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Barbituric Acid as a Substituent at Aryl Methylium Ions

Stefan Spange,*[,†] Mirko Bauer,[†] Bernhard Walfort,[‡] and Heinrich Lang[‡]

Department of Polymer Chemistry and Department of Inorganic Chemistry, Institute of Chemistry, Chemnitz University of Technology, Strasse der Nationen 62, D-09111 Chemnitz, Germany

stefan.spange@chemie.tu-chemnitz.de

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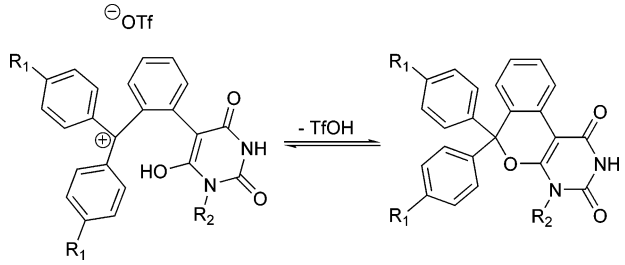

Activation of different benzophenone derivatives with triflic anhydride for electrophilic aromatic substitution of 5-phenylbarbituric acids leads to regioselective formation of the ortho-substituted product. The resulting triphenylmethylium salt can be isolated when the Michlers ketone is used. More electrophilic cations form cyclic enol ethers such as 1-*n*-butyl-9,9-diaryl-1,9-dihydro-10-oxa-1,3-diazaphenanthrene-2,4-diones. Alternatively, supramolecular complex formation with 2,6-diacetamido pyridine as well as carbenium ion generation have been studied. Although in dilute acid only protonation of one of the carbonyl oxygens occurs, ring opening of the cyclic enol ether toward the carbenium ion is observed in 96% sulfuric acid.

Substituted triarylmethylium ions are well-established compounds for various applications.[1,2] The substituents at the central carbenium ion determine the electrophilicity of the carbenium ion as well as the sterical accessibility toward various nucleophiles.[3] We searched for such a substituent which can control the reactivity of the carbocation by external chemically induced change of the substituent's electronic effects in a more complex way than simple protonation does, e.g., at the dimethylamino group of crystal violet.

The objective of this note is to show the first results on a way to construct novel compounds which are principally suitable for both molecular recognition by means of complementary hydrogen bond formation and carbenium ion generation. As the strength of hydrogen bonds, and thus their influence on the substituent's electronic effects, can be varied nearly infinitely, these systems may be a new attempt toward a fine-tuning of the electrophilicity of carbenium ions.

We chose the unsubstituted and mono-*N*-substituted barbituric acid moiety as the substituent as it provides at least one ADA (D = hydrogen bond donor, A = hydrogen bond acceptor) pattern which can form complementary hydrogen bonds toward receptors containing a DAD sequence.[4−9] Related structures containing a tropylium moiety were already prepared by Nitta et al. as flavin model systems but were not yet examined concerning supramolecular features.[10]

In this communication, we report on the results of the electrophilic substitution reaction of 5-phenylbarbituric acid and 5-phenyl-1-*n*-butylbarbituric acid, respectively, with several benzophenone derivatives as an approach to the target compound class.

The synthetic approach toward those barbituric acid substituted triarylmethylium ions was initially inspired from the electrophilic substitution reaction of 5-phenylbarbituric acids with 2-methylsulfanyl-1,3-dithiolium ions, leading to *para*-quinoid systems.[11,12] However, this method proved not to be that simple as the activation of benzophenones with $ZnCl_2$, BCl_3, or HBF_4 failed to give any product with 5-phenyl-1-*n*-butylbarbituric acid. The electrophilic activation of these aromatic carbonyl compounds has been accomplished solely by triflic anhydride (Tf_2O). It is known that triflic anhydride reacts with various carbonyl groups to give a trifluoromethansulfonyloxy carbenium ion which equilibrates with a dication ether.[13] In the case of 4,4′-dimethoxybenzophenone, the cation **1b** is formed (Scheme 1) as is indicated by its ^{19}F NMR spectrum which shows two peaks at −72.2 and −78.8 ppm relative to $CFCl_3$ for the covalently bound and anionic triflate, respectively.[13a] It seems reasonable to assume similar intermediates for the other benzophenone derivatives as well.

The Friedel−Crafts alkylation of 5-phenylbarbituric acids with Tf_2O-activated benzophenones exclusively takes place at

† Department of Polymer Chemistry.

‡ Department of Inorganic Chemistry. To whom correspondence pertaining to X-ray structure analyses should be addressed.

