# The Chemistry of Acylated Quinone Imine Ketals. Nucleophilic and Organolithium Addition Reactions

John S. Swenton,* Brian R. Bonke, William M. Clark, Chung-Pin Chen, and Kevin V. Martin

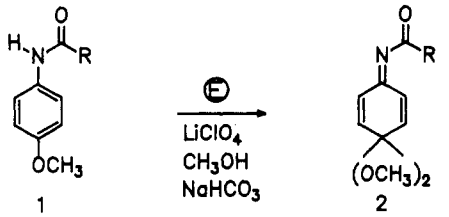
*Department of Chemistry, The Ohio State University, Columbus, Ohio 43210*

*Received September 15, 1989*

Acylated quinone imine ketals are readily available via anodic oxidation of *p*-methoxybenzanilides and *p*-methoxyacetanilides. These compounds react with a variety of nucleophiles to give the corresponding substituted 2- and/or 3-substituted-4-methoxyanilide derivative. Interestingly, the formation of the 2- or 3-substituted product in this reaction is dependent upon both the nucleophile and the reaction conditions. For example, the reaction of *N*-benzoylbenzoquinone imine dimethyl ketal with ethanethiol catalyzed by methanesulfonic acid gives an 8:1 mixture of *N*-[2-(ethylthio)-4-methoxyphenyl]benzamide and *N*-[3-(ethylthio)-4-methoxyphenyl]benzamide. However, reaction of *N*-benzoylbenzoquinone imine dimethyl ketal with sodium ethanethiolate gives only the latter product in 84% yield. Organolithium reagents add to the imine carbon of the acylated quinone imine ketals, affording *N*-acyl derivatives of 4-substituted-4-amino-2,5-cyclohexadienones. The acid hydrolysis and rearrangement chemistry of these latter compounds are also presented.

## Introduction

The preceding paper describes the preparation of quinone imine ketals and some of their chemical transformations.[1] Although reactions of these quinone imine ketals with alkyllithium reagents led to interesting chemistry, it did not lead to carbon–carbon bond-forming reactions at the imine carbon. Since much of the synthetic potential we envisioned for the quinone imine ketal unit rested upon this unobserved carbon–carbon bond-forming reaction, a second general approach to effect this desired reaction was investigated.[2] Acylated quinone imine ketals, available in one step via anodic oxidation of *p*-methoxyanilides,[3] were chosen as substrates for this study. We report herein the results from nucleophilic substitution reactions and organolithium addition reactions of these compounds.



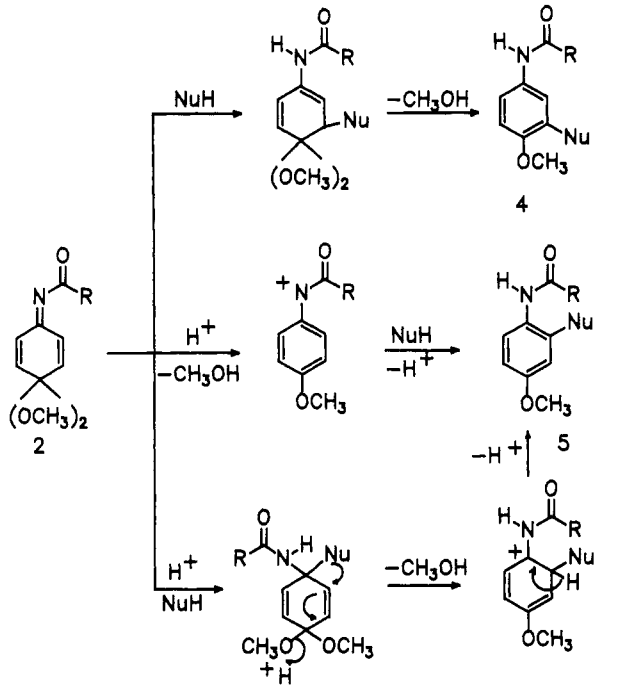

1 2

a, R=Ph; b, R=$CH_3$

## Nucleophilic Additions to Acylated Quinone Imine Ketals

The acid-catalyzed addition of nucleophiles to acylated quinone imine ketals was investigated first. The majority of the reactions studied employed the *N*-benzoyl derivative **2a**. Although the *N*-acetyl derivative **2b** showed much the same chemistry in the limited number of examples studied, the yields were generally somewhat lower. Either a 2- or 3-substituted aromatic compound could result from the reaction of **2a,b** with nucleophiles. Reasonable pathways for these conversions are outlined in Scheme I. In the first case, 1,4-addition of nucleophile followed by elimination of methanol would give the 3-substituted derivative. Two

**Scheme I. Reaction of Nucleophiles with Acylated Quinone Imine Ketals**




mechanisms could account for the formation of the 2-substituted product. Loss of methanol from C-4 would afford a nitrenium ion type intermediate[4–6] which, upon reaction with nucleophiles and loss of a proton, would give the 2-substituted product. Alternatively, addition of nucleophile to the imine linkage followed by a 1,2-migration

(1) Swenton, J. S.; Shih, C.; Chen, C.-P.; Chou, C.-T. *J. Org. Chem.*, preceding paper in this issue.

(2) For a preliminary report dealing with a minor portion of this work, see: Chen, C.-P.; Chou, C.-T.; Swenton, J. S. *J. Am. Chem. Soc.* **1987**, *109*, 946.

(3) Swenton, J. S.; Bonke, B. R.; Chen, C.-P.; Chou, C.-T. *J. Org. Chem.* **1988**, *54*, 51.

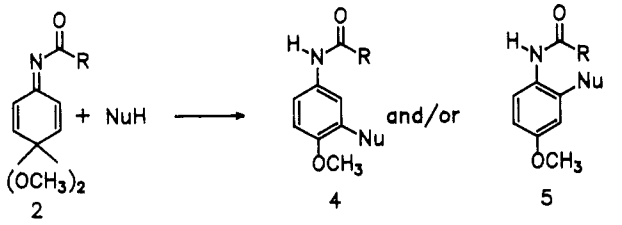
(4) For a review of the older literature of nitrenium ions, see: Gassman, P. G. *Acc. Chem. Res.* **1970**, *3*, 26. For related chemistry, see: Endo, Y.; Namikawa, K.; Shudo, K. *Tetrahedron Lett.* **1986**, *27*, 4209 and papers cited therein.

(5) For more recent mechanistic studies, see: (a) Gassman, P. G.; Granrud, J. E. *J. Am. Chem. Soc.* **1984**, *106*, 1498; (b) **1984**, *106*, 2448.

(6) For more recent chemistry concerned with *N*-acetyl quinone imines and the involvement of nitrenium ions in these reactions, see: (a) Fernando, C. R.; Calder, I. C.; Ham, K. N. *J. Med. Chem.* **1980**, *23*, 1153. (b) Dahlin, D. C.; Nelson, S. D. *J. Med. Chem.* **1982**, *25*, 835. (c) Novak, M.; Pelecanou, M.; Roy, A. K.; Andronico, A. F.; Plourde, F. M.; Olefirowicz, T. M.; Curtin, T. J. *J. Am. Chem. Soc.* **1984**, *106*, 5623. (d) Novak, M.; Pelecanou, M.; Pollack, L. *Ibid.* **1986**, *108*, 112. (e) Novak, M.; Pelecanou, M.; Zemis, J. N. *J. Med. Chem.* **1986**, *29*, 1424. (f) Novak, M.; Bonham, G. A.; Mulero, J. J.; Pelecanou, M.; Zemis, J. N.; Buccigross, J. M.; Wilson, T. C. *J. Am. Chem. Soc.* **1989**, *111*, 4447.

0022-3263/90/1955-2027$02.50/0 

**Table I. Nucleophilic Addition to *N*-Acyl-*p*-benzoquinone Imine Monoketal**

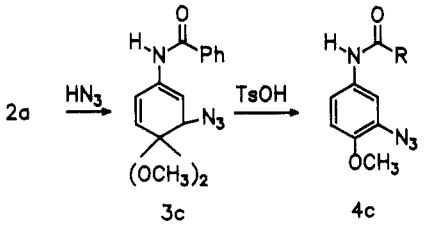



| entry | R | Nu-H | 4, Nu = | 5, Nu = | yield (%) |
|---|---|---|---|---|---|
| 1 | Ph | $CH_3O$-H | **a**, $OCH_3$ | | 84 |
| 2 | Ph | $CH_3CO_2$-H | **b**, $OCOCH_3$ | | 68 |
| 3 | Ph | H-$N_3$ | **c**, $N_3$ | | 78[a] |
| 4 | Ph | $CH_3CH_2S$-H | | **d**, $SCH_2CH_3$ | 86 |
| | Ph | $CH_3CH_2S$-H | **d**, $SCH_2CH_3$ | | 11 |
| 5 | Ph | $CH_3CH_2SNa$ | **d**, $SCH_2CH_3$ | | 84 |
| 6 | Ph | $(CH_3)_3SiCl$ | | **e**, Cl | 98 |
| 7 | Ph | pyrrole | **f**, 2-$C_4H_4N$ | | 61 |
| 8 | $CH_3$ | $CH_3CH_2S$-H | | **g**, $SCH_2CH_3$ | 44 |
| | $CH_3$ | $CH_3CH_2S$-H | **g**, $SCH_2CH_3$ | | 24 |
| 9 | $CH_3$ | $CH_3CH_2SNa$ | **g**, $SCH_2CH_3$ | | 73 |
| 10 | $CH_3$ | $(CH_3)_3SiCl$ | | **h**, Cl | 57 |
| | $CH_3$ | $(CH_3)_3SiCl$ | **h**, Cl | | 22 |

[a] After aromatization of the 1,4-addition product with *p*-TsOH.

and aromatization would afford the 2-substituted product.

