A New Reaction of Nitrenium Ions: Carbon–Carbon Bond-Forming Reactions of *p*-Alkoxy-Substituted Nitrenium Ions†

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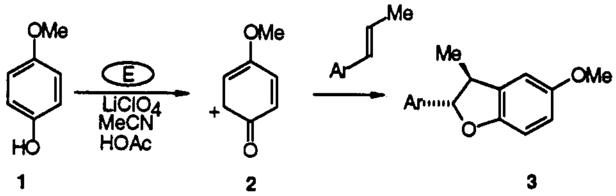
Summary: Reaction of *N*-acylquinone imine ketals with acid generates reactive intermediates which undergo carbon–carbon bond-forming reactions with electron-rich styrene derivatives.

Methods for carbon–carbon bond formation under mild conditions are of paramount interest in synthetic organic chemistry. Electrochemical and chemical oxidations of phenols generate phenoxonium ions which undergo formal 1,3-cycloaddition reactions with electron-rich styrene derivatives to produce substituted dihydrobenzofurans (**1** → **2** → **3**)[1] in one step. A similar reaction of an arylnitrenium ion would give a dihydroindole ring system.



The pioneering studies by Gassman and co-workers[2] have established methods for generating aryl-substituted nitrenium ions and explored the basic reactions of these important intermediates. However, no reactions involving direct carbon–carbon bond formation between an *N*-acylnitrenium ion and olefin have been reported. The useful carbon–carbon bond-forming reaction between phenoxonium ions and electron-rich styrene derivatives prompted a study of nitrenium-like intermediates in the **1** → **2** → **3**-type cycloaddition. We report herein the chemistry of reactive intermediates generated from *N*-acylated quinone imine ketals with electron-rich styrene derivatives. The products from these reactions are dramatically dependent upon the nature of the acid, and a study of the reactions has resulted in an understanding of several facets of the chemistry and an efficient route to certain *ortho*-functionalized anilide derivatives.

Reaction of 3,4-dimethoxy-1-propenylbenzene, **4a**, with intermediates generated by either electrochemical[3] or iodobenzene bis(trifluoroacetate) oxidation[4] of *N*-benzoylanisidine, resulted in complicated reaction mixtures. Thus, ionization of the methoxyl group of a quinone imine ketal such as **5a** was investigated as a route to the reactive intermediates required for the cycloaddition reaction.[5] Reaction of **4a** and **5a** in acetonitrile at room temperature with acetic acid led to a nearly quantitative yield of the aromatic substitution product **6a** (Table I, entry 1). The formation of **6a** reasonably arises from selective protonation of the imine nitrogen followed by Michael addition of acetate to the protonated acylated quinone imine ketal[6] and subsequent aromatization to form **6a**. For nitrenium ion generation, protonation of the methoxyl group, not the imine nitrogen, is required; the formation of **6a** suggests the latter process is occurring. Previous work has shown that *N*-protonation of *N*-acetyl-*p*-benzoquinone imine is favored over *O*-protonation.[7b] Furthermore, the *N*-benzoylquinone imine derivatives are about 30 times less basic than the corresponding *N*-acetyl compounds.[7a] If this were the case, then perhaps the use of the *N*-benzoyl derivative **5b** would lead to generation of the required reactive intermediate. Indeed, reaction of **4a** and **5b** at 25 °C gave the acetate adduct **6b** (28%), the reduced compound **7b** (30%), and two new compounds assigned as **8b** (17%) and **9b** (5%) (entry 2). Although **8b** and **9b** were formed in low yield, the formation of products arising from carbon–carbon bond formation at the *ortho*-position was encouraging. In order to prevent nucleophilic attack of the catalytic acid's conjugate base, *p*-toluenesulfonic acid was employed as the catalyst. In this case, **8b** and **9b** were formed as expected, but a new product assigned as **10b** was the major product from the reaction (entries 3 and 4). The structures for compounds **8b**,[8] **9b**,[11] and **10b**[15] were assigned based on analytical and spectroscopic data (see supplementary material for spectra). Further support for the structure of **9b** was its hydrolysis to **11** (80%).[14]

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† Dedicated to the memory of Paul G. Gassman, a valued colleague and superb scientist.

