 H), 1.80 (t, *J* = 6.8 Hz, 2 H), 1.33 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 129.6, 129.4, 127.2, 119.6, 117.2, 115.3, 74.0, 32.8, 26.9, 22.4 ppm. **7,8-Dihydro-6,6-dimethyl-6*H*-1,3-dioxolo[4,5-γ][1]benzopyran (3b):**[9] IR 2975, 2930, 2770, 1629, 1503, 1480, 1439, 1383, 1360, 1346, 1326, 1269, 1234, 1184, 1154, 1121, 1071, 1039, 940, 926, 896, 856, 832, 776, 743, 655, 519, 437 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 6.49 (s, 1 H), 6.33 (s, 1 H), 5.83 (s, 2 H), 2.66 (t, *J* = 6.9 Hz, 2 H), 1.74 (t, *J* = 6.9 Hz, 2 H), 1.29 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 148.4, 146.4, 140.9, 112.2, 108.0, 100.6, 98.9, 73.8, 32.8, 26.6, 22.6 ppm. **3,4-Dihydro-6,7-dimethoxy-2,2-dimethyl-2*H*-1-benzopyran (3c):**[8] IR: 2972, 2933, 1619, 1514, 1451, 1411, 1383, 1368, 1275, 1242, 1196, 1154, 1123, 1021, 1000, 923, 902, 851, 819 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 6.55 (s, 1 H), 6.37 (s, 1 H), 3.81 (s, 6 H), 2.69 (t, *J* = 6.7 Hz, 2 H), 1.78 (t,, *J* = 6.7 Hz, 2 H), 1.32 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 148.4, 147.6, 142.6, 112.2, 111.2, 101.2, 73.9, 56.4, 55.8, 33.0, 26.7, 22.1 ppm. **3,4-Dihydro-6-methoxy-2,2-dimethyl-2*H*-1-benzo-pyran (3d):**[8] IR: 3409, 2973, 2932, 1611, 1495, 1465, 1383, 1369, 1321, 1274, 1247, 1202, 1158, 1122, 1038, 923, 890, 844, 809, 724, 514, 448 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 6.96 (m, 1 H), 6.68 (m, 1 H), 6.60 (s, 1 H), 3.75 (s, 3 H), 275 (t, *J* = 7.0 Hz, 2 H), 1.81 (m, 2 H), 1.31 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 152.9, 148.0, 117.7, 113.9, 113.4, 111.1, 73.8, 55.7, 32.8, 26.8, 22.8 ppm. **3,4-Dihydro-2,2,6-trimethyl-2*H*-1-benzopyran (3e):**[8] IR: 2975, 2929, 2860, 1619, 1586, 1498, 1451, 1385, 1498, 1452, 1385, 1368, 1346, 1301, 1278, 1253, 1208, 1157, 1123, 1055, 1035, 996, 947, 919, 892, 814, 788, 733, 706, 659, 566, 544, 517, 494, 466, 445 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 6.87 (m, 2 H), 6.67 (d, *J* = 8.1 Hz, 1 H), 2.73 (t, *J* = 6.6 Hz, 2 H), 2.24, (s, 3 H), 1.78 (t, *J* = 6.6 Hz, 2 H), 1.32 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 151.7, 129.8, 128.7, 127.9, 120.5, 116.9, 73.9, 32.9, 26.8, 22.4, 20.4 ppm. **1-(3,4-Dihydro-2,2-dimethyl-2*H*-1-benzopyran-6-yl)-ethanone (3f):**[10] IR: 2975, 2932, 1675, 1065, 1575, 1495, 1451, 1425, 1451, 1384, 1358, 1316, 1264, 1240, 1156, 1112, 1018, 946, 880, 828, 723, 701, 603, 581, 494, 447 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.74 (m, 2 H), 6.79 (d, *J* = 8.6 Hz, 1 H), 2.82 (t, *J* = 6.7 Hz, 2 H), 2.53 (s, 3 H), 1.83 (t, *J* = 6.7 Hz, 2 H), 1.36 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 197.0, 158.6, 130.5, 129.4, 128.3, 120.7, 117.2, 75.5, 32.5, 26.9, 26.24, 23.3 ppm. **3,4-dihydro-2,2-Dimethyl-2*H*-1-benzopyran-6-carboxaldehyde (3g):**[8] IR: 2974, 2930, 2731, 1690, 1604, 1576, 1493, 1451, 1384, 1371, 1349, 1325, 1270, 1236, 1210, 1454, 1119, 1016, 949, 880, 827, 764, 745, 670, 641, 552, 493, 449 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 9.83 (s, 1 H), 7.56 (m, 2 H), 6.87 (d, *J* = 9.0 Hz, 1 H), 2.85 (t, *J* = 6.9 Hz, 2 H), 1.85 (t, *J* = 6.7 Hz, 2 H), 1.37 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 191.0, 159.8, 131.9, 129.6, 129.1, 121.4, 117.9, 75.9, 32.4, 26.9, 22.2 ppm.

