ability owes to the reduced electron density of the anthraquinone nucleus noted earlier[15] and is further manifested in a fine balance of product distribution where in the presence of triethylamine, solvent capture of TFE supplants rearrangement as the observed reaction path. Third, the 1′-oxygen in averufin, which might be supposed to stabilize the developing positive charge at C-1′ in the transition state, in fact, almost certainly retards the rearrangement process through powerful inductive effects.[16] In summary, these factors may provide a thermodynamic basis for why nidurufin (1, R = OH) is bypassed in the biosynthesis of aflatoxin $B_1$ (6),[4] although oxidation at C-2′ of averufin without hydroxylation would lead in the cationic regime to furanoid products. For the moment, however, any more definitive connection between the in vivo chemistry and these model systems must await further experiments to evaluate other valid mechanistic possibilities.

**Acknowledgment.** The National Institutes of Health are gratefully acknowledged for their support of the work at Hopkins (ES 01670) and Michigan (ES 02851). The high-field NMR spectrometers used were acquired with the assistance of major instrumentation grants (JHU, NSF PCM 83-03176 and NIH RR 01934; UM, NSF CHE 79-09108).

**Registry No.** 7, 98652-28-9; 7A (R = OMOM), 98652-30-3; *cis*-7B (R = OH), 98652-31-4; *trans*-7B (R = OH), 98652-32-5; *trans*-7B (R = OMOM), 98677-59-9; 7C (R = OMOM) (isomer 1), 98719-06-3; 7C (R = OMOM) (isomer 2), 98652-33-6; 8, 98757-09-6; 9, 98652-29-0; 9A, 98652-34-7; 9B, 98652-35-8; 10, 3465-69-8; 11 (R = H), 98652-36-9; 12 (R = H), 98652-37-0; 13 (R′ = H), 98717-44-3; 13 (R′ = $CH_2CF_3$), 98652-41-6; 13 (R′ = Ms), 98652-38-1; 14 (R′ = H), 98717-45-4; 14 (R′ = $CH_2CF_3$), 98717-46-5; 15, 98652-39-2; 16, 98652-40-5; aflatoxin $B_1$, 1162-65-8.

† Research Fellow of the Alfred P. Sloan Foundation 1982–1986; Camille and Henry Dreyfus Teacher–Scholar 1983–1988.

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(16) Martin, J. C.; Bartlett, P. D. *J. Am. Chem. Soc.* **1957**, *79*, 2533–2541. Paquette, L. A.; Dunkin, I. R. *Ibid.* **1972**, *95*, 3067–3068. For an interesting discussion of the effects of methoxyl on carbonium ion rearrangements and an entry into the earlier literature, see: Van Cantfort, C. K.; Coates, R. M. *J. Org. Chem.* **1981**, *46*, 4331–4339.

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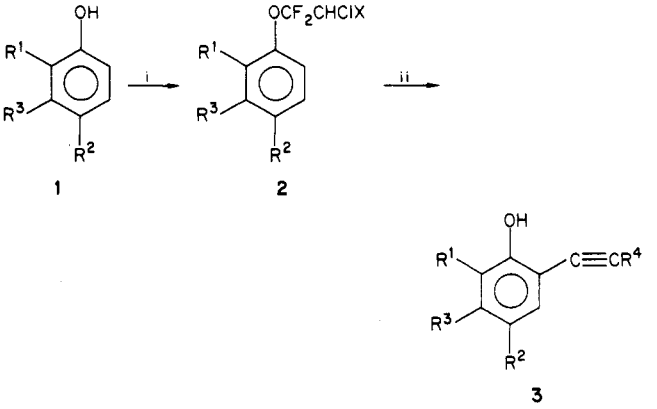
## Halocarbon Chemistry. 1. (2-Hydroxyaryl)acetylenes from Haloethyl Aryl Ethers. A New O to C Rearrangement

*Summary:* A new base-induced (BuLi) oxygen-to-carbon rearrangement is described which involves the direct conversion of phenyl tetra(or tri)haloethyl ethers and the related intermediate phenoxyalkynes to the corresponding 1-(2-hydroxyphenyl)alkynes in good to excellent yield.