The acid-catalyzed reaction of **2a** with methanol and acetic acid gave the 3-substituted compounds as the major product (Table I, entries 1 and 2). In the reaction of **2a** and hydrazoic acid, an intermediate addition product **3c** (79%) was isolated. The vinyl and methine signals in the



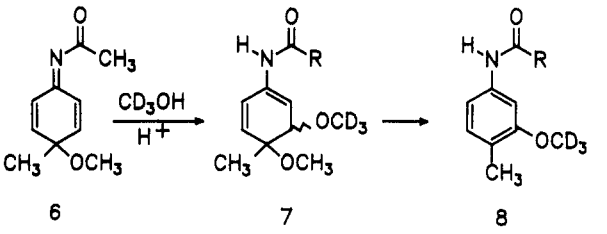

$^1$H NMR spectrum of the product were most informative in assigning this structure: $\delta$ 6.53 (dd, $J$ = 5.6, 2.0 Hz, 1 H), 6.28 (dd, $J$ = 10.1, 2.0 Hz, 1 H), 5.94 (d, $J$ = 10.3 Hz, 1 H), 3.87 (br d, $J$ = 5.6 Hz, 1 H). This compound reverted to **2a** when reacted with base, but heating the compound with *p*-toluenesulfonic acid gave the 3-substituted aryl azide **4c** (Nu = $N_3$, Table I, entry 3). Presumably, all of the 3-substituted anilides formed in this work arise from aromatization of initially formed addition products.

In contrast to the reactions noted above, the reaction of **2a** with ethanethiol in the presence of methanesulfonic acid gave an 86:11 mixture of two aromatic substitution products (entry 4). Raney nickel reduction of these products individually afforded 4-methoxybenzanilide, establishing that the two products were regioisomers. The product assigned as the 2-isomer showed one hydrogen in the $^1$H NMR spectrum at unusually low field: $\delta$ 8.5 (d, $J$ = 9 Hz). The deshielding effect, which was absent in the 3-isomer, could have arisen from a change in conformation of the benzamide linkage caused by the steric effect of the 2-ethyl sulfide linkage. This would place the C-6 hydrogen of the aromatic ring into a deshielding region. This same effect was noted with the 2-chloro compound discussed below. Interestingly, the reaction of sodium ethanethiolate with **2a** gave only the 3-substituted compound in 84% yield (entry 5).

The reaction of **2a** with trimethylsilyl chloride gave the 2-substituted product (entry 6) in excellent yield. This product also showed a deshielded proton at $\delta$ 8.4 ($J$ = 8.7 Hz), similar to that noted above for the ethyl sulfide product. The product obtained from this reaction was different than the regioisomer that was prepared from benzoylation of commercial 3-chloro-*p*-anisidine.[7] The reaction of **2b** with trimethylsilyl chloride was less selective, giving a 57:22 mixture of the 2- and 3-substitution products (entry 10).

Although only one example was studied, electron-rich aromatic systems can also serve as nucleophiles toward the acylated quinone imine ketals. The zinc chloride catalyzed reaction of **2a** with pyrrole (entry 7) gave an addition product that has been assigned as **4f** (R = 2-$C_4H_4N$) since the $^1$H NMR spectrum of the compound did not show the deshielded aromatic proton exhibitied for the 2-substituted compounds noted above. However, the structure of the **2a**–pyrrole product should be considered tentative.

In summary, under basic conditions a 1,4-addition of nucleophile to the acylated quinone imine ketal followed by aromatization gives the respective 3-substituted *p*-methoxyanilide derivative. However, the chemistry is more complicated under acidic conditions since at least two competing processes appear to be operating. Addition of methanol, acetic acid, and hydrazoic acid gives a formal Michael product that undergoes loss of methanol to afford the aromatic compound. A similar process occurs in the acid-catalyzed addition of methanol to **6**, which gives **8** via the intermediacy of the 1,4-addition product **7**.[5b] However, 2-substituted products must arise via a different reaction pathway. One possibility for formation of the 2-substituted *p*-methoxyanilides involves an *N*-acyl nitrenium ion intermediate (Scheme I). Such a reaction is precedented in a related system[5a] in which chloroform solutions of methanesulfonate esters of *N*-hydroxyacetanilides rearranged to methanesulfonate derivatives of 2-hydroxyacetanilides. In fact, *N*-acyl quinone imine ketals could serve as alternative sources of *N*-acyl nitrenium ions. However, a second pathway (Scheme I) involving addition of the nucleophile to the imine carbon followed by 1,2-migration of the nucleophile and aromatization cannot be ruled out especially in the case of sulfur nucleophiles in which the 1,2-shift might be especially favorable. Further studies are needed before a decision on these choices can be made.



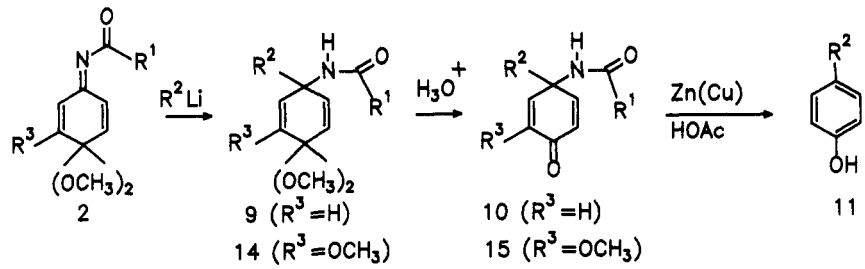

## Reaction of N-Acylated Quinone Imine Ketals with Organolithium Reagents

The addition of organolithium reagents to the imine carbon of *N*-acyl quinone imine ketals was envisioned as a key reaction for the utilization of these compounds in synthesis. Indeed, the reaction of acylated quinone imine ketals with methyl- or aryllithium reagents gave **9** and/or **10** in good yields (Table II). However, reaction of **2a** with

(7) This product has a melting point (165–167 °C) almost 60 °C higher than that reported in the literature.[8] However, **5e** is different than the authentic 3-chloro isomer (mp 151–152 °C), and it seems likely that the reported melting point is of a different crystalline form or the value is in error.

(8) El-Sheikh, M.; Marks, A.; Biehl, E. R. *J. Org. Chem.* **1981**, *46*, 3256.

**Table II. Organolithium Additions to *N*-Acyl-*p*-benzoquinone Imine Monoketal**

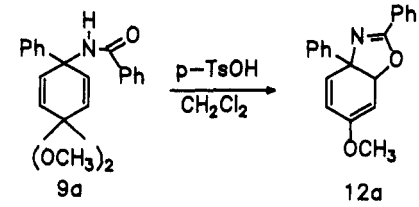



| entry | $R^1$ | $R^2$ | $R^3$ | products (% yield) | | |
|---|---|---|---|---|---|---|
| 1 | Ph | PhLi | H | **9a** (83) | **10a** (88) | **11a** (65) |
| 2 | Ph | $CH_3Li$ | H | **9b** (77) | **10b** (88) | **11b** (72) |
| 3 | Ph | *n*-BuLi | H | **9c** | **10c** (57)[a] | |
| 4 | Ph | *s*-BuLi | H | **9d** | **10d** (40)[a] | |
| 5 | Ph | *t*-BuLi | H | [b] | | |
| 6 | $CH_3$ | PhLi | H | **9f** (80) | **10f** (80) | |
| 7 | O-*t*-Bu | PhLi | H | **9g** | **10g** (89)[a] | |
| 8 | Ph | PhLi | $OCH_3$ | **14a** (86) | **15a** (61) | |
| 9 | Ph | *p*-$OCH_3C_6H_4$ | $OCH_3$ | **14b** (57) | | |
| 10 | Ph | *c* | $OCH_3$ | **14c** (48) | | |

[a] Overall yield for organolithium/hydrolysis steps. [b] The only product characterized was 4-methoxybenzanilide (50%) (**1a**). [c] [2-[3-(*tert*-Butyldimethylsiloxy)propyl]-4,5-dimethoxyphenyl]lithium.

*n*- and *sec*-butyllithium gave only modest overall yields of the dienones **10c** and **10d**, and *tert*-butyllithium afforded the reduced compound **1a**. Although the yields of addition product do depend on the nature of the alkyllithium reagent, the success of these additions does not depend dramatically on the nature of the acyl substituent (entries 6 and 7) nor on substitution of a methoxy group at the 3-position (entries 8–10). Although the ketals **9** can be isolated, it is more convenient to hydrolyze the products directly to the corresponding dienones **10**. The structures for the latter compounds were supported by spectroscopic data and the zinc/copper couple reduction of **10a,b** to *p*-methyl- and *p*-phenylphenol in 68 and 72% yield, respectively. In fact, this sequence serves as a method for replacement of the amino group on a *p*-methoxyaniline with an alkyl or aryl group.

Although the dienones **10a,b** are the final products from the hydrolysis reactions of **9a,b** in aqueous acid, their chemistry in acidic media is dependent upon the reaction conditions. Since the chemistry of compounds analogous to **9a** was of most concern in our *Erythrina* alkaloid studies,[9] the reactions of **9a** and several other aryl-substituted systems were studied under different acidic conditions. The phenyllithium addition product **9a** decomposed to a mixture of products on standing, apparently due to adventitious acid, although the major product isolated from extended hydrolysis was the dienone **10a**. However, when **9a** was reacted with *p*-toluenesulfonic acid in methylene chloride, careful chromatography afforded a product mixture from which **12a** could be isolated in 40% yield. The $^1H$ NMR and $^{13}C$ NMR spectra of the product strongly support this structural assignment. The $^1H$ NMR spectrum of **12a** in the region $\delta$ 6.0–5.0 showed an AB quartet centered at $\delta$ 5.92 ($J$ = 10.0 Hz) with the higher field component having an additional coupling of $J$ = 2.0 Hz, a clean doublet at $\delta$ 5.26 ($J$ = 5.8 Hz) assigned to the methine hydrogen, and a doublet of doublets at $\delta$ 5.07 ($J$ = 5.8, 2.0 Hz) for the vinyl ether hydrogen. The $^{13}C$ NMR spectrum showed the imino ether carbon at $\delta$ 165.7; the signal for the analogous carbon in 2-phenyl-5,5-dimethyloxazoline[10] occurs at $\delta$ 161. Reaction of **12a** with aqueous acid results in formation of **10a**.




