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Investigation of an Unusual Rearrangement‡

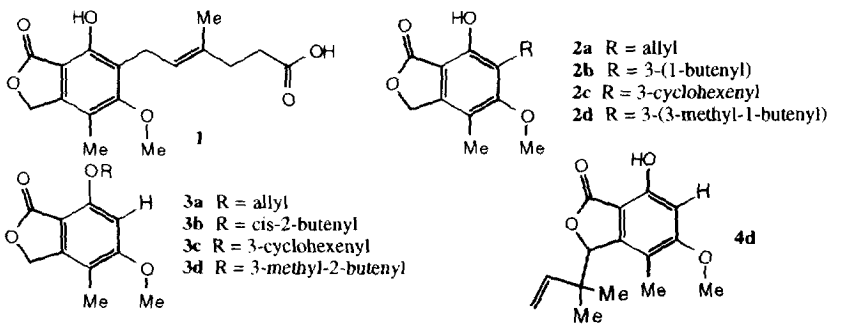
David B. Smith*, Todd R. Elworthy, David J. Morgans, Jr., Janis T. Nelson†, John W. Patterson, Alfredo Vasquez, and Ann Marie Waltos

Institute of Organic Chemistry
and
†Institute of Analytical Research
Syntex Discovery Research
3401 Hillview Avenue, Palo Alto, CA 94304

Abstract: An unusual rearrangement of allyl phenyl ethers 3 related to mycophenolic acid has been investigated. The intramolecularity of the rearrangement has been established via a crossover experiment.

While engaged in a medicinal chemistry program centered about the synthesis of sidechain analogues of mycophenolic acid (**1**), we required access to hexasubstituted aromatic systems such as **2a-d** (Figure 1).[1] Compounds **2a-c** were routinely prepared via Claisen rearrangement[2] of the corresponding allyl phenyl ethers **3a-c**, however, the analogous reaction to form **2d** from the appropriate prenyl phenyl ether **3d** was less straightforward. Instead of obtaining the expected **2d**, unprecedented rearrangement to **4d** was observed. The details of our investigation of the unusual rearrangement of this system are described herein.

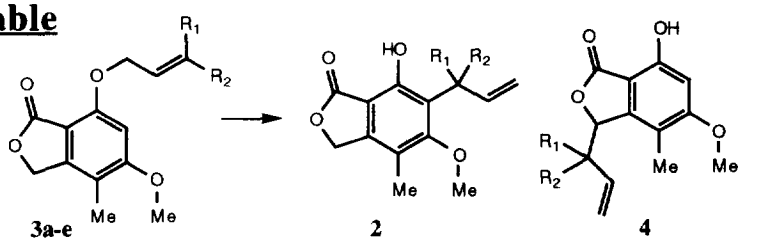
Figure 1

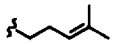
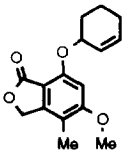


From the outset in our attempts to prepare **2d**, we realized that the rearrangement of highly substituted systems such as **3d** could be problematic.[3] We were nonetheless quite surprised to discover that under our standard conditions (vide infra), **3d** had rearranged to afford **4d** as the only cyclo-rearranged product. A mechanism that accounts for the unusual product is given in Scheme 1. Initially, our attempts focused on employment of known strategies[3] designed to trap the (presumed) intermediate phenol **2d**. Under one set of conditions reported[3a] to suppress *anomalous* Claisen rearrangement, formation of **4d** occurred with a marked

improvement in yield (81%). The facility of the unusual rearrangement to **4d** prompted us to explore both the generality and the mechanism of the reaction in greater detail.

