Pergamon

Tetrahedron Letters, Vol. 38, No. 27, pp. 4725-4728, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00949-0

The Florisil® Catalyzed [1,3]-Sigmatropic Shift of Allyl Phenyl Ethers - An Entryway Into Novel Mycophenolic Acid Analogues†

Francisco X. Talamás*, David B. Smith*, Alicia Cervantes, Fidencio Franco, Serena T. Cutler, David G. Loughhead, David J. Morgans, Jr., and Robert J. Weikert

Syntex, S. A. de C. V., División de Investigación
Apartado Postal 272 (CIVAC)
Jiutepec, Morelos, México, cp 62500

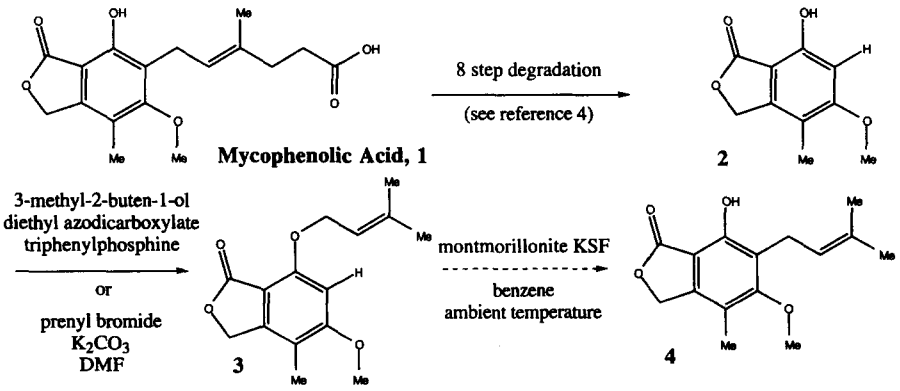
and

Roche Bioscience
Inflammatory Diseases Unit
3401 Hillview Avenue, Palo Alto, CA 94304

Abstract: Florisil® was found to be effective in promoting the [1,3]-sigmatropic shift of mycophenolic acid related allyl phenyl ethers. Several novel mycophenolic acid analogues were thus prepared. Through a crossover experiment using two deuterated analogues of the model system, the reaction was shown to be intramolecular.

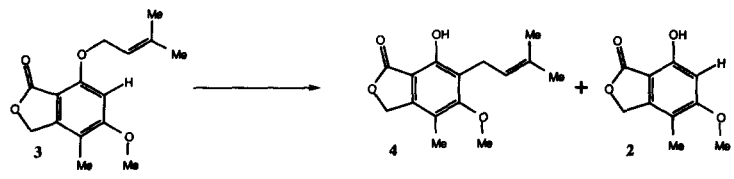
In 1990, Dauben reported on the montmorillonite clay catalyzed [1,3]-sigmatropic rearrangement of allyl phenyl ethers.[1,2] Due to our interest in side-chain variants of the immunosuppressive agent mycophenolic acid[3] (**1**, Scheme 1), we have investigated the Dauben protocol for utility in this regard.

Scheme 1



Although we were readily able to reproduce the [1,3]-shift using the reported Dauben substrates, our mycophenolic acid related model system **3** gave only recovered starting material under those conditions.[4] Using more forcing conditions (T = 70 °C), near complete loss of the prenyl group of **3** was observed, along with only about a 10% yield of the desired product **4**. In order to effect a more efficient transformation using our system **3**, we began an examination of various conditions that might prove useful. A survey of our results is recorded in the Table.

Table



Entry[a]	Additive	Solvent (time)	Temperature	%3	%4	%2
1	montmorillonite KSF	benzene (21h)	ambient	95	-	5
2	montmorillonite KSF	benzene (16h)	70 °C	-	10	90
3	trifluoroacetic acid	toluene (12h)	ambient	20	-	80
4	$ZnCl_2$	toluene (20h)	ambient	-	24[b]	56[b]
5	$ZnCl_2$	CH_2Cl_2 (1h)	ambient	-	40	60
6	$ZnBr_2$	toluene (10m)	110 °C	-	-	100
7	$BF_3 \cdot Et_2O$	CH_2Cl_2 (15h)	0 °C	-	<5	>95
8	Florisil®	toluene (3h)	110 °C	-	50[b]	20[b]
9	silica (flash)	toluene (3h)	110 °C	20	40	40
10	alumina	toluene (2h)	110 °C	-	-	100