However, reaction of **9a** with trimethylsilyl triflate in methylene chloride afforded an aromatic product in 87% yield. Two biphenyl derivatives—one arising from migration of the phenyl group, **13a**, and the second from migration of a benzamide group, **13b**—were possible products. Since both groups are known to migrate in the dienone–phenol rearrangement,[11] firm evidence was desired for structural assignment. The product from this rearrangement showed a deshielded aromatic proton at $\delta$ 8.2 (d, $J$ = 9 Hz), suggesting **13a** as the structure. This deshielding was observed previously for a proton ortho to a benzamide linkage that was itself ortho to a second substituent. Authentic **13b** was prepared as outlined below; although it had virtually the same melting point as **13a**, it had similar, but different, spectroscopic properties. Most informative was the $^1H$ NMR spectrum, which did exhibit a deshielded proton at $\delta$ 8.2, but the magnitude of the coupling constant ($J$ = 2.6 Hz) was only consistent with a meta relationship to the aromatic proton to which it was coupled.

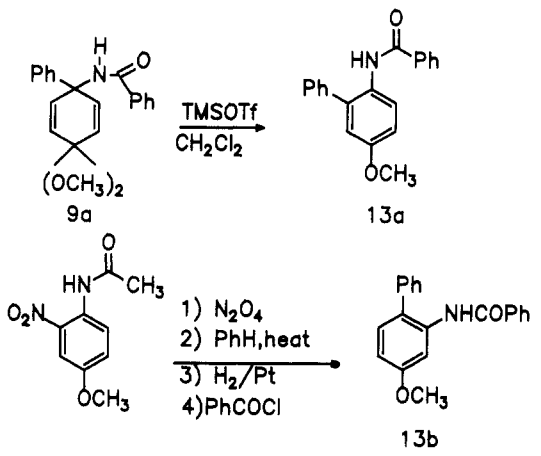
Under acidic conditions, three basic processes are in competition for the 4-aryl-4-benzamido-2,5-cyclohexadienone dimethyl ketals such a **9a**. Apparently, the fastest reaction is intramolecular cyclization as shown for the **9a** → **12a** conversion.[12] However, this reaction is

(9) Chou, C.-T.; Swenton, J. S. *J. Am. Chem. Soc.* **1987**, *109*, 6898.

(10) This compound was prepared by using the standard procedure (Meyers, A. I.; Temple, D. L.; Haidukewych, D.; Mihelich, E. D. *J. Org. Chem.* **1974**, *39*, 2787), and its $^{13}C$ NMR spectrum was obtained in $CDCl_3$.

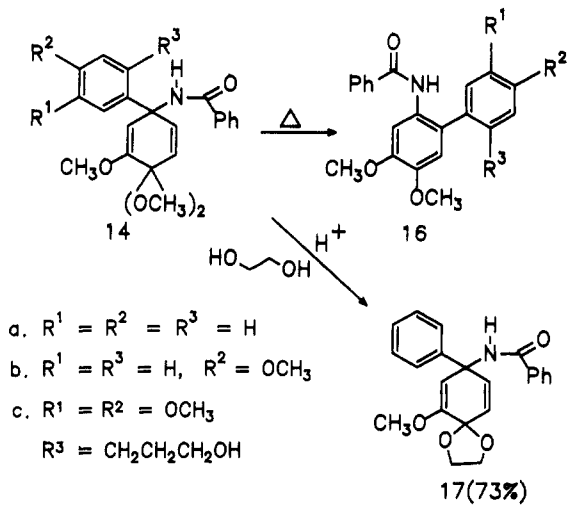
(11) For leading references, see: Kikugawa, Y.; Kitamura, T.; Kawase, M. *J. Chem. Soc., Chem. Commun.* **1989**, 525.

(12) For an example of this type of amide participation in a similar ring system, see: Eckhardt, H. H.; Hege, D.; Massa, W.; Perst, H.; Schmidt, R. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 699.




9a 13a 13b

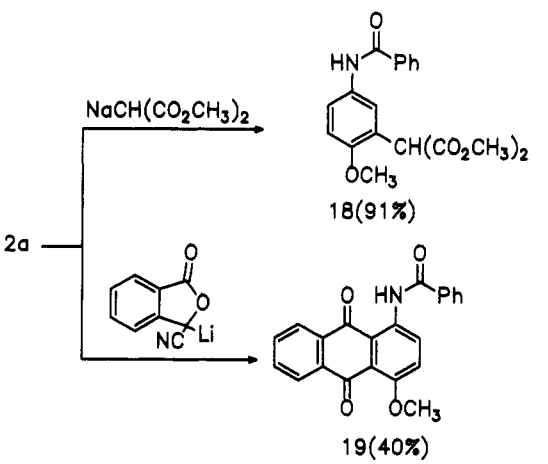
reversible; in acidic aqueous media the final product is that of ketal hydrolysis, i.e., **9a** → **10a**. Under acidic nonaqueous conditions, the final product is aryl migration. The nature of the aryl group effects the rate of the migration and thus the chemistry that can be performed on these ketals. Although compound **14a** is stable to heating at 90 °C, the *p*-methoxy analogue **14b** rearranges to **16b** and **14c** rearranges to **16c** at this temperature; adventitious acid may catalyze this process. Both compounds give the aryl-migrated product when reacted with *p*-toluenesulfonic acid in dry methylene chloride. The dimethyl ketal **14a** can be transketalized to give **17** (73%); however, **14c**—having a dimethoxy-substituted ring—gave exclusively the aryl-migrated product **16c** (92%) under the same reaction conditions. In summary, aryl migration limits the number of chemical transformations that can be performed on ketals such as **9** and **14**.




14 16 17(73%)

## 1,4-Addition–Annelation Chemistry

The 1,4-additions and annelation reactions of N-acylated quinone imines were not studied extensively. However, reaction of **2a** with the sodium salt of dimethyl malonate gave **18** in 91% yield. Finally, annelation of **2a** with the lithiated cyanophthalide[13] gave the known anthroquinone **19** in 40% yield. Although the yield was substantially lower than the analogous reaction with a quinone monoketal,[14] no attempts were made to optimize the conditions of this reaction.




18(91%) 19(40%)

## Summary

The N-acylated quinone imine ketals available in one-step via anodic oxidation of the corresponding amide derivatives of *p*-methoxyanilines serve as convenient sources of masked quinone imines. These compounds react with nucleophiles to give 2- and/or 3-substituted *p*-methoxyanilides. Thus, this sequence of anodic oxidation/nucleophilic substitution serves as a procedure for effecting overall nucleophilic substitution of a *p*-methoxyaniline. Organolithium reagents react at the imine carbon of the N-acylated quinone imines to give good yields of 4-(*N*-acylamino)-4-aryl(alkyl)-2,5-cyclohexadienone ketals. These compounds can be hydrolyzed with aqueous acid to their respective 2,5-cyclohexadienones or else rearranged under nonnucleophilic acid conditions to highly substituted biphenyls. The easy availability of these N-acylated quinone imine ketals coupled with their substitution chemistry indicates use for the compounds in the preparation of highly functionalized aromatic amines and some alkaloid natural products. An example utilizing these compounds in the latter connection has appeared.[9]

## Experimental Section[15]

***N*-(3,4-Dimethoxyphenyl)benzamide (4a).** The imine ketal **2a** (0.299 g, 1.17 mmol) was dissolved in a 9:1 mixture of

(13) Frescos, J. N.; Morrow, G. W.; Swenton, J. S. *J. Org. Chem.* **1985**, *50*, 805.

(14) For leading references, see: Swenton, J. S. *The Chemistry of Quinonoid Compounds*, Rappoport, Z., Patai, S., Eds.; John Wiley: New York, 1988; Vol. 2, Part 2, p 899.

(15) The imine ketals used in this work were prepared via anodic oxidation of the respective *p*-methoxyanilide as described.[3] Melting points were determined in capillaries in a Thomas-Hoover Unimelt apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer Model 283B spectrometer on KBr disks, and strong peaks are reported unless otherwise noted. Routine $^1H$ NMR and $^{13}C$ NMR spectra were determined at 80 MHz (20.1 MHz for $^{13}C$ NMR spectra) on an IBM NR 80 spectrometer using deuteriochloroform as solvent and residual chloroform or tetramethylsilane as internal standard unless noted otherwise. Mass spectra, FAB, and exact mass measurements were obtained on a Kratos MS-30 spectrometer or VG 70-250S mass spectrometers at The Ohio State University Chemical Instrumentation Center. Combustion analyses were performed by Scandanavian Microanalytical Laboratory, Herlev, Denmark. Alumina and silica gel (Kieselgel 60, 230–400 mesh) were obtained from E. Merck Co. When indicated as base-washed, the silica gel was slurried in 5% aqueous $NH_4OH/CH_3OH$ (1:1), filtered, and vacuum dried at 110 °C. Tetrahydrofuran was purified by distillation from benzophenone ketyl. Thin-layer chromatography (TLC) was done on Merck silica gel 60 $F_{254}$ pre-coated aluminum-backed plates, 0.2-mm thickness. Visualization was by UV or by spraying with 5% ethanolic phosphomolybdic acid and then heating. Unless otherwise noted purified material showed one concentric spot in the $R_f$ range 0.3–0.6. All organometallic reactions were done under nitrogen or argon. Extractive workup refers to the following sequence of operations: concentration of the reaction mixture in vacuo, extraction of the organic product with diethyl ether or methylene chloride, washing the organic layer with brine (diethyl ether only), drying the organic layer over calcium sulfate (Drierite), removal of the solvent in vacuo, and drying to constant weight under <0.3 Torr vacuum. Throughout the Experimental Section, the following abbreviations are used: petroleum ether, bp 35–60 °C (PE), diethyl ether ($Et_2O$), tetrahydrofuran (THF), *tert*-butyldimethylsilyl (TBDMS).

