Notes

New Conditions for Controlled Claisen Rearrangements of Allyl Aryl Ethers

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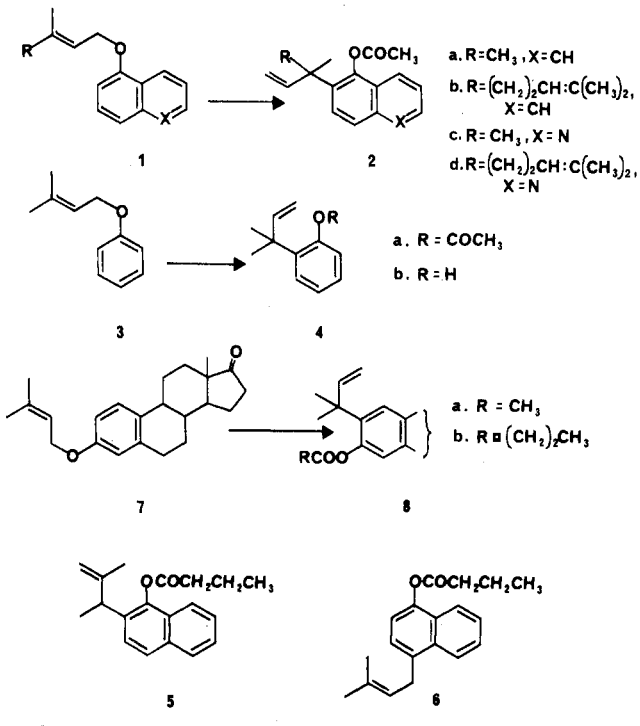
The Claisen rearrangement[1] of allyl aryl ethers is often complicated by the occurrence of abnormal rearrangements leading to structural isomerization of the migrating group, and in some cases by competitive ortho and para migrations. Although the ortho/para ratio can sometimes be effectively controlled by solvent polarity,[2,3] the abnormal rearrangement[4] becomes a serious problem in the rearrangement of ethers bearing γ-alkyl substituents on the allyl group. The occurrence of abnormal and para Claisen products has been attributed[3] to multiple sigmatropic rearrangements. Clearly, in order to obtain good yields of the thermodynamically unstable normal Claisen product, one needs to employ a base to ensure rapid enolization and an efficient trapping agent to prevent participation of the phenolic hydrogen in a (1,5) homosigmatropic hydrogen shift.[3]

In connection with synthetic studies on dihydroteleocidin B,[5] we sought to establish conditions which would afford only normal Claisen products from geranyl aryl ethers. Butyric anhydride in *N,N*-dimethylaniline has been reported[6,7] to be an effective trap of the normal Claisen product. However, this method is not general. Thus, when 3-methyl-2-butenyl 1-naphthyl ether (**1a**) was subjected to the above conditions,[8] the product mixture showed less than 7% of the normal Claisen product. The major products were the abnormal Claisen product (**5**) and the para Claisen product (**6**) in a ratio of 2.7:1, respectively.[9]

We wish to report that normal Claisen products can be obtained in good yields as the corresponding acetate by thermal rearrangement *in the presence of acetic anhydride and either sodium or potassium acetate* (Scheme I). Utilization of these conditions permitted the isolation in 76% yield of **2a**, the normal Claisen product of **1a**, in direct contrast to the results described above using the butyric anhydride/dimethylaniline conditions. Reaction conditions are given in Table I (see Experimental Section for details).

Scheme I



Claisen reported,[10] but without experimental details, that 3-methyl-2-butenyl phenyl ether (**3**) gave the expected normal product (**4b**) when heated in the presence of sodium carbonate. Attempts to repeat this work[3,11] failed to give *o*-(1,1-dimethylallyl)phenol (**4b**). Using our conditions we obtained a 3.5:1[9] mixture of **4a** and phenyl acetate along with minor amounts of unidentified compounds. After $LiAlH_4$ reduction of the crude mixture, **4b** was easily isolated in pure form (see Experimental Section) in an overall 44% yield.[12] Also, when our conditions were applied to the rearrangement of (3-methyl-2-butenyl)estrone ether (**7**), we obtained **8a** in a 41% yield, a substantial improvement over the reported[6] 14% yield using the butyric anhydride/dimethylaniline technique. The lower yields obtained with **3** and **7** are due, at least in part, to a competitive cleavage reaction of **3** and **7** to the corresponding phenols. This difficulty was not encountered with the naphthalene or quinoline derivatives.