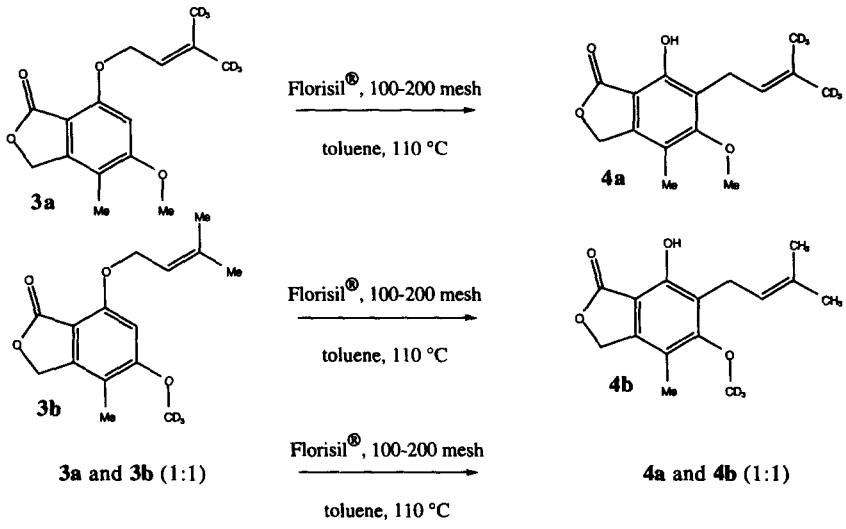
a - This data is based on 250 MHz ^1H NMR spectra of the crude reaction products.

b - Isolated yield of purified, fully characterized product.

Our best results were obtained using 100-200 mesh Florisil® at 110 °C in toluene (Table entry 8). Under these conditions, we were able to isolate a 50-60% yield of the desired [1,3]-rearrangement product **4**. We also recovered ca. 20% of material **2** resulting from simple loss of the prenyl group under these conditions. Also somewhat effective in promoting the desired transformation was zinc chloride (Table entries 4 and 5). Attempts to improve the zinc related results by changing the counter ion or reaction conditions were unsuccessful. Silica gel also gave some desired rearrangement (Table entry 9), and with boron trifluoride a trace of the desired product was evident (Table entry 7). Use of a variety of other reagents gave only mixtures of unreacted **3** and de-prenylation to **2**.

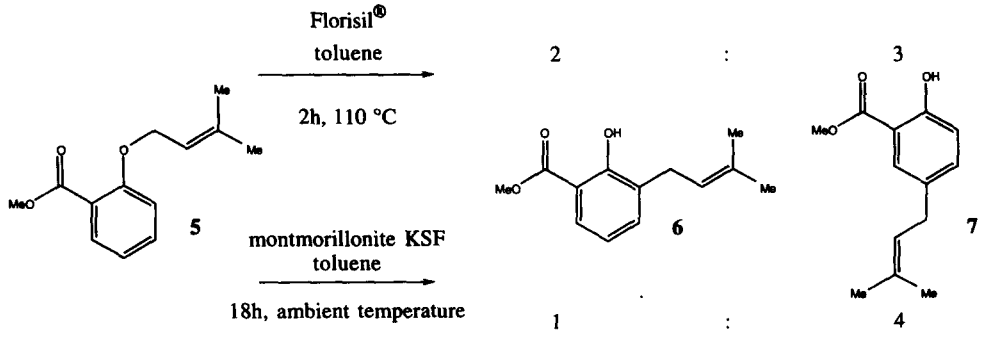
The data presented in the Table show that in every instance where **4** is formed, **2** is a significant by-product. We were curious as to whether this loss of the prenyl group occurs as a side-reaction that may be preventable, or if it occurs as an unavoidable by-product of an intermolecular reaction in which the product is formed *via* a disconnection/reconnection of the prenyl moiety. The classic crossover experiment was performed and the reaction was demonstrated to be intramolecular (Scheme 2).[5] Thus, it may be possible to find a set of conditions that avoids de-prenylation to **2** entirely.