$CH_3OH$/trimethyl orthoformate (10 mL), and a mixture of methanesulfonic acid (0.015 mL, 0.25 mmol) and $CH_3OH$ (5.0 mL) was added. After the reaction mixture was stirred for 3 h, a white precipitate formed. The solid was collected by filtration and washed with a 1:1 mixture of $CH_3OH/H_2O$ (5 mL) to yield *N*-(3,4-dimethoxyphenyl)benzamide (0.197 g, 66%), mp 174–175 °C. To the filtrate was added $H_2O$ (5 mL), and the solution was concentrated in vacuo to yield after filtration a white solid (0.088 g), mp 167–169 °C. Recrystallization of this second crop from $CH_2Cl_2$/PE gave the title compound (0.054 g, 0.251 g total, 84%), mp 173–175 °C (lit.[16] mp 178 °C).

***N*-(3-Acetoxy-4-methoxyphenyl)benzamide (4b).** The imine ketal **2a** (0.300 g, 1.17 mmol) was mixed in a 1:1 mixture of glacial acetic acid/acetic anhydride (2 mL) at room temperature for 2.3 h, during which time a white solid formed. $Et_2O$ (2 mL) was added, the solution was cooled in an ice bath, and the product was filtered and washed with $Et_2O$ (3 mL) to give *N*-(3-acetoxy-4-methoxyphenyl)benzamide (0.147 g, 46%), mp 142–145 °C (mp 144.5–145 °C after two recrystallizations from $CH_2Cl_2$). The filtrate was concentrated in vacuo to a brown oil, which was filtered on silica gel (4 cm × 1 cm column, 5% EtOAc/$CH_2Cl_2$ as eluant) to give a light brown solid (0.118 g), mp 132 °C. Two recrystallizations from $CH_2Cl_2$/light PE yielded the title compound (0.071 g, 0.218 g total, 68%): mp 143–144 °C; IR (KBr) 1765, 1660, 1651, 1530, 1515, 1225, 1215 $cm^{-1}$; $^1H$ NMR $\delta$ 7.9–7.7 (br m, 3 H), 7.6–7.4 (br m, 5 H), 6.88 (d, $J$ = 8.6 Hz, 1 H), 3.76 (s, 3 H), 2.29 (s, 3 H); mass spectrum, exact mass calcd for $C_{16}H_{15}NO_4$ $m/e$ 285.1001, obsd $m/e$ 285.0982.

***N*-(6-Azido-5,5-dimethoxy-1,3-cyclohexadien-2-yl)benzamide (3c).** To a slurry of sodium azide (1.26 g, 19.4 mmol) in dry THF (20 mL) was added dropwise trifluoroacetic acid (0.75 mL, 9.74 mmol). The mixture was stirred at room temperature for 2 h, during which time a fine white solid formed in addition to the suspended sodium azide. Then the imine ketal **2a** (0.5 g, 1.94 mmol) was added, and the reaction mixture was stirred for 4 h. The mixture was poured into 1:1 $H_2O$/saturated $NaHCO_3$ (80 mL), extracted with EtOAc (2 × 20 mL), and worked up to give an oil (0.571 g, 97%), which solidified. Recrystallization from $CH_2Cl_2$/light PE gave **3c** in 2 crops (0.462 g, 79%), mp 118–120 °C. Two recrystallizations gave a constant melting solid: mp 121–123 °C; IR (KBr) 2100, 1657, 1523, 1118, 1065 $cm^{-1}$; $^1H$ NMR $\delta$ 7.9–7.7 (m, 2 H), 7.6–7.3 (m, 4 H), 6.53 (dd, $J$ = 2.0, 5.6 Hz, 1 H), 6.28 (dd, $J$ = 2.0, 10.1 Hz, 1 H), 5.94 (d, $J$ = 10.3 Hz, 1 H), 3.87 (br d, $J$ = 5.6 Hz, 1 H), 3.39 (s, 3 H), 3.29 (s, 3 H). Anal. Calcd for $C_{15}H_{16}N_4O_3$: C, 59.99; H, 5.37. Found: C, 59.96; H, 5.41.

***N*-(3-Azido-4-methoxyphenyl)benzamide (4c).** The adduct **3c** (0.300 g, 1.0 mmol) was suspended in dry benzene (20 mL), and anhydrous *p*-toluenesulfonic acid (10 mg, 0.06 mmol) was added. After 5 min, no starting material could be detected by TLC, and the reaction was quenched by addition of saturated $NaHCO_3$ (5 mL). Extractive workup [$CH_2Cl_2$ (2 × 10 mL)] gave a light brown solid (0.259 g, 97%), mp 140–142 °C, which was filtered on silica gel (3 g, 5 × 1 cm column, 5% EtOAc/$CH_2Cl_2$ as eluant) to give a light yellow solid (0.252 g, 94%), mp 140.5–142 °C. Recrystallization from $CHCl_3$/PE gave white crystalline *N*-(3-azido-4-methoxyphenyl)benzamide: mp 142–143 °C; IR (KBr) 2110, 1642, 1530, 1510, 1245, 685 $cm^{-1}$; $^1H$ NMR $\delta$ 7.9–7.8 (m, 3 H), 7.6–7.2 (m, 5 H), 6.85 (d, $J$ = 9.3 Hz, 1 H), 3.87 (s, 3 H); mass spectrum, exact mass calcd for $C_{14}H_{12}N_4O_2$ $m/e$ 268.0960, obsd $m/e$ 268.0993.

**Reaction of 2a with Ethanethiol under Acidic Conditions.** The imine ketal **2a** (0.300 g, 1.17 mmol) was dissolved in THF (5 mL), and the mixture was cooled to 0 °C. A mixture of THF (2.5 mL), ethanethiol (0.175 mL, 2.36 mmol), and methanesulfonic acid (0.015 mL, 0.23 mmol) was added dropwise, and the mixture was stirred at 0 °C for 0.5 h and then warmed to room temperature. This solution was added to EtOAc (20 mL) and worked up to yield a white solid (0.335 g) as a mixture of two compounds. The mixture was chromatographed on silica gel (45 g, 10 × 3 cm column, 0–4% EtOAc/$CHCl_3$ as eluant).

***N*-[2-(Ethylthio)-4-methoxyphenyl]benzamide (5d)** (0.287 g, 86%) showed mp 144–147 °C. Two recrystallizations from $CH_2Cl_2$/PE gave a constant melting solid: mp 147–147.5 °C; IR (KBr) 1640, 1480 $cm^{-1}$; $^1H$ NMR $\delta$ 9.13 (br s, 1 H), 8.48 (d, $J$ = 9.0 Hz, 1 H), 8.0–7.8 (m, 2 H), 7.5–7.4 (m, 3 H), 7.10 (d, $J$ = 3.0 Hz, 1 H), 6.97 (dd, $J$ = 9.0, 3.0 Hz, 1 H), 3.82 (s, 3 H), 2.83 (q, $J$ = 7.3 Hz, 2 H), 1.25 (t, $J$ = 7.3 Hz, 3 H); mass spectrum, exact mass calcd for $C_{16}H_{17}NO_2S$ $m/e$ 287.0980, obsd $m/e$ 287.0942. Anal. Calcd for $C_{16}H_{17}NO_2S$: C, 66.87; H, 5.97. Found: C, 66.66; H, 5.92.

***N*-[3-(Ethylthio)-4-methoxyphenyl]benzamide (4d)** (0.050 g), mp 174–178 °C, was recrystallized from $CHCl_3$/PE to yield a white solid (0.038 g, 11%), mp 183–185 °C. Three recrystallizations gave a constant melting solid: mp 185–185.5 °C; IR (KBr) 1640, 1485 $cm^{-1}$; $^1H$ NMR $\delta$ 7.9–7.8 (m, 3 H, reduced to 2 H when exchanged with $D_2O$), 7.6–7.4 (br m, 5 H), 6.83 (d, $J$ = 8.8 Hz, 1 H), 3.89 (s, 3 H), 2.96 (q, $J$ = 7.3 Hz, 2 H), 1.35 (t, $J$ = 7.4 Hz, 3 H); mass spectrum, exact mass calcd for $C_{16}H_{17}NO_2S$ $m/e$ 287.0980, obsd $m/e$ 287.0961. Anal. Calcd for $C_{16}H_{17}NO_2$: C, 66.49; H, 5.93. Found: C, 66.87; H, 5.93.

**Reaction of 2a with Sodium Thioethoxide.** Sodium hydride (0.05 g, 1.45 mmol, as a 60% dispersion in mineral oil) was washed with THF (2 × 2 mL) and suspended in THF (3 mL). A solution of ethanethiol (0.095 mL, 1.28 mmol) in THF (5 mL) was added, and hydrogen evolution ceased after 0.5 h. A solution of the imine ketal **2a** (0.300 g, 1.16 mmol) dissolved in THF (5 mL) was added, and after being stirred for 0.25 h, no starting material could be detected by TLC. The mixture was poured into EtOAc (20 mL) and worked up to give **4d** as a white solid (334 mg, 100%), mp 178–184 °C. Recrystallization from $CHCl_3$ yielded white crystals in two crops (282 mg, 84%), mp 184–185 °C. This material had the same IR, $^1H$ NMR, and exact mass spectra as those described above for the minor isomer produced by the acid-catalyzed reaction of **2a** with ethanethiol.