(1) (a) Wang, S.; Gates, B. D.; Swenton, J. S. *J. Org. Chem.* **1991**, *56*, 1979. (b) Gates, B. D.; Dalidowicz, P.; Tebben, A.; Wang, S.; Swenton, J. S. *Ibid.* **1992**, *57*, 2135 and references cited therein.

(2) (a) Gassman, P. G. *Acc. Chem. Res.* **1970**, *3*, 26. (b) Gassman, P. G.; Hartman, G. D. *J. Am. Chem. Soc.* **1973**, *95*, 449 and references cited therein.

(3) (a) Chen, C.-P.; Chou, C.-T.; Swenton, J. S. *J. Am. Chem. Soc.* **1987**, *109*, 946. (b) Swenton, J. S.; Bonke, B. R.; Chen, C.-P.; Chou, C.-T. *J. Org. Chem.* **1989**, *54*, 51.

(4) Positive iodine reagents are known to generate phenoxonium-like intermediates from phenols; for leading references, see ref 1b. Recently, the oxidation of aromatic amides to *N*-acylated quinone imine ketals by iodosobenzene in methanol has been reported, and an *N*-acylnitrenium ion intermediate could be involved here; see: Barret, R.; Daudon, M. *Tetrahedron Lett.* **1991**, *32*, 2133.

(5) Reactions presented here were conducted on a ≅1 mM scale using solutions of ≅0.06 M *N*-acylquinone imine and ≅0.12 M propenylbenzene derivative. Acetic acid was employed in excess (ca. 3 equiv), and *p*-toluenesulfonic acid was 0.06 M.

(6) Michael addition adducts have been characterized in similar reactions.[8b] See also: Gassman, P. G.; Granrud, J. E. *J. Am. Chem. Soc.* **1984**, *106*, 1498.

(7) (a) Novak, M.; Helmick, J. S.; Oberlies, N.; Rangappa, K. S.; Clark, W. M.; Swenton, J. S. *J. Org. Chem.* **1993**, *58*, 876. (b) Novak, M.; Martin, K. A. *J. Org. Chem.* **1991**, *56*, 1585.

(8) The structure assigned to **8b** was based on combustion analysis, exact mass measurement, and IR, ^{1}H, and ^{13}C NMR spectra. The IR spectrum showed a strong absorption at 1648–1638 cm^{-1} characteristic of a tertiary amide,[9] and the ^{13}C NMR spectrum showed the amide carbonyl absorption at 169.5 ppm. The ^{1}H NMR spectrum showed in addition to benzoyl protons δ 7.4–7.2 (5 H), aromatic protons δ 6.8–6.4 (6 H), and methoxyl protons δ 3.80, 3.79, 3.69 (three singlets, 9 H), a broad singlet[10] at δ 4.8 (1 H), a structured multiplet centered at δ 3.14 (1 H), and a methyl doublet at δ 1.38 (J = 7.1 Hz, 3 H). Spin decoupling experiments strongly support the structure **8b** since irradiation of the proton at δ 4.8 collapses the multiplet centered at δ 3.14 to a quartet (J = 7.1 Hz). Irradiation of the methyl group at δ 1.38 causes the multiplet at δ 3.14 to collapse to a broad singlet.

(9) Nakinishi, K.; Solomon, P. H. *Infrared Absorption Spectroscopy*, 2nd ed.; Holden-Day Inc.: San Francisco, 1977; p 42. Tertiary amide stretching at 1650 cm^{-1} is reported here.

(10) The broad coupling associated with the proton at δ 4.8 may result from the quadrapole moment of nitrogen or inversion at the nitrogen of the amide.