*Sir:* We report a new base-induced rearrangement which we believe has potentially broad synthetic utility. The general reaction is shown below (**2** → **3**) and was discovered

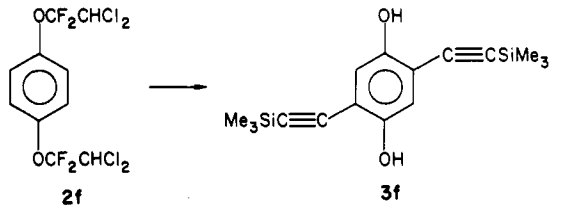



reagents: i, $CF_2CClX$/40%KOH/$Bu_4{}^+N^-OH$/$CH_2Cl_2$; ii, 4 equiv of BuLi/THF/−78 °C to 25 °C

in the course of investigations on the use of simple haloalkyl groups as protecting agents for phenols. It proceeds in good yield in all cases examined so far.

Methods for the synthesis of haloalkyl ethers using, principally, based-catalyzed additions of haloalkenes to phenols have been reported[1] previously but yields were found to be capricious.[2] We have now developed an adaptation[3] of this reaction using phase-transfer catalysis and this generates the required ethers (**2**; X = Cl, F, or H) from the corresponding phenols (**1**) consistently and in high yields in all of the cases studied. In this paper we deal only with examples (**2**) where X = Cl.

The acetylenic phenols (**3**; $R^4$ = H) themselves appear to be somewhat sensitive to aerial oxidation and although they may be isolated as such, they are frequently more conveniently obtained as the C-acetylenic trimethylsilyl derivatives (**3**; $R^4$ = $SiMe_3$). The latter are formed directly in situ simply by quenching the reaction mixture with $(CH_3)_3SiCl$ followed by flash chromatography. The generality of the procedure can be seen from Table I but its versatility perhaps is better illustrated by example **2f** in which the bis(1,1-difluoro-2,2-dichloroethyl) ether of hydroquinone gives the corresponding bisacetylene **3f**.[6]

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(2) In general the use of an homogeneous solution containing a strong base to effect the addition exposes the desired product **2** to dehydrohalogenation and formation of some phenoxyhalo olefin, which we found frequently contaminated the product. Although we have observed that these olefins also are intermediates in the production of **3** from **2**, their presence was a nuisance with regard to obtaining good analytical data.

(3) A general procedure for the preparation of phenolic 1,1-difluoro-2,2-dichloroethyl ethers is as follows: The phenol (50 mequiv) is dissolved in 40% KOH solution (14 mL) to which is added an aqueous solution of 40% $Bu_4N^+OH^-$ (2 mL). To this mixture at 0 °C is added 1,1-dichloro-2,2-difluoroethylene (75 mequiv) and methylene chloride (35 mL). The flask is tightly capped and shaken vigorously at 25 °C for 16 h. Isolation of the product using a normal procedure gives the desired ether in 90% yield.

(4) Satisfactory analytical data were obtained for all new compounds reported.

(5) Compound **3d** was not trapped as the trimethylsilyl derivative because of problems arising out of lithiation ortho to the methoxy group in the product.

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Table I[4,5]