***N*-(2-Chloro-4-methoxyphenyl)benzamide (5e).** The imine ketal **2a** (0.502 g, 1.95 mmol) was dissolved in dry THF (10 mL), and chlorotrimethylsilane (0.272 mL, 2.15 mmol) was added. After being stirred for 6 h, no starting material could be detected by TLC. The mixture was poured into $H_2O$ (30 mL) and extracted with $CH_2Cl_2$ (3 × 10 mL). Workup gave *N*-(2-chloro-4-methoxyphenyl)benzamide (0.512 g, 98%) as a white solid, mp 165–167 °C (lit.[8] mp 107–108 °C). Recrystallization from hot 2-propanol yielded white crystals (0.471 g, 90%): mp 167.5–168.5 °C; IR (KBr) 3220, 1645, 1515, 1495, 1212, 1050 $cm^{-1}$; $^1H$ NMR $\delta$ 8.39 (d, $J$ = 8.7 Hz, 1 H), 8.22 (br s, 1 H, washed out with $D_2O$), 7.95–7.85 (m, 2 H), 7.6–7.4 (m, 3 H), 6.97 (d, $J$ = 2.9 Hz, 1 H) overlapping with 6.87 (dd, $J$ = 2.9, 8.8 Hz, 1 H), 3.80 (s, 3 H); mass spectrum, exact mass calcd for $C_{14}H_{12}ClNO_2$ $m/e$ 261.0557, obsd $m/e$ 261.0528.

***N*-[4-Methoxy-3-(2-pyrrolyl)phenyl]benzamide (4f).** The imine ketal **2a** (0.300 g, 1.17 mmol) was dissolved in pyrrole (6 mL). Reagent grade anhydrous zinc chloride (0.177 g, 1.3 mmol) was added, and the mixture was stirred for 3.5 h, during which time a white solid formed. The pyrrole was removed in vacuo, and the remaining solid was triturated with $CH_3OH$ (2 × 10 mL) at 0 °C to give a green-gray solid (0.252 g, 73%), mp 208–216 °C dec. Recrystallization from dimethyl sulfoxide/$H_2O$ gave a light gray solid, *N*-[4-methoxy-3-(2-pyrrolyl)phenyl]benzamide (0.210 g, 61%), with an inseparable impurity (<10% by $^1H$ NMR spectroscopy): mp 255–257 °C dec; IR (KBr) 3430, 3270, 1640, 1495 $cm^{-1}$; $^1H$ NMR ($d_6$-DMSO) $\delta$ 10.89 (br s, 1 H, exchanged with $D_2O$), 10.11 (br s, 1 H, exchanged with $D_2O$), 7.95 (m, 3 H), 7.55 (m, 4 H), 7.04 (d, $J$ = 8.8 Hz, 1 H), 6.80 (br s, 1 H), 6.47 (br s, 1 H), 6.10 (m, 1 H), 3.86 (s, 3 H); mass spectrum, exact mass calcd for $C_{18}H_{16}N_2O_2$ $m/e$ 292.1212, obsd $m/e$ 292.1221.

**4-(*N*-Benzoylamino)-4-phenyl-2,5-cyclohexadienone (10a).** To a THF (30 mL) solution of **2a** (750 mg, 2.9 mmol) at −78 °C was added a 1.7 M PhLi solution (1.86 mL, 1.1 equiv). The mixture was stirred for 2 h at −70 °C and then for 20 min at room temperature. After addition of $H_2O$ (2 mL) and concentration in vacuo, extractive workup [$CH_2Cl_2$ (3 × 40 mL)/$H_2O$ (40 mL)] gave a light brown solid (82 mg, 92%). The $^1H$ NMR spectrum showed the product to be >90% pure. This light brown solid was recrystallized ($CH_2Cl_2$) to give **9a** (805 mg, 83%) in two crops: mp 151–154 °C; IR (KBr) 3390, 1640, 1535, 1110, 1075, 930, 795 $cm^{-1}$; $^1H$ NMR $\delta$ 7.9–7.6 (m, 2 H), 7.6–7.2 (m, 8 H), 6.47 (br s, overlapping AB q, 1 H), 6.30 (AB q, $\Delta\nu$ = 37.4 Hz, $J_{AB}$ = 10 Hz, 2 H), 3.36 (s, 3 H), 3.31 (s, 3 H).

(16) Fetscher, C. A.; Bogart, M. T. *J. Org. Chem.* **1939**, *4*, 71.

A solution of **9a** (180 mg, 0.54 mmol), saturated $NH_4Cl$ (10 mL), and THF (20 mL) was stirred at room temperature overnight. Concentration and extractive workup [$CH_2Cl_2$ (3 × 30 mL)/$H_2O$ (30 mL)] gave a light brown oil. Flash column chromatography ($CH_2Cl_2$ as eluant) gave **10a** (145 mg, 88%) as a white solid. Recrystallization ($CH_2Cl_2$) gave **10a** (96 mg, 78%): mp 180.5–182 °C; IR (KBr) 3300, 1670, 1640, 1580, 1520, 1490, 1305, 1225, 855, 700 $cm^{-1}$; $^1H$ NMR $\delta$ 7.85–7.65 (m, 2 H), 7.5–6.95 (m, 8 H), 7.16 (d, $J$ = 10 Hz, 2 H), 6.7–6.55 (br s, 1 H), 6.28 (d, $J$ = 10 Hz, 2 H); mass spectrum, exact mass calcd for $C_{19}H_{15}NO_2$ $m/e$ 289.1103, obsd $m/e$ 289.1074.

**4-(*N*-Benzoylamino)-4-methyl-2,5-cyclohexadienone Dimethyl Ketal (9b).** To a THF (40 mL) solution of **2a** (205 mg, 0.80 mmol) at −78 °C was added a 1.4 M $CH_3Li$ solution (0.63 mL, 1.1 equiv). The mixture was stirred at −70 °C for 1 h and at room temperature for 5 min. After addition of saturated $NaHCO_3$ (5 mL) and concentration in vacuo, extractive workup [$CH_2Cl_2$ (3 × 30 mL)/$H_2O$ (30 mL)] gave a light brown solid (186 mg, 86%). Recrystallization ($CH_2Cl_2$/PE) gave **9b** (168 mg, 77%) as white crystals: mp 89–90.5 °C; IR (KBr) 3300, 1650, 1540, 1410, 1315, 1105, 1040, 950 $cm^{-1}$; $^1H$ NMR $\delta$ 7.8–7.5 (m, 2 H), 7.5–7.24 (m, 3 H), 6.0 (br s, 1 H), 6.15 (AB q, $\Delta\nu$ = 34.3 Hz, $J_{AB}$ = 10 Hz, 4 H), 3.35 (s, 3 H), 3.31 (s, 3 H), 1.65 (s, 3 H); mass spectrum, exact mass calcd for $C_{16}H_{19}NO_3$ $m/e$ 273.1341, obsd $m/e$ 273.1352.

**4-(*N*-Benzoylamino)-4-methyl-2,5-cyclohexadienone (10b).** Chromatography of **9b** (172 mg, 0.63 mmol) on silica gel (15:1 $CH_2Cl_2$/acetone as eluant) gave hydrolyzed product **10b** (126 mg, 88%) as white crystals: mp 178.5–180 °C; IR (KBr) 3320, 1660, 1615, 1530, 1305, 1290, 885, 710 $cm^{-1}$; $^1H$ NMR $\delta$ 7.8–7.5 (m, 2 H), 7.5–7.24 (m, 3 H), 6.95 (d, $J$ = 10 Hz, 2 H), 6.4 (br s, 1 H), 6.30 (d, $J$ = 10 Hz, 2 H), 1.63 (s, 3 H); mass spectrum, exact mass calcd for $C_{14}H_{13}NO_2$ $m/e$ 227.0946, obsd $m/e$ 227.0960.

**4-(*N*-Benzoylamino)-4-*n*-butyl-2,5-cyclohexadienone (10c).** To a THF (2.5 mL) solution of **2a** (228 mg, 0.87 mmol) at −78 °C was added a 2.1 M *n*-BuLi solution (0.5 mL, 1.2 equiv). The mixture was stirred at −70 °C for 1.5 h and at room temperature for 5 min. After addition of 40% aqueous $CH_3OH$ (1 mL), extractive workup [$CH_2Cl_2$ (2 × 5 mL)] gave a light brown oil (270 mg). This material was dissolved in acetone (2 mL) and cooled to 0 °C, 10% HCl (1.5 mL) was added, and the reaction mixture was stirred for 0.5 h. After addition of 10% NaOH (2 mL), extractive workup [$CH_2Cl_2$ (2 × 10 mL)] gave a brown oil. Recrystallization from EtOAc/PE gave **10c** (119 mg, 50%) as a light brown solid, mp 123–124 °C. Silica gel chromatography of the mother liquors (10% EtOAc/PE as eluant) gave an additional 16 mg (total yield 57%): mp 124.5–125.0 °C; IR (KBr) 3310, 1670 (sh), 1660, 1615, 1530 $cm^{-1}$; $^1H$ NMR $\delta$ 7.8–7.7 (m, 2 H), 7.5–7.24 (m, 3 H), 6.61 (AB q, $\Delta\nu$ = 45 Hz, $J_{AB}$ = 10 Hz, 4 H), 1.9–2.1 (m, 2 H), 1.6–1.2 (m, 4 H), 0.9 (t, $J$ = 6 Hz, 3 H), NH proton not detected; mass spectrum, exact mass calcd for $C_{17}H_{19}O_2N$ $m/e$ 269.1416, obsd $m/e$ 269.1415.

**4-(*N*-Acetylamino)-4-phenyl-2,5-cyclohexadienone (10f).** To a THF (25 mL) solution of **2b** (0.621 g, 3.18 mmol) at −78 °C was added a 1.7 M PhLi solution (1.97 mL). The mixture was stirred at −70 °C for 0.5 h and then at room temperature for 10 min. Addition of $NH_4Cl$ (40 mL), concentration in vacuo, and extractive workup [$CH_2Cl_2$ (3 × 40 mL)/$H_2O$ (40 mL)] gave crude **9f** as a light brown solid, which was then dissolved in THF (50 mL), and 5% HCl (5 mL) was added. After 2 min, the reaction was quenched by addition of saturated $NaHCO_3$ (20 mL). After concentration of the mixture in vacuo, extractive workup [$CH_2Cl_2$ (3 × 50 mL)/$H_2O$ (40 mL)] gave a brown solid. Recrystallization from $CH_2Cl_2$ gave **10f** (0.576 g, 80%) as a light yellow solid: mp 155–157 °C; IR (KBr) 3295, 1670, 1660, 1535, 855 $cm^{-1}$; $^1H$ NMR $\delta$ 7.84 (s, 1 H), 7.24 (s, 5 H), 6.94 (d, $J$ = 10 Hz, 2 H), 6.07 (d, $J$ = 10 Hz, 2 H), 1.79 (s, 3 H); $^{13}C$ NMR $\delta$ 185.3, 170.2, 149.4 (2 C), 137.8, 128.7 (2 C), 127.9, 126.7 (2 C), 125.1 (2 C), 57.9, 22.8; mass spectrum, exact mass calcd for $C_{14}H_{13}NO_2$ $m/e$ 227.0946, obsd $m/e$ 227.0950.

