via Lythgoe coupling[19] into nature 1α,25-dihydroxyvitamin D_3.[18] Such vitamin D_3 hormonally active compounds are becoming popular as clinically useful regulators of such fundamental physiological processes as bone calcium mobilization (e.g., in chemotherapy of osteoporosis)[20] and cell proliferation and differentiation (e.g., in chemotherapy of psoriasis and leukemia).[20,21]

In summary, the overall reaction sequence from pyrone sulfone 1 to A-ring chiron (−)-**9e** required only 14 steps and proceeded in 34.6% overall yield, which compares very favorably indeed with other recent syntheses of the same[18] and similar[22] A-ring units as precursors to vitamin D_3 derivatives. Also of considerable potential is use of a new sulfinyl orthoacetate for efficient conversion of some allylic alcohols into the corresponding dienoate esters via consecutive Claisen rearrangements and sulfoxide β-eliminations occurring at 100 °C *all in one reaction flask*. We are actively pursuring this protocol for asymmetric synthesis of other A-ring units as precursors to analogues of 1α,25-dihydroxyvitamin D_3.

Acknowledgment. We thank the NIH (GM 30052) for financial support and Professor Gilbert Stork for a stimulating discussion on dihydroxyvitamin D_3 synthesis. Purchase of an NMR spectrometer was made possible by the NIH (Grant 1510 RR01934) and by the NSF (Grant PCM-83-03776).

Supplementary Material Available: Characterization data of compounds **3–9** (3 pages). Ordering information is given on any current masthead page.

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1,2-Addition of Sulfur Nucleophiles to the N-Acylated Imine Linkage. A Model Study for the Incorporation of Sulfur Nucleophiles during Metabolism of Acylated Aromatic Amines

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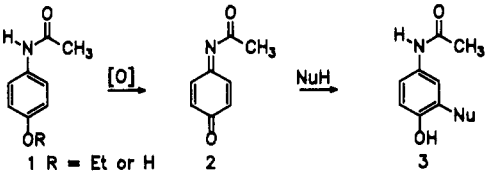
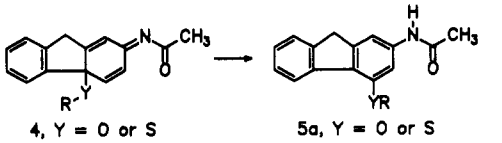
Summary: The imine linkage of an acylated quinone imine ketal reacts with ethanethiol to afford an isolable addition product which subsequently rearranges by a facile 1,2-shift to afford an ortho-substituted aromatic amide.

An understanding of the chemistry involved in the metabolism of acylated aromatic amines is central to establishing the mechanism of toxicity associated with drugs such as acetaminophen[1a-c] and phenacetin[1d-f] and the carcinogenicity of N-hydroxylated amides[2] (e.g., *N*-hydroxy-2-(acetylamino)fluorene). An important step in the metabolism of these compounds is oxidation of the amide nitrogen[1] with eventual production of aromatic substitution products of the parent amide. For example, metabolism of phenacetin (1, R = Et) gives amides[1d] such as **3**. The mechanism for formation of **3** is thought to involve 1,4-addition of a nucleophile to **2**, followed by aromatization. A second proposed mechanism[2a] for effecting aromatic substitution involves formation of a 4-substituted quinone imide intermediate such as **4**, followed by a 1,2-shift and aromatization.





However, the metabolism of (*N*-acetylamino)fluorene, **6**, in the rat affords glutathione conjugates at the 1- and

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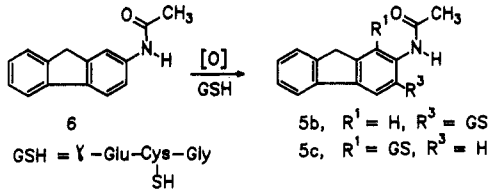
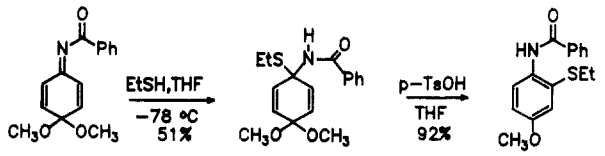
3-positions of the fluorene nucleus, **5b,c**[2a]—*products that could not arise via either of the two mechanisms mentioned above.*[3] We report herein that ethanethiol adds to the carbon–nitrogen double bond of an acylated quinone imine ketal to form a labile, but isolable, adduct which undergoes a facile 1,2-shift, resulting in the formation of an ortho-substituted amide. Chemistry analogous to that described herein would account for the formation of glutathione conjugates at the 1- and 3-positions of **6** and the incorporation of sulfur nucleophiles in the metabolism of acylated amines.