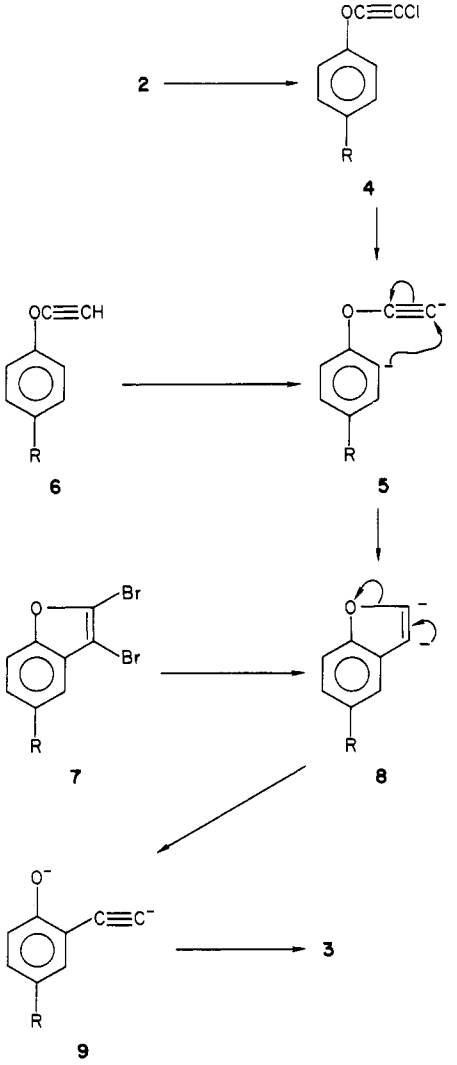
| | 1 | 2 °C/mm | 2 yield, % | 3 | 3 yield, % |
|---|---|---|---|---|---|
| a | $R^1 = R^2 = R^3 = H$ | 71/4 | 85 | $R^1 = R^2 = R^3 = H$; $R^4 = (CH_3)_3Si$ | 80 |
| b | $R^1 = R^3 = H$; $R^2 = C(CH_3)_3$ | 123/1 | 85 | $R^1 = R^3 = H$; $R^2 = C(CO_3)_3$; $R^4 = (CH_3)_3Si$ | 80 |
| c | $R^1 = CH_3$; $R^2 = R^3 = H$ | 84/1.3 | 80 | $R^1 = CH_3$; $R^2 = R^3 = R^4 = H$ | 70 |
| d | $R^1 = R^3 = H$; $R^2 = OCH_3$ | 119/1.5 | 80 | $R^1 = R^3 = R^4 = H$; $R^2 = OCH_3$ | 70 |
| e | $R^1 = C_6H_5$; $R^2 = R^3 = H$ | 82/0.3 | 75 | $R^1 = C_6H_5$; $R^2 = R^3 = H$; $R^4 = (CH_3)_3Si$ | 70 |
| f | $R^1 = R^3 = H$; $R^2 = OH$ (2, $R^2 = OCF_2CHCl_2$) | 98/0.2 | 75 | $R^1 = H$; $R^2 = OH$; $R^3 = C{\equiv}CSi(CH_3)_3$; $R^4 = Si(CH_3)_3$ | 70 |

The following illustrates the general experimental procedure for the preparation of the *C*-silyl derivatives of the acetylenic phenols. The 1,1-difluoro-2,2-dichloroethyl aryl ether (10 mmol) in THF (30 mL) at −78 °C under nitrogen is treated dropwise with butyllithium (41.0 mmol; 20 mL of 2 M solution) in hexane over 10 min with stirring. After 6 h at −78 °C, the mixture is allowed to warm to room temperature overnight and then quenched with $Me_3SiCl$ (1 mL). Petroleum ether (90 mL; bp 35–45 °C) is added and after filtration, the crude material is isolated by evaporation of the filtrate. Flash chromatography (petroleum ether/EtOAc (9:1)) is then utilized both to remove the $OSiMe_3$ group and to purify the product. By this procedure, the desired (2-hydroxyaryl)acetylenic silane is obtained in 70–80% yield.