**4-[*N*-(*tert*-Butoxycarbonyl)amino]-4-phenyl-2,5-cyclohexadienone (10g).** To a THF (30 mL) solution of *N*-(*tert*-butoxycarbonyl)-4,4-dimethoxybenzoquinone imine (0.7 g, 2.35 mmol) at −78 °C was added a 1.7 M PhLi solution (1.52 mL, 1.1 equiv). After being stirred for 1 h at −70 °C and for 20 min at room temperature, $H_2O$ was added, and the mixture was concentrated in vacuo. Extractive workup [$CH_2Cl_2$ (3 × 40 mL)/$H_2O$ (40 mL)] gave **9g** (0.332 g, 85%) as a light yellow oil, which was used in the next step without further purification: IR 1710 (br), 1490, 1365, 1250, 1160, 1100, 1070, 1035, 950 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.6–7.2 (m, 5 H), 6.32 (d, $J$ = 10 Hz, 2 H), 5.97 (d, $J$ = 10 Hz, 2 H), 5.09 (br s, 1 H), 3.31 (s, 3 H), 3.27 (s, 3 H), 1.32 (s, 9 H); $^{13}C$ NMR $\delta$ 153.9, 142.2, 134.5 (2 C), 128.0 (2 C), 126.6, 124.9 (4 C)8 92.7, 79.2, 56.1, 49.2, 49.0, 26.7 (3 C).

Crude **9g** (0.77 g, 2 mmol) was dissolved in THF (50 mL), 5% HCl (0.5 mL) was added, and the mixture was stirred for 1 min. After concentration in vacuo, extractive workup [$CH_2Cl_2$ (3 × 40 mL)/$H_2O$ (40 mL)] gave crude **10g**. Column chromatography (20:1 $CH_2Cl_2$/$(CH_3)CO$ as eluant) of this material gave pure **10g** (0.483 g, 89%) as a light yellow oil: IR (neat) 3320, 1710 (br), 1670, 1490, 1370, 1255, 1160 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.5–7.2 (m, 5 H), 7.0 (d, $J$ = 10 Hz, 2 H), 6.29 (d, $J$ = 10 Hz, 2 H), 5.3 (br s, 1 H), 1.39 (s, 9 H); mass spectrum no parent ($M^+ - CO_2$-*t*-Bu) was 40% of base peak calcd $m/e$ 185.0837, obsd $m/e$ 185.0877.

**4-(*N*-Benzoylamino)-4-phenyl-2-methoxy-2,5-cyclohexadienone Dimethyl Ketal (14a).** To a −78 °C solution of *N*-benzoyl-3-methoxy-*p*-benzoquinone imine dimethyl ketal (0.60 g, 2.1 mmol) in dry THF (6.0 mL) was added over 3 min a 1.9 M phenyllithium solution in 30% $Et_2O$/cyclohexane. After 15 min at −78 °C, TMEDA (0.6 mL) was added. After an additional 15 min at −78 °C, the dry ice bath was removed, the solution was stirred for 45 min, and the reaction was quenched by adding $H_2O$ (1 mL). Extractive workup [EtOAc (4 mL)] gave a yellow solid (0.767 g). Recrystallization from $CH_2Cl_2$/$Et_2O$/PE yielded a white solid in two crops (0.66 g, 86%), mp 148–151 °C. A portion was recrystallized from $CH_2Cl_2$/$Et_2O$/PE to constant mp: mp 152–153 °C; IR (KBr) 3400 (br), 1650, 1520, 1490, 1210, 1100, 1070 $cm^{-1}$; $^1H$ NMR [$(CD_3)_2CO$] $\delta$ 7.97–7.85 (m, 3 H), 7.57–7.23 (m, 8 H), 6.76 (dd, $J$ = 10 Hz, 2 Hz, 1 H), 5.81 (d, $J$ = 10 Hz, 1 H), 5.80 (d, $J$ = 2 Hz, 1 H), 3.63 (s, 3 H), 3.29, 3.26 (two overlapping s, 6 H). Anal. Calcd for $C_{22}H_{23}O_4N$: C, 72.31; H, 6.34. Found: C, 71.73; H, 6.36.

**4-(*N*-Benzoylamino)-4-phenyl-2-methoxy-2,5-cyclohexadienone (15a).** To **14a** (0.2207 g, 0.6 mmol) in THF (50 mL) was added a 5% AcOH solution (6 drops). After 16 h at room temperature, there was no reaction; however, after addition of TsOH (2 mg) and an additional 28 h at room temperature, hydrolysis occurred. Extractive workup [$CH_2Cl_2$ (80 mL)] gave a white solid, which was recrystallized from $Et_2O$/$CH_2Cl_2$ to give **15c** (128.5 mg, 61%) as a colorless solid: mp 188.5–190 °C; IR (KBr) 3340, 1664, 1643, 1612, 1520, 1483, 1291, 1209, 853, 708, 693 $cm^{-1}$; $^1H$ NMR $\delta$ 7.9–7.7 (m, 2 H), 7.6–7.18 (m, 9 H), 6.84 (br s, 1 H), 6.4–6.2 (m, 2 H), 3.70 (s, 3 H); $^{13}C$ NMR $\delta$ 180.7, 166.7, 150.6, 149.4, 139.3, 133.8, 131.9, 129.1, 128.6, 128.2, 126.9, 126.7, 124.9, 116.4, 59.9, 54.9; mass spectrum, exact mass calcd for $C_{20}H_{17}NO_3$ $m/e$ 319.1209, obsd $m/e$ 319.1209.

**4-(*N*-Benzoylamino)-4-(4′-methoxyphenyl)-2-methoxy-2,5-cyclohexadienone Dimethyl Ketal (14b).** To a solution of *p*-bromoanisole (0.25 g, 1.35 mmol) in dry THF (3.0 mL) at −78 °C was added over 3 min a 1.4 M *n*-BuLi solution (1.0 mL, 1.4 mmol) in hexane. After 35 min a solution of *N*-benzoyl-3-methoxy-*p*-benzoquinone imine dimethyl ketal (0.34 g, 1.2 mmol) in dry THF (3 × 1.0 mL) was added, followed by addition of TMEDA (0.6 mL) after 25 min. After an additional 30 min at −78 °C, the dry ice bath was removed, the solution was stirred for 2.5 h, and the solvent was removed in vacuo. Extractive workup [$CH_2Cl_2$ (2 × 2 mL)] gave a yellow oil (0.56 g), which was chromatographed on silica gel (10 g, 8 × 2 cm column, 40% EtOAc/PE as eluant) to yield the product as an off-white solid (0.22 g, 57%). Three recrystallizations from $CH_2Cl_2$/$Et_2O$/PE yielded a white solid: mp 139.5–140 °C; IR (KBr) 1650, 1510, 1250, 1080 $cm^{-1}$; $^1H$ NMR [$(CD_3)_2CO$] $\delta$ 7.93–7.81 (m, 3 H), 7.48–7.34 (m, 5 H), 6.89–6.63 (m, 3 H), 5.79–5.66 (m, 2 H), 3.75 (s, 3 H), 3.60 (s, 3 H), 3.25, 3.22 (two overlapping s, 6 H). Anal. Calcd for $C_{23}H_{25}O_5N$: C, 69.85; H, 6.37. Found: C, 69.60; H, 6.44.

**12a.** The imine ketal **2a** (800 mg, 2.4 mmol) was dried at 60 °C for 0.5 h, then placed in an oven-dried flask with a catalytic amount of *p*-TsOH (8.0 mg, 0.042 mmol). This mixture was then dissolved in dry $CH_2Cl_2$ (6.0 mL), and the solution was stirred for 3 min at room temperature. After addition of triethylamine (0.5 mL, 3.6 mmol) and water (5.0 mL), the solution was extracted ($CH_2Cl_2$, 20 mL) and dried over $CaSO_4$. Removal of the solvent gave a brown oil (655 mg), showing three spots by TLC. Chro-

matography on silica gel (39.5 g, 2.5 × 10 cm column, 5% EtOAc/H as eluant) resulted in some decomposition of the major product. However, the resulting colorless oil (289 mg, 40%) was crystallized from $(CH_3)_2CO$ to give a white solid, mp 91–93 °C. Recrystallization ($CH_3OH$) produced white crystals, mp 94–95 °C: IR (KBr) 1670, 1640, 1330, 1240 $cm^{-1}$; $^1H$ NMR [250 MHz, $(CD_3)_2CO$] $\delta$ 8.04 (d, $J$ = 8.2 Hz, 2 H), 7.55–7.24 (m, 8 H), 5.92 (AB q, $\Delta\nu$ = 21 Hz, $J_{AB}$ = 10 Hz, with higher field component coupled with $J$ = 2 Hz, 2 H), 5.26 (d, $J$ = 5.8 Hz, 1 H), 5.07 (dd, $J$ = 5.8, 2.0 Hz, 1 H), 3.69 (s, 3 H); $^{13}C$ NMR [$(CD_3)_2CO$, 62.9 MHz] $\delta$ 165.7, 157.6, 145.8, 135.3, 132.3, 129.5, 129.3, 129.0, 128.3, 126.1, 120.9, 87.4, 85.6, 74.5, 55.2; FAB mass spectrum, exact mass calcd for $C_{20}H_{18}O_2N$ $m/e$ 304.1337, obsd $m/e$ 304.1337.