Table I

Compd	Registry no.	Base	Reaction temp, °C	Reaction time, h	Product	Mp, °C	Yield,[a] %	Registry no.
1a	59671-60-2	NaOAc	170	3	**2a**	81.5–82.0	76	59671-64-6
1b	59671-61-3	KOAc	170	3	**2b**	130–132[g]	82	59671-65-7
1c	59671-62-4	NaOAc	160	4	**2c**	104–105	80	59671-66-8
1d	59671-63-5	KOAc	160	3.5	**2d**	73–75	76	59671-67-9
3	14309-15-0	NaOAc	200	21	**4a**	105–105.5[g]	44[b]	18272-61-2 (**4b**)
7	6562-03-4	NaOAc	190	15.5	**8a**	179–180	41 (53[e])	59671-68-0
1a[c]		$C_6H_5N(CH_3)_2$	170	3	**5** (2.7), **6** (1)		96[f]	59671-69-1 (**5**) 59671-70-4 (**6**)
7[c,d]		$C_6H_5N(CH_3)_2$	Reflux	15	**8b**	140–141	14	6561-99-5

[a] Isolated yields of pure product. [b] Isolated yield of corresponding free phenol (**4b**) obtained by $LiAlH_4$ reduction of **4a**. [c] Using butyric anhydride as a trapping agent. [d] Reference 6. [e] Corrected for recovered starting material. [f] No attempt was made to separate these two compounds. [g] Melting point of corresponding phenylurethane.

Experimental Section

General. Melting points were taken on a Kofler hot stage apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer 727 spectrometer. NMR spectra were determined on a Varian HA-100 spectrometer using Me_4Si as an internal standard. Analytical gas chromatography was carried out on a Fisher Series 4800 gas chromatograph with a flame ionization detector, using a 6 ft × 0.125 in. column packed with 6% SE-30 in 90–100 mesh Chromosorb W. Microanalyses were performed by Scandinavian Microanalytical Laboratory, Herlev, Denmark.

Allyl aryl ethers were prepared by reaction of either 1-chloro-3-methyl-2-butene or geranyl bromide[13] with the corresponding phenols in the presence of K_2CO_3 in either acetone or DMF and purified by silica gel chromatography.

The following is a typical procedure for Claisen rearrangement.

Rearrangement of 5-Quinolinyl Geranyl Ether. A magnetically stirred mixture of 1.0 g of 5-quinolinyl geranyl ether (**1d**), 1.0 g of KOAc, and 15 ml of Ac_2O was heated at 160 °C (bath temperature) in a heavy-walled sealed tube for 3.5 h in an argon atmosphere. The cooled mixture was poured into 35 ml of distilled water and stirred vigorously for 0.5 h. The resulting aqueous solution was extracted with two 150-ml portions of ether. The combined ether extracts were washed with saturated $NaHCO_3$ solution until the washings were basic. The resulting organic fraction was washed with 50 ml of saturated NaCl solution, dried over $MgSO_4$, and ether evaporated. After filtration through silica gel (15 g; EtOAc/hexane 1/2) the residue (1.098 g) was crystallized from pentane to give 814 mg of **2d** as tan crystals. Purification of the mother liquor by preparative layer chromatography (20 × 20 × 0.25 cm silica gel plate; EtOAc/hexane 1/1) yielded an additional 63 mg of **2d.** After one recrystallization from pentane **2d** was obtained as small plates: mp 73–75 °C; ir (CH_2Cl_2) 1760, 1200 cm^{-1}; NMR ($CDCl_3$) δ 1.48 (s, 3, CH_3), 1.50 (s, 3, CH_3), 1.62 (s, 3, CH_3), 2.34 (s, 3, $OCOCH_3$), 1.7–2.3 (m, 4, CH_2CH_2), ~5.1 (m, 3, $C{=}CH_2$, $C{=}CH$), 6.16 (dd, 1, J = 10, 18 Hz, $CH{=}CH_2$), 7.2–8.9 (m, 5, aromatic).

Anal. Calcd for $C_{21}H_{25}NO_2$: C, 77.98; H, 7.79; N, 4.33. Found: C, 77.91; H, 7.66; N, 4.37.

***o*-(1,1-Dimethylallyl)phenol (4b).** 3-Methyl-2-butenyl phenyl ether (**3**, 1.0 g), 1.0 g of anhydrous NaOAc, and 15 ml of Ac_2O was heated for 21 h under argon in a stainless steel bomb at 200 °C (bath temperature). The mixture was worked up exactly as described in the previous experiment. After evaporation of the ether, the crude residue was filtered through silica gel (15 g; CH_2Cl_2/petroleum ether 1/3) giving 0.976 g of a pale yellow oil. GLC analysis[14] showed *o*-(1,1-dimethylallyl)phenyl acetate (**4a**, 66.5%), phenyl acetate (19%), **3** (6.3%), and two unidentified compounds (total of 8.2%).