Investigation of the mechanism quickly revealed in the case of **2b** that the chloroacetylenic ether **4** (R = 4-*t*-Bu) is an intermediate,[7] because the latter is the major product when only 2 equiv of BuLi are used. Presumably in the unsubstituted series **2a**, the chloro compound (**4**; R = H) also is formed with additional BuLi, because phenyl ethynyl ether[8] (**6**; R = H) also gives **3a** in equal yield when treated with 2 equiv[9] of BuLi under the general reaction conditions. Our investigations of the interconversion of dianions **5** and **9** are limited[10] but we believe at this time that the general intermediate involved is the 2,3-bis anion (**8**) of the benzofuran. This type of dianion is known[11] to be stable at −78 °C. We have found that in the simplest case, **8** (R = H), derived from **7** (R = H), rearranges[12] essentially irreversibly when the temperature is raised, to give approximately the same yield of **3a** after quenching as when **2a** is treated with 4 equiv of BuLi. Thus we consider that the mechanism outlined in Scheme I represents the pathway (post-dehalogenation) of this rearrangement and that the driving force is the energy difference between dianions **5** and **9**.

Attempts to extend the reaction to aromatic amines and sulfides corresponding to **2** are under investigation, as are further studies of the synthetic utility of **8** and related dianions.

Scheme I. Mechanistic Diagram




Compounds represented by **3** have synthetic utility because of their facile conversion either to benzofurans (base catalysis)[13,14] or to 2-hydroxyacetophenones (acid catalysis).[15]

(6) Small amounts (<5%) of a second compound are also produced. This may be the 2,3-bisacetylene isomer of **3f** but structure proof is lacking at this point.

(7) It has been observed previously that the analogous 1-chloro-1-alkynes are intermediates in the LDA dehalogenation of terminal 1,2-dichloroalkenes. Kende, A. S.; Fludzinski, P.; Hill, J. H.; Savenson, W.; Clardy, J. *J. Am. Chem. Soc.* **1984**, *106*, 3551.

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(9) The treatment of **6** with 1 equiv of butyllithium gives only the acetylenic anion (Masaki, H.; Miyake, H.; Kori, S.; Tanouchi, T.; Wakatsuta, H.; Arai, Y.; Yamoto, T.; Kajiwara, I.; Konishi, Y.; Tsuda, T.; Matsumoto, K. *J. Med. Chem.* **1980**, *23*, 519) which is stable under the conditions used and which on aqueous workup simply regenerates **6** (R = H) with no trace of the rearrangement product **3a**.

(10) The internal attack of the ortho anion on the acetylenic anion in **5** can be countenanced if the latter is regarded as largely a contact ion pair in which the lithium–carbon bond has substantial covalent character.

(11) Cugnon de Sevricourt, M.; Robba, M. *Bull. Soc. Chim. Fr.* **1977**, *197*, 139, 142.

(12) Attempts to trap dianion **8** during the rearrangement reaction were uniformly unsuccessful. Current evidence suggests that the temperature at which the halo ethers **2** are converted to the acetylenic ethers is higher than the temperature at which **8** is transformed into **9**.

(13) (a) Toda, F.; Nakagawa, M. *Bull. Chem. Soc. Jpn.* **1959**, *32*, 514; **1960**, *33*, 1287. (b) Ried, W. *Angew. Chem.* **1958**, *70*, 273.

(14) Reference 13 deals only with the conversion of disubstituted acetylenes to benzofurans and we were unable to find, by cursory examination of the literature, a case involving a monosubstituted acetylene. However, under the basic conditions cited in ref 13, compound **3d** was converted smoothly to 5-methoxybenzofuran, a natural product first isolated from a mold that grows on oak beer casks. Birkinshaw, J. H.; Chaplen, P.; Findlay, W. P. K. *Biochem. J.* **1957**, *66*, 188.

(15) (a) Stang, P. J. *Prog. Phy. Org. Chem.* **1972**, *10*, 205. (b) Modena, G.; Tonellato, U. *Adv. Phys. Org. Chem.* **1971**, *9*, 185.

(16) Dichlorodifluoroethylene is commercially available from PcR. Research Chem. Inc., Gainesville, FL.

**Acknowledgment.** We thank The Dow Chemical Company for a generous gift of dichlorodifluoroethylene[16] and the National Institutes of Health for a grant (AI-19709) which made this work possible.