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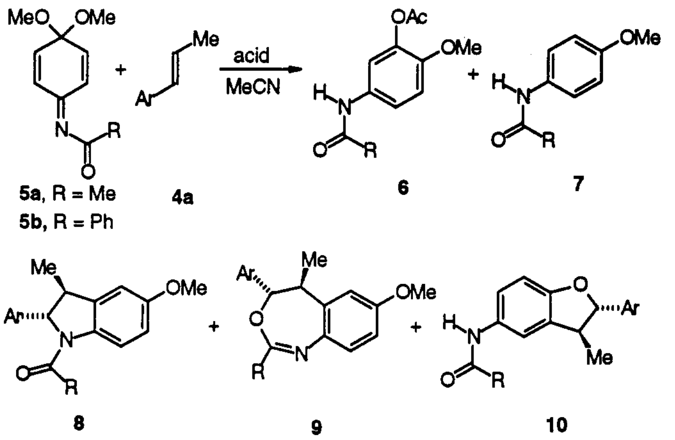
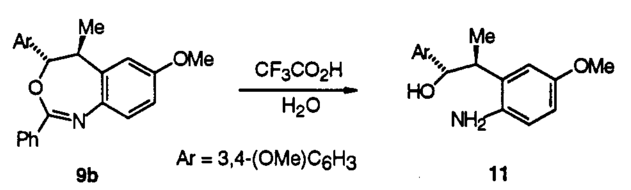


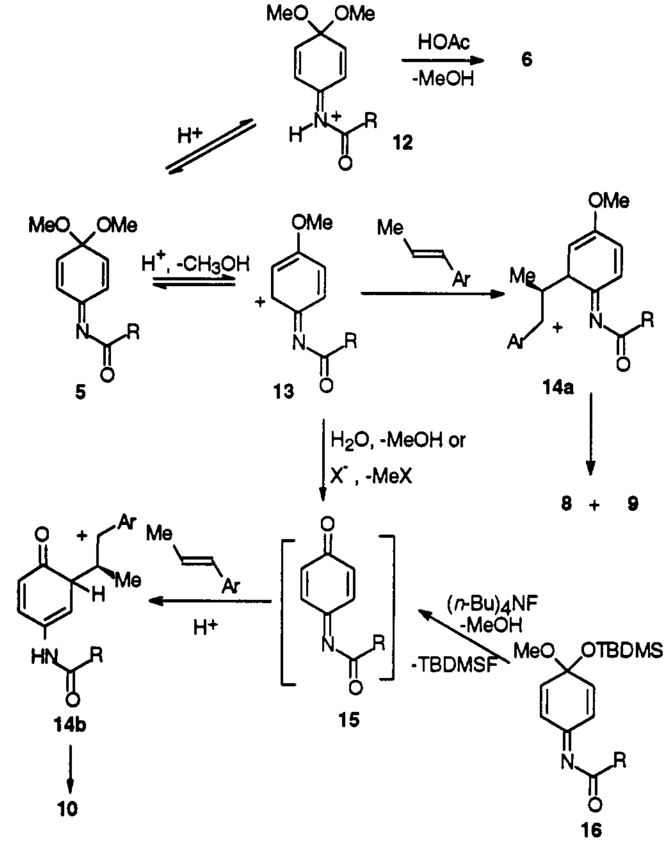
Table I. Product Yield Dependence on Acid

entry	compd	acid	yield (%) 6	7	8	9	10
1	**5a**	HOAc	95				
2	**5b**	HOAc	28	30	17	5	
3	**5a**	TsOH			18	26	39
4	**5b**	TsOH			23	25	47