***N*-[2-(4-Methoxybiphenylyl)]benzamide (13b).** To a solution of 4-methoxy-2-nitrobiphenyl[17] (106 mg) in EtOAc (15.0 mL) were added platinum oxide (15 mg) and EtOAc (5.0 mL). Hydrogenation of this mixture on a Parr apparatus at 64 psi for 10 h gave after workup a yellow-brown oil (100 mg), which was dissolved in THF (5.0 mL) with subsequent addition of triethylamine (1.0 mL). A solution of benzoyl chloride (0.5 mL) and THF (5.0 mL) was then added slowly, forming a white precipitate. Addition of $NaHCO_3$ (10.0 mL), concentration, and addition of water gave a yellow precipitate (100 mg), mp 107.0–112.0 °C. Recrystallization (EtOH/H) yielded a white solid (52 mg, 37% overall yield), mp 142.0–142.5 °C (lit.[18] mp 144.0–145.0 °C): IR (KBr) 3315, 1610, 1650, 1500, 1480 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 8.20 (d, $J$ = 2.6 Hz, 1 H), 8.00 (br s, 1 H), 7.55–7.31 (m, 10 H), 7.13 (d, $J$ = 8.5 Hz, 1 H), 6.72 (dd, $J$ = 8.5, 2.6 Hz, 1 H), 3.84 (s, 3 H).

***N*-[2-(5-Methoxybiphenylyl)]benzamide (13a).** The imine ketal **9a** (246 mg, 0.733 mmol) was dissolved in dry $CH_2Cl_2$ (5.0 mL), and the solution was cooled under nitrogen to −10 °C. Trimethylsilyl trifluoromethanesulfonate (0.156 mL, 0.807 mmol) was then added slowly via syringe, and the solution was stirred for 5 min. The solution was warmed to room temperature and stirred for 2.25 h. Triethylamine (1.0 mL) was then added and the solution was stirred for an additional 2.0 h. A 10% NaOH solution was added to the mixture, and the organic phase was separated and filtered through $Na_2SO_4$. Concentration gave a light brown solid (192 mg, 86.5%), mp 132–135 °C. Recrystallization from $CH_3OH$ gave a white solid: mp 142.0–142.5 °C; IR (KBr) 3285, 1645, 1525, 1490, 1220 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 8.20 (d, $J$ = 9.0 Hz, 1 H), 7.76 (br s, 1 H), 7.61–7.34 (m, 10 H), 6.97 (dd, $J$ = 9.0, 3.0 Hz, 1 H), 6.86 (d, $J$ = 3.0 Hz, 1 H), 3.83 (s, 3 H); mass spectrum, exact mass calcd for $C_{20}H_{17}O_2N$ $m/e$ 303.1259, obsd $m/e$ 303.1265.

***N*-[2-(4,5-Dimethoxybiphenylyl)]benzamide (16a).** A solution of **14a** (66 mg, 0.18 mmol) and $p$-toluenesulfonic acid monohydrate (ca. 2 mg) in dry $CH_2Cl_2$ (1.0 mL) under $N_2$ was stirred at room temperature for 45 min. The solution turned yellow after 15 min, and saturated aqueous $NaHCO_3$ (0.5 mL) was added. Extractive workup [$CH_2Cl_2$ (2 × 0.5 mL)] gave an off-white solid (49 mg). Column chromatography on silica gel (1 g, 8 × 1 cm column, 40–50% $Et_2O$/H as eluant) yielded **16a** (45 mg, 75%) as an off-white solid, mp 172–176 °C, followed by a small amount of the hydrolyzed ketal **15a** (3 mg, 0.5%). Recrystallization of the off-white solid from $CH_2Cl_2/Et_2O$/PE yielded a white solid: mp 179.5–180 °C; IR (KBr) 3320, 1650, 1520, 1490, 1280, 1220 $cm^{-1}$; $^1H$ NMR $\delta$ 8.20 (s, 1 H), 7.9 (br s, 1 H), 7.67–7.34 (m, 10 H), 6.81 (s, 1 H), 3.99 (s, 3 H), 3.89 (s, 3 H). Anal. Calcd for $C_{21}H_{19}O_3N$: C, 75.66; H, 5.74. Found: C, 75.06; H, 5.81.

***N*-[2-(4,4′,5-Trimethoxybiphenylyl)]benzamide (16b).** A sample of **14b** (100 mg, 0.29 mmol) under vacuum (0.25 mm Hg) was heated at 85–90 °C for 2 days. The sample was then passed through silica gel (1.5 g, 12 × 1 cm column, 30% EtOAc/PE as eluant) to yield the product as a white solid (82 mg, 78%). Recrystallization from $CH_2Cl_2/Et_2O$/PE yielded a white solid: mp 115–115.5 °C; IR (KBr) 1670, 1610, 1530, 1500, 1480, 1450, 1400, 1250, 1210, 1200, 1160 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 8.20 (s, 1 H), 7.91 (br s, 1 H), 7.65–7.61 (m, 2 H), 7.52–7.33 (m, 5H), 7.03 (d, $J$ = 9 Hz, 2 H), 6.79 (s, 1 H), 3.98 (s, 3 H), 3.87, 3.86 (two overlapping s, 6 H); mass spectrum, exact mass calcd for $C_{22}H_{21}O_4N$ $m/e$ 363.1471, obsd $m/e$ 363.1461.

**4-(*N*-Benzoylamino)-4-phenyl-2-methoxy-2,5-cyclohexadienone Ethylene Ketal (17).** To a solution of **14a** (103 mg, 0.28 mmol) in THF (2 mL) and ethylene glycol (1 mL) at 0 °C was added a solution of $p$-TsOH (2 mg) in THF (1 mL). After 40 min the reaction was quenched by addition of saturated aqueous $NaHCO_3$ (1 mL), and the solution was diluted with $H_2O$ (3 mL). Extractive workup [$CH_2Cl_2$ (5 mL, 2 × 2 mL)] gave a white solid (82 mg), which was chromatographed on silica gel (2 g, 6 × 1 cm column, 40% EtOAc/PE as eluant) to yield the title compound as a white solid (74 mg, 73%): mp 186–188 °C; IR (KBr) 3290, 1640, 1520, 1210, 1180, 1150, 1100, 960 $cm^{-1}$; $^1H$ NMR (250 MHz) $\delta$ 7.79 (d, $J$ = 7 Hz, 2 H), 7.51–7.22 (m, 8 H), 6.51 (s, 1 H), 6.46 (dd, $J$ = 10, 2 Hz, 1 H), 5.79 (d, $J_{AB}$ = 10 Hz, 1 H), 5.54 (d, $J_{AB}$ = 2 Hz, 1 H), 4.27–4.24 (m, 2 H), 4.14–4.11 (m, 2 H), 3.65 (s, 3 H); mass spectrum, exact mass calcd for $C_{22}H_{21}O_4N$ $m/e$ 363.1471, obsd $m/e$ 363.1471. Anal. Calcd for $C_{22}H_{21}O_4N$: C, 72.71; H, 5.82. Found: C, 72.05; H, 5.98.

**Dimethyl 2-[2-Methoxy-5-(*N*-benzoylamino)phenyl]malonate (18).** To a solution of dimethyl malonate (0.132 mL, 1.05 equiv) in THF (15 mL) was added NaH (46.2 mg, 1.05 equiv of mineral oil dispersion), and the mixture was stirred for 15 min. To the solution was added **2a** (0.27 g, 1.05 mmol) in THF (5 mL), and the mixture was stirred overnight and concentrated in vacuo. Extractive workup [$CH_2Cl_2$ (3 × 30 mL)/$H_2O$ (30 mL)] gave a light yellow oil. Flash column chromatography gave the title compound (344 g, 91%) as a colorless oil: IR (solution cell) 3420, 2950, 1760, 1740, 1675, 1530, 1505, 1440, 1320, 1295, 1240, 1200, 1185, 1160, 1030 $cm^{-1}$; $^1H$ NMR $\delta$ 8.15–7.9 (br s, 1 H), 7.9–7.7 (m, 3 H), 7.55–7.30 (m, 4 H), 6.83 (d, $J$ = 9 Hz, 1 H), 5.13 (s, 1 H), 3.75 (s, 3 H), 3.72 (s, 6 H); mass spectrum, exact mass calcd for $C_{19}H_{19}NO_6$ $m/e$ 357.1213, obsd $m/e$ 357.1259.

**1-Benzamido-4-methoxy-9,10-anthraquinone (19).** A mixture of dry THF (10 mL) and dimethyl sulfoxide (3 mL) was cooled to 0 °C, methyllithium (0.654 mL, 0.82 mmol, as a 1.25 M solution in $Et_2O$) was added, and the mixture was stirred for 5 min. The 3-cyano-1(3*H*)-isobenzofuranone[13] (0.129 g, 0.82 mmol) dissolved in dimethyl sulfoxide (3 mL) was added rapidly to the above solution, and the mixture was stirred for 5 min, during which time the solution turned orange. *N*-Benzoyl-*p*-benzoquinone imine dimethyl ketal (**2a**) (0.100 g, 0.39 mmol) dissolved in dry THF (5 mL) was added, and the reaction mixture was stirred at 0 °C for 0.5 h and at room temperature for 1 h. The reaction was quenched by addition of 5% aqueous HCl (2 mL), the mixture was concentrated in vacuo, and the resulting orange precipitate was collected by filtration to yield crude 1-benzamido-4-methoxy-9,10-anthraquinone (**19**) (0.068 g, 49%), mp 206–216 °C. Recrystallization from $CHCl_3/Et_2O$ yielded product (0.055 g, 40%): mp 240–242 °C (lit.[19] mp 244.4–245.4 °C); IR (KBr) 1680, 1665, 1590, 1525, 1250 $cm^{-1}$; $^1H$ NMR $\delta$ 13.27 (br s, 1 H), 9.35 (d, $J$ = 9.7 Hz, 1 H), 8.2 (m, 4 H), 7.6 (m, 5 H), 7.1 (br s, 1 H), 4.07 (s, 3 H); mass spectrum, exact mass calcd for $C_{22}H_{15}NO_4$ $m/e$ 357.1001, obsd $m/e$ 357.1013.