**Registry No.** **1a**, 108-95-2; **1b**, 98-54-4; **1c**, 95-48-7; **1d**, 150-76-5; **1e**, 90-43-7; **1f**, 108-46-3; **2a** (X = Cl), 456-61-1; **2b** (X = Cl), 99299-68-0; **2c** (X = Cl), 328-00-7; **2d** (X = Cl), 99299-69-1; **2e** (X = Cl), 99299-70-4; **2f** (X = Cl), 736-32-3; **3a**, 81787-62-4; **3b**, 99299-71-5; **3c**, 99299-72-6; **3d**, 99299-73-7; **3e**, 99299-74-8; **3f**, 99299-75-9; 1,1-dichloro-2,2-difluoroethylene, 79-35-6.

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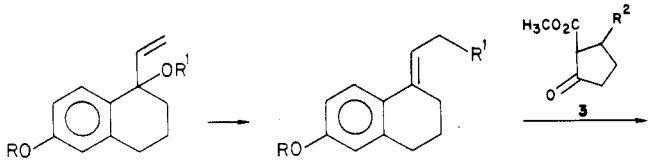
## Halocarbon Chemistry. 2. Use of the 1,1-Difluoro-2,2-dichloroethyl Group for Phenol Protection. Regulation of Ionization during the Torgov Steroid Synthesis[1]

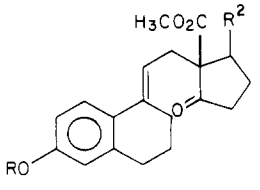
*Summary:* The use of the easily cleavable (dilute base) $HCl_2CCF_2O$ in place of $CH_3O$ in the Torgov steroid intermediate completely inhibits solvolysis of the tertiary alcohol during acetylation and the derived acetate, via a ($\pi$-allyl)Pd complex, is extremely useful for the previously difficult alkylation of cyclic $\beta$-keto esters that are precursors of ring D in steroids.

*Sir:* In many syntheses of estra-1,3,5(10)-trienes the Torgov approach[2] is utilized because of its brevity and simplicity. Early work[3] employing this route utilized **1**, but attempts to convert this alcohol to the more desirable **2** in which $R^1$ is either OH or a good leaving group (e.g.,




**1**, R = $CH_3$; R = H
**6**, R = $CH_3$; $R^1$ = Ac
**9**, R = $CF_2CHCl_2$; $R^1$ = H
**10**, R = $CF_2CHCl_2$; $R^1$ = Ac