Acknowledgment

DePaul University's College of Liberal Arts & Science and the Claire Boothe Luce Foundation are gratefully acknowledged for funding and support.

References

(1) (a) Hepworth, J. D.; Gabbutt, C. D.; Heron, M. B. In *Comprehensive Heterocyclic Chemistry II*; Pergamon: New York, **1996**, 301–350. (b) Green, G. R.; Evans, J. M.; Vong, A. K. In *Comprehensive Heterocyclic Chemistry II*; Pergamon: New York, **1996**, 469–500.

(2) (a) Jin, T.-S.; Xiao, J.-C.; Wang, S.-J.; Li, T.-S.; Song, X.-R. *Synlett* **2003**, 2001. (b) Pachamuthu, K.; Schmidt, R. R. *Synlett* **2003**, 1351. (c) Mann, A.; Muller, C.; Tyrrell, E. *J. Chem. Soc., Perkin Trans. 1* **1998**, *8*, 1427. (d) Kalena, G. P.; Jain, A.; Banerji, A. *Molecules* **1997**, *2*, 100. (e) Bigi, F.; Carloni, S.; Maggi, R.; Muchetti, C.; Sartori, G. *J. Org. Chem.* **1997**, *62*, 7024. (f) Muller, C.; Tyrrell, E. *Abstracts of Papers*, 213th National Meeting of the American Chemical Society, San Francisco, 1997; American Chemical Society: Washington, DC, 1997; ORGN-588. (g) Berge, J.; Claridge, S.; Mann, A.; Muller, C.; Tyrrell, E. *Tetrahedron Lett.* **1997**, *38*, 685. (h) Giles, R. G. F.; Joll, C. A. *Tetrahedron Lett.* **1995**, *36*, 1125. (i) Ismail, F. M. D.; Hilton, M. J.; Stefinovic, M. *Tetrahedron Lett.* **1992**, *33*, 3795. (j) Kametani, T.; Kigasawa, K.; Hiiragi, M.; Ishimaru, H.; Wagatsuma, N. *Heterocycles* **1975**, *3*, 521.

(3) (a) Nicolaou, K. C.; Pfefferkorn, J. A.; Roeker, A. J.; Cao, G.-Q.; Barluenga, S.; Mitchell, H. J. *J. Am. Chem. Soc.* **2000**, *122*, 9939. (b) Nicolaou, K. C.; Pfefferkorn, J. A.; Cao, G.-Q. *Angew. Chem. Int. Ed.* **2000**, *39*, 734. (c) Nicolaou, K. C.; Cao, G. Q.; Pfefferkorn, J. A. *Angew. Chem. Int. Ed.* **2000**, *39*, 739.

(4) Nagendrappa, G. *Resonance* **2002**, 64.

(5) For one example, see: Corey, E. J.; Wu, L. I. *J. Am. Chem. Soc.* **1993**, *115*, 9327.

(6) Dintzner, M. R.; Morse, K. M.; McClelland, K. M.; Coligado, D. M. *Tetrahedron Lett.* **2004**, *45*, 79.

(7) Dauben, W. G.; Cogen, J. M.; Behar, V. *Tetrahedron Lett.* **1990**, *31*, 3241.

(8) Bernard, A. M.; Cocco, M. T.; Onnis, V.; Piras, P. P. *Synthesis* **1998**, 256.

(9) Camps, F.; Coll, J.; Messeguer, A.; Pericas, M. A.; Ricart, S. *Synthesis* **1979**, 126.

(10) Tsukayama, M.; Kikuchi, M.; Kawamura, Y. *Heterocycles* **1994**, *38*, 1487.