**Acknowledgment.** We acknowledge primary support from the National Institutes of Health with secondary support from the National Science Foundation.

**Registry No.** **1a**, 7472-54-0; **2a**, 106501-69-3; **2b**, 106501-77-3; **2** ($R^1$ = OBu-t), 106501-78-4; **2** ($R^1$ = Ph, $R^3$ = OMe), 117559-80-5; **3c**, 125593-44-4; **4a**, 39078-05-2; **4b**, 125593-40-0; **4c**, 125593-41-1; **4d**, 125593-42-2; **4f**, 125593-43-3; **4g**, 125593-59-1; **4h**, 7073-42-9; **5d**, 125593-45-5; **5e**, 77791-10-7; **5g**, 125593-60-4; **5h**, 31601-42-0; **9a**, 106501-81-9; **9b**, 106501-70-6; **9c**, 125593-55-7; **9f**, 125593-56-8; **9g**, 125593-57-9; **10a**, 106501-82-0; **10b**, 106501-71-7; **10c**, 125593-46-6; **10d**, 125593-66-0; **10f**, 106501-73-9; **10g**, 125593-47-7; **12a**, 125593-61-5; **13a**, 125593-51-3; **13b**, 54147-93-2; **14a**, 125593-48-8; **14b**, 125593-50-2; **14c**, 125593-58-0; **14** ($R^1$ = $R^2$ = OMe, $R^3$ = $(CH_2)_3OSi(Me)_2Bu$-*t*), 125610-32-4; **15a**, 125593-49-9; **16a**, 125593-52-4; **16b**, 125593-53-5; **16c**, 125593-65-9; **17**, 125593-54-6; **18**, 106501-72-8; **19**, 6409-75-2; $H_3CCH_2SH$, 75-08-1; PhLi, 591-51-5; $p$-$BrC_6H_4OMe$, 104-92-7; $F_3CSO_2OSiMe_3$, 27607-77-8; $MeOCOCH_2CO_2Me$, 108-59-8; $p$-$PhC_6H_4OH$, 92-69-3; $p$-$MeC_6H_4OH$, 106-44-5; pyrrole, 109-97-7; 4-methoxy-2-nitro-

(17) Smith, P. A. S.; Hall, J. H. *J. Am. Chem. Soc.* **1962**, *84*, 480.
(18) Campbell, I. G.; Morrill, D. J. *J. Chem. Soc.* **1955**, 1662.
(19) Lukin, A. M.; Mozgova, K. K. *Zhur. Obshchei. Khim.* **1950**, *20*, 1510.

biphenyl, 16098-16-1; 4-methoxy-2-aminobiphenyl, 38088-00-5; 3-cyano-1(3*H*)-isobenzofuranone, 27613-27-0; *N*-[3-chloro-4-methoxyphenyl]benzamide, 125593-62-6; 3-chloro-*p*-anisidine, 5345-54-0; 1-bromo-2-(3-hydroxypropyl)-4,5-dimethoxybenzene, 125593-63-7; 1-bromo-2[3-(*tert*-butyldimethylsilyloxy)propyl]-4,5-dimethoxybenzene, 125593-64-8; 3-(2-bromo-4,5-dimethoxyphenyl)propionic acid, 52679-49-9.

**Supplementary Material Available:** Raney nickel reduction of **4d** and **5d** to **1a**, all nucleophilic substitution reactions of **2b**, zinc-copper reductions of **10a** and **10b**, all compounds dealing with the preparation of **14c** and its chemistry, the reaction of **2b** with *s*-BuLi, and $^1$H NMR spectra of **3c**, **4d-f**, **5d,e**, and **12a** (15 pages). Ordering information is given on any current masthead page.

# Descriptive Photochemistry of Polyfluorinated Azide Derivatives of Methyl Benzoate

N. Soundararajan and Matthew S. Platz*

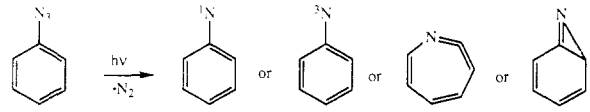
*Department of Chemistry, The Ohio State University, 120 W. 18th Avenue, Columbus, Ohio 43210*

*Received May 31, 1989*

The photochemistry of several polyfluorinated azide derivatizes of methyl benzoate have been studied in a variety of solvents. We have photolyzed methyl 3-azido-6-fluorobenzoate, methyl 3-azido-4-fluorobenzoate, methyl 4-azido-2-fluorobenzoate, methyl 3-azido-2,4-difluorobenzoate, methyl 3-azido-2,6-difluorobenzoate, methyl 3-azido-2,4,6-trifluorobenzoate, and methyl 4-azido-2,3,5,6-tetrafluorobenzoate in toluene, cyclopentane, tetramethylethylene, diethylamine, dimethyl sulfide, dimethyl disulfide, and methanol in an attempt to capture the photogenerated reactive intermediates. Adducts were not formed in cyclopentane, dimethyl disulfide, and methanol solvents. Adducts were formed, however, but in modest yields, in the other solvents. In general the yield of adducts increases with the number of fluorine substituents present, and ortho and para fluorine substituents relative to the azide group are more effective in enhancing the yield of adducts relative to meta fluorine substitution.

## Introduction

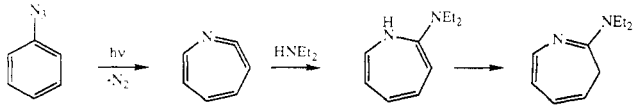
The photochemistry of aryl azides has been described as wonderfully complex.[1] Photolysis of parent phenyl azide (**1**) leads to fragmentation to produce molecular nitrogen and reactive intermediate $C_6H_5N$. The structure of $C_6H_5N$ might in principle be either singlet phenylnitrene **2S**, triplet phenylnitrene **2T**, azacycloheptatetraene **3**, or benzazirine **4**.[2] To our knowledge singlet phenylnitrene




1 2S 2T 3 4

**2S** has never been chemically intercepted at ambient temperature. Braumann and Drzaic[3] have determined that the energy separation between singlet and triplet phenylnitrene is approximately 4.3 kcal/mol, with the triplet nitrene being the lower energy species.

Work performed in several laboratories is in agreement that the major, trappable, reactive species present in solution upon photolysis of **1** is the ketenimine **3**.[1,4] Doering an Odum[5] have trapped **3** with diethylamine to produce **5** in greater than 30% yield.




1 3 6 5

The absolute kinetics of this reaction were first studied by Sundberg[6] and subsequently by Schuster and Schrock[1] by flash photolysis with UV-vis detection of **6**. Very recently Schuster and Poliakof[1] have studied the dynamics of **3** directly by flash photolysis with IR detection.[1]

In the absence of amines, ketenimine **3** polymerizes; thus photolysis of **1** in nonnucleophilic solvents gives small amounts of aniline and azobenzene and mostly tar.[7]

These results do not automatically extrapolate to other aryl azides. It is now established that photolysis of various substituted aryl azides do indeed produce nitrenes and benzazirines as trappable intermediates in solution. Thus the nature of the reactive intermediate produced from a given azide is not readily predictable and as a consequence neither are the identities of the adducts that they might ultimately form in the presence of a particular trapping agent.

These considerations are of special importance in photoaffinity labeling,[8] a biochemical technique that frequently employs aromatic azides.[9] In a photoaffinity labeling (PAL) experiment one appends a light-sensitive moiety (e.g., an azide group) to a natural ligand of a biological receptor. The light-sensitive ligand is allowed to bind to a biological receptor. Upon photolysis of the complexed ligand a reactive intermediate is released that in a successful PAL experiment will react quickly and irreversibly with a nearby residue to produce a robust new covalent bond between the labeling reagent and the receptor. This results in "permanent" attachment of the label to the target biomolecule. An ideal reactive intermediate for PAL work will be one that reacts with the first bond it encounters, even an unactivated CH bond. Thus,

(1) (a) Schrock, A. K.; Schuster, G. B. *J. Am. Chem. Soc.* **1984**, *106*, 5229. (b) You-Zhuo, Li; Kirby, J. P.; George, M. V.; Poliakoff, M.; Schuster, G. B. *J. Am. Chem. Soc.* **1988**, *110*, 8092.

(2) Smith, P. A. S. *Azides and Nitrenes*; Scriven, E. F. V., Ed.; Academic Press: San Diego, 1984; p 95.

(3) Drzaic, P. S.; Braumann, J. I. *J. Am. Chem. Soc.* **1984**, *106*, 3443.

(4) (a) Leyva, E.; Platz, M. S.; Persy, G.; Wirz, *J. J. Am. Chem. Soc.* **1986**, *108*, 3783. (b) Li, Y.-Z.; Kirby, J. P.; George, M. W.; Poliakoff, M.; Schuster, G. B. *J. Am. Chem. Soc.* **1988**, *110*, 8092.

(5) Doering, W. von E.; Odum, R. A. *Tetrahedron* **1966**, *22*, 81.

(6) DeGraff, B. A.; Gillespi, D. W.; Sundberg, R. J. *J. Am. Chem. Soc.* **1973**, *95*, 7491.

(7) Meijer, E. W.; Nijhuis, S.; von Vroonhaven, F. C. B. M. *J. Am. Chem. Soc.* **1988**, *110*, 7209.

(8) Bayley, H. *Photogenerated Reagents in Biochemistry and Molecular Biology*; Elsevier: New York, 1983.

(9) Bridges, A. J.; Knowles, J. R. *Biochem. J.* **1974**, *143*, 663.

0022-3263/90/1955-2034$02.50/0 