6
GSH = γ-Glu-Cys-Gly
SH

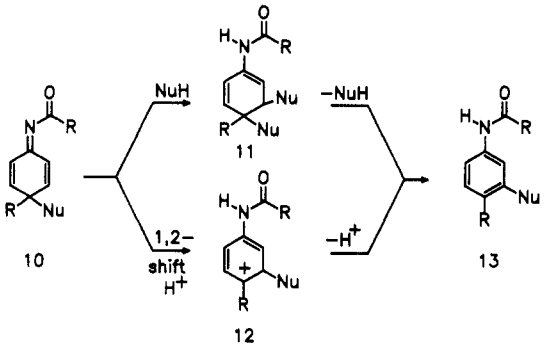
5b, R^1 = H, R^3 = GS
5c, R^1 = GS, R^3 = H

Recently, we reported[5] that the acid-catalyzed reaction of acylated quinone imine ketal **7** with ethanethiol gave primarily the 2′-substituted benzamide **9**. Since the ortho-substitution product was analogous to that observed in the metabolism of (*N*-acetylamino)fluorene noted above, this reaction was studied in more detail. Addition of **7** to a solution of ethanethiol containing a catalytic amount of *p*-toluenesulfonic acid at −78 °C, followed by quenching of the reaction with sodium bicarbonate after 2 min led to a mixture of **7** and a new product identified as **8**. Although **8** is labile, it was obtained in 51% yield (>95% pure) from this reaction mixture by careful fractional crystallization, mp 103–104 °C. The infrared spectrum of **8** indicated the presence of the secondary amide (1645, 1525, and 3295 cm^{-1}), and the ^1H NMR spectrum (250 MHz) essentially established the structure: δ 7.8–7.6 (m, 2 H), 7.5–7.3 (m, 3 H), 6.27 (br s, 1 H), 6.17 (AB q, J = 10 Hz, $\Delta\nu$ = 27 Hz, 4 H), 3.35 (s, 3 H), 3.31 (s, 3 H), 2.49 (q, J = 7 Hz, 2 H), 1.21 (t, J = 7 Hz, 3 H). The ethanethiol adduct **8** rearranges slowly to **9** on standing and rapidly gives **9** with acid catalysis. *This experiment demonstrates for the first time the formation of a 1,2-adduct from a thio group and an acylated quinone imine and the facile 1,2-migration of the thio group with formation of an ortho-substituted amide.*[7]



7 8 9

Scheme I. Two Mechanisms for Nucleophilic Substitution on Quinone Imine Derivatives



10 11 12 13

The facile 1,2-migration of an alkyl sulfur linkage in **8** prompted us to examine the migration of a thiol group from the 4-position of an acylated quinone imine derivative. The two mechanisms considered for the formation of meta-substituted amides in the metabolites of acylated amides are outlined in Scheme I. Recent studies[8] have strongly favored a sequence of 1,4-addition followed by aromatization, **10** → **11** → **13**; however, this mechanistic work dealt with oxygen nucleophiles. A second proposed mechanism involved a 1,2-shift of the group followed by aromatization, **10** → **12** → **13**.

The chemistry of a mixed oxygen–sulfur ketal of an acylated quinone imine derivative would give information about the facility of a 1,2-alkylthio shift in acylated quinone imine systems. Mixed oxygen–sulfur ketals are known;[9] however, they have not been reported for quinone systems, and attempts to prepare these compounds by anodic oxidation of thioanisole derivatives or exchange reactions using **7** were unsuccessful. A different approach—protection of the acylated quinone imine linkage, ketal exchange, and then deprotection to regenerate the acylated quinone imine was examined. To demonstrate the feasability of this method, the exchange of the dimethyl ketal for an ethylene ketal was investigated. Reaction of **7** with potassium cyanide using 18-crown-6 as catalyst gave **14**.[10] The dimethyl ketal of **14** was then exchanged for the ethylene ketal by reaction with ethylene glycol, followed by deblocking with potassium *tert*-butoxide at room temperature to give **15**.