Table



R_1	R_2	Substrate	Conditions	2	4
H	H	**3a**	1	42%	9%
			2	25%	16%
			3	45%	1%
Me	H	**3b**	1	65%	10%
			2	65%	10%
			3	40%	0.5%
Me	Me	**3d**	1	--	35%
			2	--	81%
			3	--	trace
Me		**3e**	1	--	51%
			2	--	52%
			3	--	trace
		**3c**	1	77%	--
			2	68%	--
			3	14%	--

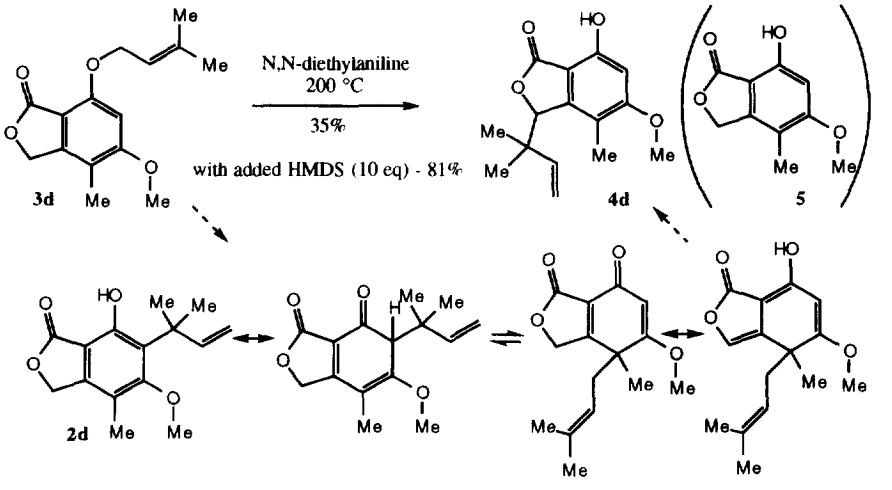
Conditions: 1 - Diethylaniline, 200 °C. 2 - Diethylaniline, 200 °C, HMDS. 3 - Tetramethylbenzene, 200 °C. Yields refer to isolated yields of purified products.

Listed in the Table are the results from several substrates we chose to examine.[4,5] Under our standard conditions (diethylaniline, 200 °C), the unusual rearrangement product predominates only in the highly substituted prenyl systems. Using those same conditions, we were able to detect 9-10% of the unusual product in the rearrangement of the ethers **3a** and **3b**. Under non-basic conditions (tetramethylbenzene, 200

°C), we were able to detect ca. 1% of the unusual product with substrates **3a** and **3b**. Following conditions reported by Fukuyama[3a] to suppress anomalous rearrangement (addition of hexamethyldisilazane, HMDS), a substantial improvement in the yield of the unusual product was seen for the rearrangement of **3d**.[6] With the cyclic allyl phenyl ether **3c**, we observed only normal [3,3] rearrangement under all conditions examined.

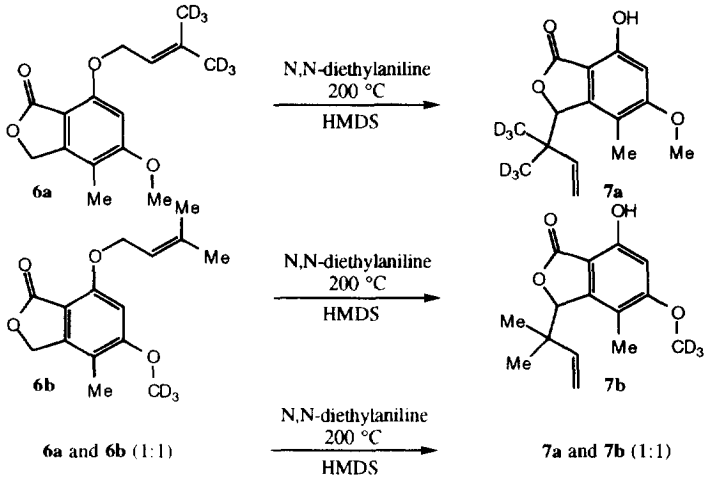
This increase in yield associated with the presence of HMDS was observed mainly in the 3,3-disubstituted system **3d**. The addition of HMDS appears to suppress formation of **5**, a major sideproduct observed for this substrate in the absence of HMDS (Scheme 1).

Scheme 1



In order to rule out the possibility of an intermolecular pathway, we prepared the labeled compounds **6a** and **6b** (Scheme 2).[7] Individually, these compounds were found to rearrange smoothly upon heating in diethylaniline in the presence of HMDS to afford compounds **7a** and **7b**.