**2**, R = $CH_3$
**5**, R = $CH_3$; $R^1$ = $SC(NH_2)_2^+OAc^-$
**7**, R = $CH_3$; $R^1$ = OAc

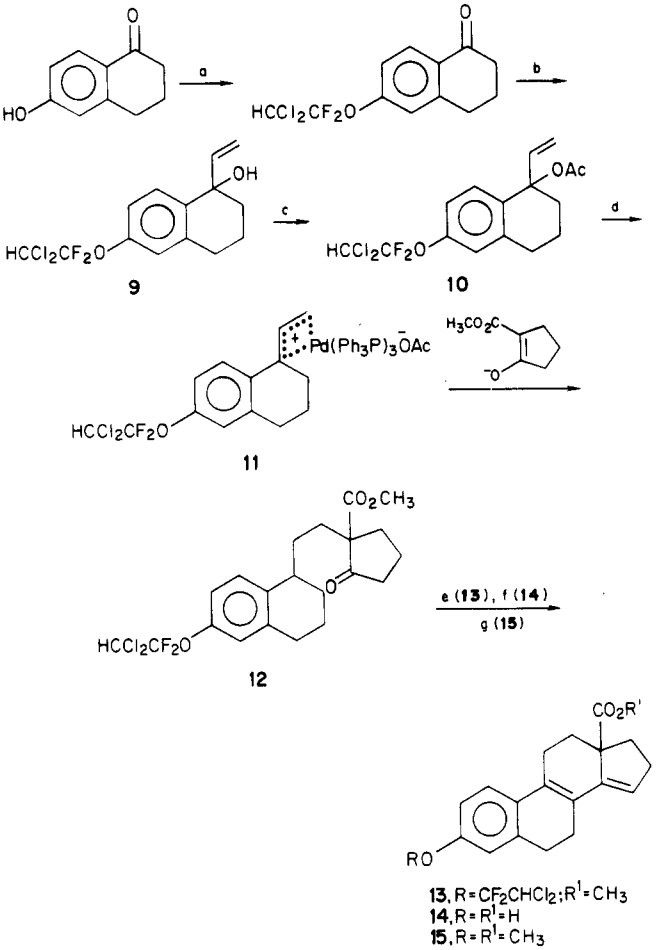



**4**

Br, Cl, or OTs) were thwarted by either the facility with which **1** undergoes dehydration[4] and then dimerization or by poor yields.[5] The only truly useful derivative that has emerged is the isothiouronium acetate[6] **5**, but its use until recently was limited to the alkylation of relatively acidic cyclic 1,3-diketones.[2,6,7] Our own work[8,9] has extended the range of application of **5** to the $\beta$-keto esters **3** but we were dissatisfied with the yields (50–70%) of the alkylation products **4** (R = $CH_3$).

In order to circumvent the problems associated with known Torgov intermediates we elected to try to obtain the acetate **6** or its isomer **7**, with the objective of utilizing

Scheme I[a]




[a] Reagents: (a), 40% KOH, $Bu_4N^+OH^-$, $CF_2=CCl_2$, $CH_2Cl_2$, room temperature, 92%; (b) $CH_2=CHMgBr$, THF, 0 °C, room temperature, 24 h, 91%; (c) $Ac_2O$, DMAP, $CH_2Cl_2$, room temperature, 12 h, 91%; (d) $Pd^0(PPh_3)_4$ (0.05 equiv), toluene, room temperature, 1 h, 2-(methoxycarbonyl)cyclopentanone, DBU, toluene, room temperature, 1 h, mixed, then 80 °C, 24 h, 80%; (e) TFA, room temperature, 5 min, 85%; (f) 6% KOH in $H_2O$/$Me_2SO$ (6:1), room temperature, 12 h then (g) $CH_2N_2$, $Et_2O$ 85%.

(1) For part 1 of this series, see the preceding communication. This communication (part 2) should also be regarded as part 4 of a series of papers on steroids. For part 3 of the steroid series, see ref 9.

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(3) Ananchenko, S. N.; Torgov, I. V *Tetrahedron Lett.* **1963**, 1553.

(4) Torgov, I. V.; Nazarov, I. N. *Zh. Obshch. Khim.* **1959**, *29*, 787.

(5) Crispin, D. J.; Vanstone, A. E.; Whitehurst, J. S. *J. Chem. Soc. C* **1970**, 10.

(6) Kuo, C. H.; Taub, D.; Wendler, N. L. *J. Org. Chem.* **1968**, *33*, 3126.

(7) Windolz, T. B.; Brown, R. D.; Patchett, A. A. *Steroids* **1965**, *6*, 409. Yoshioka, K.; Goto, G.; Asako, T.; Hiraga, K.; Miki, T. *Chem. Commun.* **1971**, 336; Ananchenko, S. N.; Limanov, V. E.; Leonov, V. N.; Rzheznikov V. M.; Torgov, L. V. *Tetrahedron* **1962**, *18*, 1355. An example of a $\beta$-keto ester that can be alkylated by **5** is 2-methyltetranic acid (Simpson, W. R. J.; Babbe, D.; Edwards, J. A.; Fried, J. H. *Tetrahedron Lett.* **1967**, 3209), but the latter unlike most other $\beta$-keto esters is very acidic (p$K$ ~ 3.8).

(8) Magriotis, P. A.; Murray, W. V.; Johnson, F. *Tetrahedron Lett.* **1982**, *23*, 1983.

(9) Magriotis, P. A.; Johnson, F. *J. Org. Chem.* **1984**, *49*, 1460.

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