Having established conditions for the exchange reaction with oxygen nucleophiles, **14** was reacted with ethanethiol with acid catalysis to give the mixed ketal **16**.[11] However, deblocking of **16** with potassium *tert*-butoxide under a variety of reaction conditions did not lead to the expected

(3) Products having ortho substitution relative to the amide group have been obtained from solvolysis reactions of *N*-chloroanilines[4a] and *N*-arylhydroxamic acids *O*-methanesulfonates.[4b] In most cases these products arise from reaction of the leaving group with the nitrenium ion in a tight ion pair. However, the nitrenium ion derived from *N*-(sulfonatooxy)-2-(acetylamino)fluorene does lead to incorporation of external chloride.[4d] For studies on nucleophilic capture of nitrenium ions see refs 1g–f, 4d,e.

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(5) Swenton, J. S.; Bonke, B.; Clark, W. M.; Chen, C. P.; Martin, K. V. *J. Org. Chem.* **1990**, *55*, 2027.

(6) This compound, mp 147.0–148.0 °C (lit.[5] mp 147–147.5 °C), showed spectroscopic properties identical with those of an authentic sample.

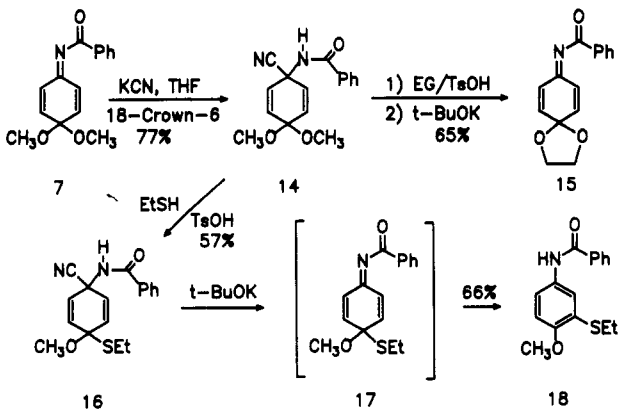
(7) Performing the **8** → **9** conversion in the presence of a 10-fold molar excess of 1-propanethiol resulted in no incorporation of the propanethiol group supporting the intramolecularity of the **8** → **9** transformation. Calder[1b] observed the addition of ethanethiol across the imine linkage of *N*-acetyl-2,6-dimethyl-*p*-benzoquinone imine, whereas the 3,5-dimethyl derivative yielded 3′,5′-dimethyl-2′-(ethylthio)-4′-hydroxyacetamide. He also proposed initial imine attack and migration to form the 2′-substituted adduct; however, this was not demonstrated experimentally. Imine linkages are known to form detectable adducts with water,[1b,h–j] ethanol,[1b] and aniline.[1b]

(8) (a) Scribner, J. D. *J. Am. Chem. Soc.* **1977**, *99*, 7383. (b) Gassman, P. G.; Granrud, J. E. *J. Am. Chem. Soc.* **1984**, *106*, 2448.

(9) Narasimhan, L.; Sanitra, R.; Swenton, J. S. *J. Chem. Soc., Chem. Commun.* **1978**, 719.

(10) We are unaware of this method for formation of α-amino nitriles. For recent papers using α-amino nitriles as protected imines, see: (a) Bunnelle, W. H.; Shevlin, C. G. *Tetrahedron Lett.* **1989**, *30*, 4203. (b) Overman, L. E.; Osawa, T. *J. Am. Chem. Soc.* **1985**, *107*, 1698. (c) Royer, J.; Husson, H. P. *J. Org. Chem.* **1985**, *50*, 670. (d) Royer, J.; Husson, H. P. *Tetrahedron Lett.* **1985**, *26*, 1515.

(11) The double exchange process of a dimethyl ketal for a dithioketal could not be effected in this system. For a similar experience, see: Kim, S.; Park, J. H.; Lee, S. *Tetrahedron Lett.* **1989**, *30*, 6697.



mixed ketal of the acylated quinone imine **17**. Instead, the meta-substituted amide **18**[12] was formed as the exclusive product. Since **15** was cleanly prepared from **14** under these reactions conditions, it appears that **18** results from an extremely rapid 1,2-migration of the ethylthio group in **17**. Thus, if products akin to **4** (Y = S) or **10** (Nu = SR) are formed in metabolic processes of acylated aromatic amines, a 1,2-shift of the alkyl sulfur group to give **5a** or **13** is a viable process.