Scheme 2



Importantly, a 1:1 mixture of **6a** and **6b**, subjected to the same conditions, gave only **7a** and **7b**; no crossover occurred and the reaction must be intramolecular.

In summary, an unusual rearrangement of substituted allyl phenyl ethers related to mycophenolic acid has been investigated. The reaction is most efficient for the 3,3-disubstituted substrates, but can deliver useful amounts of the less substituted congeners. The cyclic allylphenyl ether **3c** reacted only via the normal [3,3] pathway. By way of a crossover experiment using two deuterated analogues of **3d**, the intramolecularity of the unusual rearrangement has been established.

References and Notes

‡ Contribution #926 from the Institute of Organic Chemistry. Address correspondence to Roche Bioscience, 3401 Hillview Avenue, Palo Alto, California 94304.

1. Several manuscripts concerning the details of the synthesis and biological properties of mycophenolic acid analogues are in progress and will appear in due course. For previous work from these laboratories, see: Nelson, P. H.; Eugui, E.; Wang, C. C.; Allison, A. C. *J. Med. Chem.* **1990**, *33*, 833.

2. Claisen, L. *Chem. Ber.* **1912**, *45*, 3157.

3. a) Fukuyama, T.; Tangqing, L.; Peng, G. *Tetrahedron Lett.* **1994**, *35*, 2145. b) Karanewsky, D. S.; Kishi, Y. *J. Org. Chem.* **1976**, *41*, 3026. c) Vdovtsova, E. A. *Zh. Org. Khim.* **1969**, *5*, 498.

4. Substrates **3a-e** were prepared *via* Mitsunobu coupling (review: Mitsunobu, O. *Synthesis*, **1981**, 1) of the appropriate allylic alcohol with phenol **5**. For an efficient preparation of **5**, see: Patterson, J. W. *Tetrahedron* **1993**, *49*, 4789.

5. All substrates and products were fully characterized by ^{1}H and ^{13}C NMR, IR, MS, UV and combustion analysis.

6. Typical procedure (**3d** -> **4d**): A mixture of the aryl ether **3d** (0.20 g, 0.76 mmol) and hexamethyldisilazane (1.6 mL, 7.6 mmol) in diethylaniline (6 mL) was placed under argon atmosphere and heated in a 200 °C oil bath for 16 hours. After cooling to ambient temperature, the reaction was diluted with ethyl acetate and washed with 1 M HCl (5 times). The organic solution was dried over sodium sulfate, then filtered and concentrated under reduced pressure. The residual material was subjected to flash chromatography (hexanes/ethyl acetate 70/30) affording **4d** (0.163 g, 81%) as a solid (mp 166-170 °C). ^{1}H ($CDCl_3$, 300 MHz): 7.88 (br s, 1H, phenolic O<u>H</u>), 6.42 (s, 1H, aromatic C-<u>H</u>), 5.79 (m, 1H, vinylic C<u>H</u>=CH_2), 5.25 (s, 1H, benzylic C<u>H</u>), 5.07 (m, 2H, CH=C<u>H</u>$_2$), 3.88 (s, 3H, OMe), 2.06 (s, 3H, aromatic Me), 1.18 (s, 3H, Me), 1.00 (s, 3H, Me). ^{13}C ($CDCl_3$, 125.7 MHz): 172.3, 165.2, 156.4, 146.6, 143.2, 114.4, 104.4, 98.1, 88.4, 56.2, 43.7, 25.0, 22.1, 14.9. IR (1715 cm^{-1}). MS (262, M^+). Analysis calcd for $C_{15}H_{18}O_4$ C 68.69, H 6.92. Found: C 68.95, H 6.97.

7. Compound **6a** was prepared *via* Mitsunobu coupling of **5** with 3-methyl-d_3-2-buten-1-ol-4,4,4-d_3. For the preparation of this alkenol, see: Leonard, N. J.; Frihart, C. R. *J. Am. Chem. Soc.* **1974**, *96*, 5894. Compound **6b** was prepared using a similar coupling with d_3-**5** and 3-methyl-2-buten-1-ol. For the synthesis of d_3-**5** we adapted the method of Patterson given in reference 4.

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