The crude mixture dissolved in 15 ml of dry ether was added dropwise to a suspension of 280 mg of $LiAlH_4$ in 50 ml of dry ether under argon. Once the addition was complete the mixture was refluxed for 15 min, cooled in an ice bath, and acidified to pH 1 with 3 N HCl. The organic layer was separated and the aqueous layer back-extracted with 35 ml of ether. The combined ether extracts were washed with two 50-ml portions of saturated NaCl solution, dried over Na_2SO_4, and ether evaporated. The residue was purified by column chromatography (35 g of silica gel; CH_2Cl_2/petroleum ether 1/6) to give 438 mg (44%) of *o*-(1,1-dimethylallyl)phenol (**4b**) as a colorless oil (homogeneous by TLC): ir (CH_2Cl_2) 3460, 1620, 1575, 1480, 1340, 1200, 925 cm^{-1}; NMR ($CDCl_3$) δ 1.40 (s, 6, CH_3), 5.27 (dd, 1, J = 10, 1 Hz, $CH{=}CH_2$), 5.31 (dd, 1, J = 18, 1 Hz, $CH{=}CH_2$), 6.20 (dd, 1, J = 18, 10 Hz, $CH{=}CH_2$), 6.76–7.32 (m, 5, aromatic).

A phenylurethane of **4b** gave mp 105–105.5 °C after one recrystallization from hexane.

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Registry No.—**4a**, 59671-72-6; **4b** phenylurethane, 59671-71-5; phenyl acetate, 122-79-2; 1-chloro-3-methyl-2-butene, 503-60-6; geranyl bromide, 5389-87-7; 1-naphthol, 90-15-3; 5-quinolinol, 578-67-6.

References and Notes

(1) For recent reviews, see A. Jefferson and F. Scheinmann, *Q. Rev., Chem. Soc.*, **22**, 391 (1968); S. J. Rhoads and N. R. Raulins, *Org. React.*, **22**, 1 (1975).
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(6) A. Jefferson and F. Scheinmann, *J. Chem. Soc. C*, 243 (1969).
(7) R. D. H. Murray and M. M. Balantyne, *Tetrahedron*, **26**, 4667 (1970).
(8) Approximately 1 M solution in butyric anhydride/DMA (3/5, v/v).
(9) Product ratios determined by NMR and GLC analysis.
(10) L. Claisen, F. Kremers, F. Roth, and E. Tietze, *J. Prakt. Chem.*, **105**, 65 (1922); L. Claisen and E. Tietze, *Ber.*, **58**, 275 (1925).
(11) E. A. Vdovtsova, *Zh. Org. Khim.*, **5**, 498 (1969). The author claims to detect **4b** by GLC after heating **3** in the presence of Na_2CO_3. However, the compound was not isolated and no spectral data or other means of structure proof were presented.
(12) Yield was not optimized.
(13) Prepared by method of P. R. Oritz de Montellano, Thesis, Harvard University, 1968, p 75, using Aldrich gold label geraniol.
(14) Auto programmer: initial temperature 150 °C; final temperature 225 °C; initial delay 1 min; program rate: 20 °C/min; final delay 1 min.

Pyridopyrimidines. 5. N-Oxidations and Rearrangements in the Pyrido[2,3-*d*]pyrimidine Series

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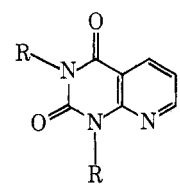
A number of pyrido[2,3-*d*]pyrimidine derivatives have been recently synthesized as potential antitumor,[1-3] carcinogenic,[4] or antibacterial[5] agents. Our interest in the antitumor properties of certain of these compounds has prompted a study of the synthesis and reactivity of the 8-*N*-oxides of 2,4-dioxopyrido[2,3-*d*]pyrimidine (**1**) and its 1,3-dimethyl derivative



1, R = H
2, R = CH_3

2; these starting materials were prepared according to Robins and Hitchings[6] and McLean and Spring,[7] respectively.

The preparation of 2,4-dioxopyrido[2,3-*d*]pyrimidine 8-*N*-oxide (**3**) was carried out very simply in 80% yield by oxidation of **1** with *m*-chloroperbenzoic acid in glacial acetic acid (Scheme I). Because of the lactam structure of **1**, the only nitrogen atom available for N-oxidation should be N-8. Indeed, only one *N*-oxide was formed, which had similar physical properties to the same compound recently prepared[4] by an involved, much lower yield (42%) procedure. Additional support for the structural assignment was found in the uv spectrum; a very intense band (not previously reported[4]) at 237 nm, characteristic of *N*-oxide bonds in heteroaromatic systems,[8] was observed.

Oxidation of the 1,3-dimethyl derivative **2** could not be accomplished, presumably because of steric hindrance of the peri methyl group at N-1. Even trifluoroperacetic acid in refluxing trifluoroacetic acid failed to oxidize compound **2**. A study of the methylation of *N*-oxide **3** was therefore undertaken. The conditions usually used for the N-methylation of heteroaromatic lactam systems, e.g., dimethyl sulfate in aqueous base[7] or methyl iodide in an aprotic solvent in the presence of potassium carbonate,[9] failed to give a reasonable yield of the desired 1,3-dimethyl derivative. The use of diazomethane, which has the smallest steric requirements of all methylating agents, gave a good yield of a dimethylpyrido[2,3-