The results presented herein establish the extremely facile 1,2-shift of an ethylthio group in acylated quinone imine systems. Analogous reactions explain the production of 1- and 3-substituted products from the metabolism of (*N*-acetylamino)fluorene in the rat. These results emphasize the different mechanisms by which oxygen and sulfur nucleophiles may be incorporated into quinone imine type intermediates. In view of the higher nucleophilicity of sulfur relative to oxygen and the presence of sulfur nucleophiles in living systems, the addition of sulfur nucleophiles to the carbon–nitrogen double bond of biologically generated imine systems followed by 1,2-rearrangements may be an important reaction.

Acknowledgment. We acknowledge partial support of this work from the National Institutes of Health.

Supplementary Material Available: Experimental procedures and ^{1}H NMR spectra of the compounds reported in this paper (12 pages). Ordering information is given on any current masthead page.

(12) This compound, mp 181–182 °C (lit.[5] mp 185–185.5 °C), showed spectroscopic properties identical with those of an authentic sample.

A Multistep Rearrangement from 2,2-Disubstituted 1,3-Cyclohexanediones to 3-Substituted 2-Cyclohexenones via Phosphonate Anions and Its Application to a Formal Synthesis of (±)-α-Acoradiene

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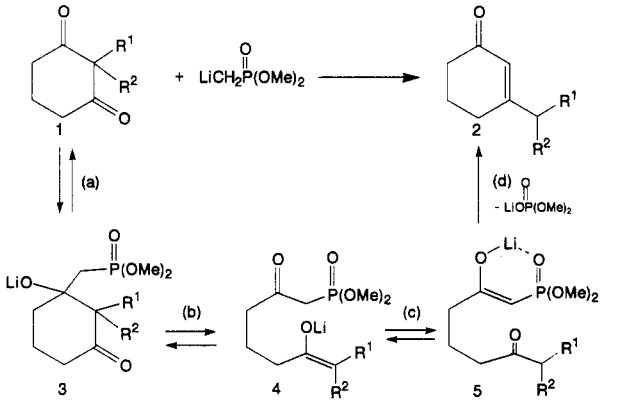
Received April 3, 1990

Summary: The reaction of 2,2-disubstituted 1,3-cyclohexanediones (**1**) with dimethyl methylphosphonate anion in the presence of trimethylsilyl chloride produces 3-substituted 2-cyclohexenones (**2**) in moderate to very good yields. This new overall reaction is accounted for by (a) attack of the phosphonate anion on a carbonyl group, (b) retro-aldol cleavage, (c) reorganization of the acidic proton, and (d) an intramolecular Wadsworth–Emmonds condensation. The new rearrangement is applied to a short synthesis of (±)-α-acoradiene.

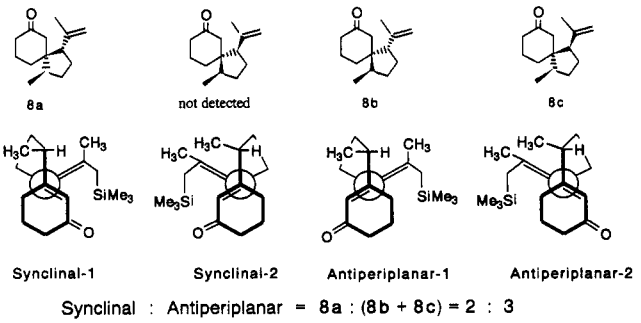
3-Substituted 2-cyclohexenones are versatile building blocks for the synthesis of complex cyclic natural products such as spirocyclic and fused ring sesquiterpenes. The synthetic method most commonly used is based either on the 1,4-addition of organocopper reagents to 3-halogenated(or acetoxy)-2-cyclohexenones[1] or on the 1,2-addition of organolithium or magnesium reagents to 3-alkoxy-2-cyclohexenones.[2] These organometallic-based procedures are subject to inherent drawbacks involved in the use of organometallic reagents; introduction of secondary alkyl groups or of functional groups often causes difficulties.

We report herein a new approach for the synthesis of 3-substituted 2-cyclohexenones via phosphonate anions. The reaction of 2,2-disubstituted 1,3-cyclohexanediones (**1**) with dimethyl methylphosphonate anion produces **2** in moderate to very good yields.

Scheme I



Scheme II



Synclinal : Antiperiplanar = 8a : (8b + 8c) = 2 : 3

(1) (a) Casey, C. P.; Marten, D. F.; Boggs, R. A. *Tetrahedron Lett.* **1973**, 2071. (b) Piers, E.; Nagakura, I. *J. Org. Chem.* **1975**, *40*, 2694.

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