Scheme 2



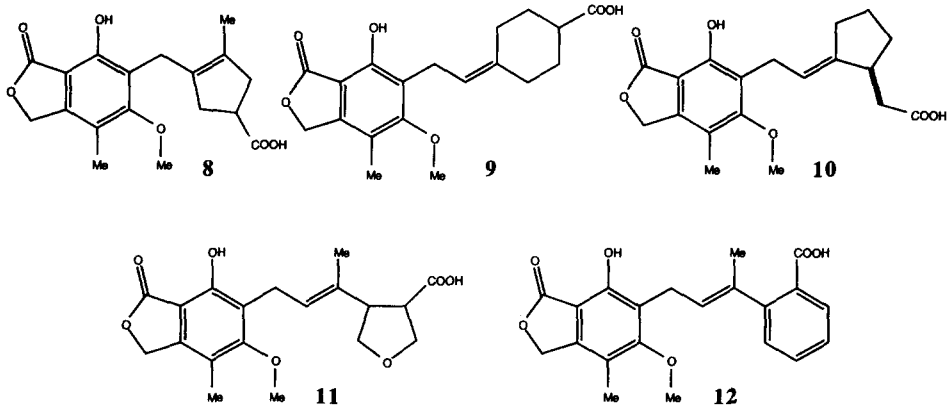
The simple system **5** was constructed to combine an electronic effect contained within the mycophenolic acid nucleus with the generally less substituted nature of the successful montmorillonite KSF substrates (Scheme 3).[1,2] This construct underwent efficient rearrangement under both the Florisil® and the Dauben protocols. With Florisil®, a near 1:1 mixture of the ortho (**6**) and para (**7**) products was obtained, whereas montmorillonite KSF gave a 1:4 ratio favoring the para product **7**. Thus, the regiochemical outcome of these Lewis acid mediated shifts is seen to be highly substrate and condition dependent, and an exploration of various conditions may be needed for every new substrate. Our Florisil® catalyzed conditions represent a complimentary alternative to the Dauben protocol that may prove useful in some instances.

Scheme 3



Finally, using our optimized conditions, a series of mycophenolic acid analogues were prepared (**8** - **12**, Scheme 4). Following allyl phenyl ether formation from the appropriate allylic alcohols under Mitsunobu coupling conditions, the ethers were subjected to heating in toluene for several hours in the presence of 10X by weight of 100-200 mesh Florisil®. Hydrolysis of the ester functionality then provided the mycophenolic acid analogues directly. Full details concerning the synthesis, characterization and biological activity of these and related compounds will be the subject of future manuscripts.[6]

Scheme 4



References and Notes

† This letter is dedicated to the late Professor William G. Dauben.

* Address correspondence to these authors at the Palo Alto address.

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

2. For an application of the Dauben procedure in the context of a total synthesis, see: Corey, E. J.; Wu, L. I. *J. Am. Chem. Soc.* **1993**, *115*, 9327.

3. (a) Nelson, P. H.; Eugui, E.; Wang, C. C.; Allison, A. C. *J. Med. Chem.* **1990**, *33*, 833. (b) Smith, D. B.; Waltos, A. M.; Loughhead, D. G.; Weikert, R. J.; Morgans, D. J. Jr.; Rohloff, J. C.; Link, J. O.; Zhu, R. *J. Org. Chem.* **1996**, *61*, 2236.

4. Compound **2** used in this study was prepared from compound **1** using an eight step sequence. This protocol was first worked out by Eric J. Sjogren of these laboratories and the details will be reported in a future paper.[6] For alternate syntheses of **2**, see: a) Patterson, J. W. *Tetrahedron* **1993**, *49*, 4789. b) Watanabe, M.; Tsukazaki, M.; Hamada, Y.; Iwao, M.; Furukawa, S. *Chem. Pharm. Bull.* **1989**, *37*, 2948.

5. For information and references related to the preparation of the deuterated substrates **3a** and **3b**, and their use in a related investigation, see: Smith, D. B.; Elworthy, T. R.; Morgans, D. J. Jr.; Nelson, J. T.; Patterson, J. W.; Vasquez, A.; Waltos, A. M. *Tetrahedron Lett.* **1996**, *37*, 21.

6. Smith, D. B.; Talamas, F. X.; Morgans, D. J. Jr., manuscripts in preparation.

(*Received in USA* 1 *May* 1997; *accepted* 8 *May* 1997)