Scheme I outlines probable reaction pathways for the chemistry discussed thus far. Protonation of the imine nitrogen would give **12**, which is the logical intermediate for production of **6** by Michael addition of acetate ion followed by aromatization via loss of methanol. Using a stronger acid as catalyst in the absence of a good nucleophile leads to loss of methanol to give **13**. Reaction of **13** with **4a** gives **14a** which then leads to formation of **8** and **9**. The competition between 5- and 7-membered ring formation, as in **8** versus **9**, suggests a less-than-ideal stereoelectronic arrangement for ring closure using the nucleophilic imine nitrogen of **14a**; otherwise, 5-membered ring formation should have given **8** as the major product. The unexpected product formed in the reaction was the dihydrobenzofuran **10**. This product most reasonably arises from reaction of a quinone imine derivative **15** with **4a**. The acylated quinone imine could be formed either by hydrolysis of **13** via adventitious water or via dealkylation. This same dihydrobenzofuran was formed in 60% yield by treatment of a mixture of **16**,[17] **4a**, and *p*-toluenesulfonic acid with tetrabutylammonium fluoride.[18] Deblocking of ketals akin to **16** to ketones with fluoride ion is known,[19] and in this csae **15** would be an intermediate. Reaction of **15** as outlined for **1** → **2** → **3** would give **10**. Thus, not only does the **16** + **4a** → **10** reaction sequence strongly support the pathway for formation of **10** in the acid-catalyzed reaction of **5** with **4a**, but it also serves as a good route to amino-substituted dihydrobenzofurans.

Scheme I. Reaction Pathways in Acid-Catalyzed Reactions of *N*-Acylquinone Imine Ketals



As noted above, there are two reasonable pathways for formation of the dihydrobenzofuran **10b**. When the reaction of **5b** and **4a** was conducted in the presence of 1 equiv of added water, the yield of **10b** increased from 47% to 67%, establishing that even small amounts of water increase the yield of **10b**.[20] However, using dry acetonitrile and taking reasonable precautions to exclude adventitious moisture, **10b** was still formed in appreciable amounts. A second pathway for formation of **15** would be dealkylation of **13** by either methanol formed in the reaction or

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(11) The structure assignment for **9b** is supported by analytical and spectroscopic data. The ^{13}C NMR spectrum exhibited the imino ether carbon at 165.8 ppm.[12] The ^1H NMR spectrum showed the deshielded *ortho*-protons of the phenyl group at δ 8.06–8.01 (d, J = 8.3 Hz, 2 H), the remaining aromatic protons at δ 7.57–7.38 (m, 3 H) and 6.9–6.6 (m, 6 H), the methine proton adjacent to oxygen at δ 6.10–6.07 (d, J = 5.5 Hz, 1 H), the methine proton adjacent to the methyl group at δ 4.1–3.9 (m, 1 H), the methoxyl protons at δ 3.86 (s, 3 H), 3.83 (3 H), 3.73 (3 H), and the methyl group at δ 1.14 (d, J = 6.6 Hz, 3H). The imino ether linkage stretch in the IR was at 1715 cm^{-1}.[13]

(12) The analogous carbon in 2-phenyl-5,5-dimethyloxazoline appears at δ 161 in the ^{13}C NMR spectrum. Swenton, J. S.; Bonke, B. R.; Clark, W. M.; Chen, C.-P.; Martin, K. V. *J. Org. Chem.* **1990**, *55*, 2027.

(13) This absorption occurs at 1670 cm^{-1} in an analogous 5-membered ring imino ether.[12] The higher energy absorption observed here probably arises from the deviation from planarity of the linkage in the 7-membered ring.

(14) ^1H NMR data suggest that the stereochemistry present in **9b** was preserved during the hydrolysis step; however, this assignment is considered tentative.

(15) The structure assigned to **10b** was based on exact mass analysis and the close similarity of the ^1H NMR spectrum to those of similar dihydrobenzofurans.[16] The methine hydrogen α to oxygen resonance occurs at δ 5.11 (d, J = 9.2 Hz) and the methyl group resonance appears at δ 1.42 (d, J = 6.8 Hz), positions almost identical with literature values.[16]

(16) See discussion and refs in 1b.

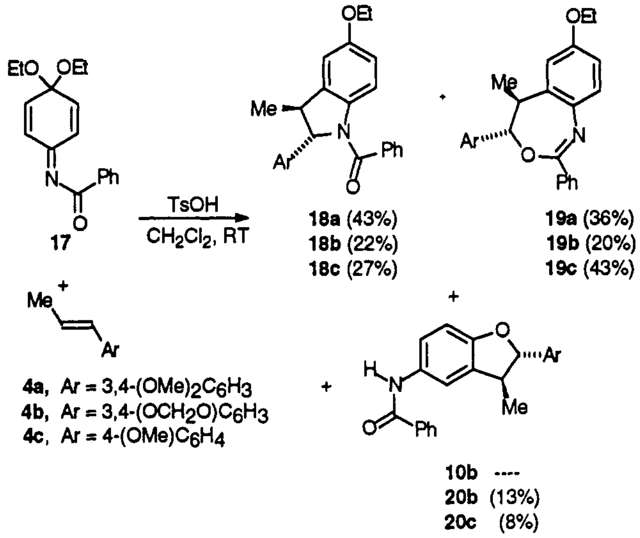
(17) Stern, A. J.; Swenton, J. S. *J. Org. Chem.* **1987**, *52*, 2763.

(18) The acid is essential for the formation of **10** from **16** and **4a**, suggesting that the *N*-protonated quinone imine of **15** is the important intermediate in the reaction. The reaction may be related to indole formation from the reaction of bis-*N*-sulfonylquinone imines with silyl enol ethers: Mukaiyama, T.; Sagawa, Y.; Kobayashi, S. *Chem. Lett.* **1987**, 2169.

(19) Stern, A. J.; Swenton, J. S. *J. Org. Chem.* **1988**, *53*, 2465.

(20) Hydrolyses analogous to the **13** → **14** conversion have been noted in quinone imine chemistry. Novak, M.; Pelecanou, M.; Pollack, L. *J. Am. Chem. Soc.* **1986**, *108*, 112. Novak, Bonham; Mulero, J. J.; Pelecanou, M.; Zemis, J. N.; Buccigross, J. M.; Wilson, T. C. *J. Am. Chem. Soc.* **1989**, *111*, 4447.

Scheme II. Cycloaddition Reactions of *N*-Acylquinone Imine Diethyl Ketals



acetonitrile. This pathway should be less important if an ethyl group, rather than a methyl group, were undergoing dealkylation.

Anodic oxidation of *p*-ethoxybenzanilide in ethanol, essentially as described[3b] for preparation of **5b**, gave **17** in 64% yield. Reaction of 17 with **4a** in acetonitrile gave **18a** (34%), **19a** (24%), and **10b** (5%). The decrease in yield of **10b** for the methyl (47%) versus the ethyl ketal (5%) suggests that dealkylation of intermediates akin to **13** plays a role in formation of dihydrobenzofuran products. As illustrated by the data in Scheme II, the solvent also has an effect on product ratio: using methylene chloride resulted in no detectable yield of **10b**. Thus, the best conditions for carbon–carbon bond formation at the position *ortho* to the nitrogen are reaction of the diethyl ketal of the *N*-benzoylquinone imine with the styrene derivative in dry methylene chloride. Under these optimum conditions, styrene derivatives **4b** and **4c** reacted with **17** to give **18b,c** and **19b,c** in addition to minor amounts of **20b,c** (see Scheme II).[21]

Viewing the reactive intermediate in these cycloadditions as an *N*-acylnitrenium ion which partitions itself as outlined in Scheme I is a useful framework for understanding the chemistry and extending these results. The chemistry presented herein comprises a short route to *ortho* functionalization of certain anilide derivatives from readily available intermediates. In addition, these studies demonstrate that dealkylation pathways for these *p*-alkoxy nitrenium ions probably occur via two different mechanisms: hydrolysis and dealkylation. Future studies will focus on a more complete understanding of the chemistry and extension of the reaction to other electron-rich alkenes.

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Supplementary Material Available: Representative procedures and ^1H NMR spectra of all new compounds (20 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(21) The small amounts of dihydrobenzofuran derivatives formed in the reactions could arise from adventitious water in the reaction mixture.