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SCHEME 1. Electrophilic Aromatic Substitution of 5-Phenylbarbituric Acids with Tf_2O-Activated Benzophenones and Equilibria between the Neutral Form and Cationic Species of the Products

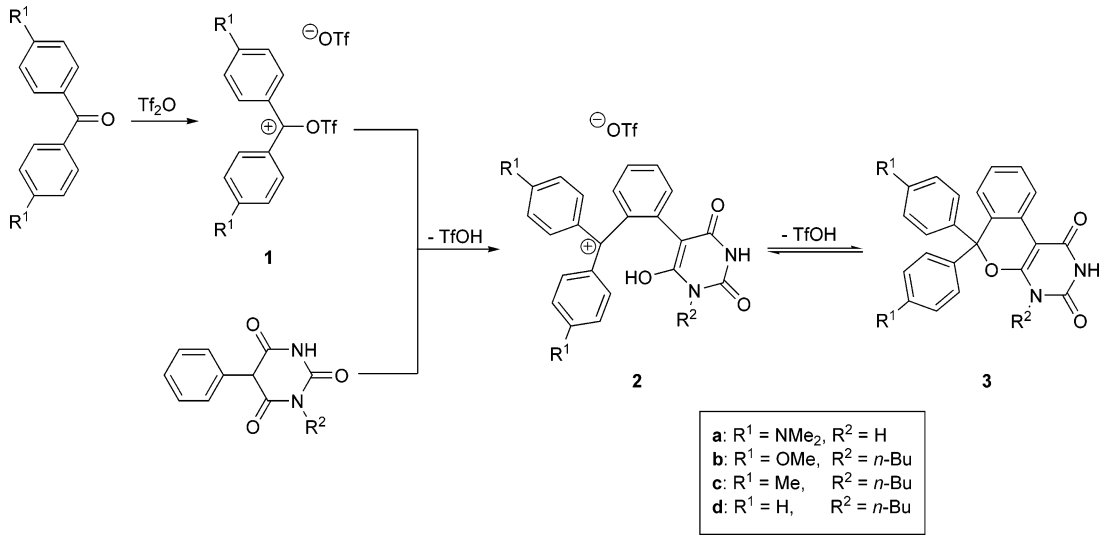

TABLE 1. Isolated Products of the Reaction of 5-Phenylbarbituric Acids with Benzophenone Derivatives According to Scheme 1 and UV/Vis Absorption Maxima Measured in 96% Sulfuric Acid

	R^1	R^2	yield [%]	pK_{R+}	λ_{max} [nm]
2a	NMe_2	H	31	7.0	378
3b	OMe	*n*-Bu	30	−1.1	525
3c	Me	*n*-Bu	17	−4.4	481
3d	H	*n*-Bu	22	−6.6	438

the ortho position of the phenyl ring (Scheme 1). A para-substituted product was never observed. Obviously, the enol form of the barbituric acid seems to be responsible for this result because phenobarbital (5-ethyl-5-phenylbarbituric acid), which cannot form a related enol form, does not react in such a way. However, mechanistic investigations on this reaction are the subject of further studies.

Results of the Friedel−Crafts reaction of 5-phenylbarbituric acids with several aromatic ketones are given in Table 1 , which also contains pK_{R+} values of structurally related carbenium ions where the barbituric acid moiety is missing,[1] as well as UV/vis spectroscopic data of the compounds measured in 96% sulfuric acid at room temperature.

The initial product of this reaction after aqueous workup is supposed to be carbenium ion **2** which equilibrates with the cyclic enol ether **3** (Scheme 1), comparable to phenolphthaleine dyes. Although N substituents at the barbituric acid moiety largely affect the solubility of these compounds, they exert hardly any influence on this intramolecular recombination reaction. The equilibrium mainly depends on the substituents at the remaining two phenyl rings and thus on the Lewis acidity of the carbenium ion.

A rough estimation of this equilibrium can be made by applying the rule for cation−anion recombination suggested by Feigel and Kessler.[14] If the difference ΔpK between pK_a (of the corresponding acid of the substituent) and pK_{R+} (of the carbenium ion) is <0, then the ionic or zwitterionic form should dominate. If $\Delta pK > 0$, then the covalent form of the compound dominates. This relation can be evaluated using a value of $pK_a = 2.3$ for 5-phenylbarbituric acid[15] and the pK_{R+} of structurally related tritylium ions where the barbituric acid moiety is missing[1] (Table 1). As expected, the bis(4-*N*,*N*-dimethylamino)-substituted derivative **2a** with $\Delta pK = -4.7$ can be isolated as a deep blue ionic compound whereas the other tritylium ions, showing $\Delta pK > 0$, form colorless covalent species.

This covalent species originates from the formation of a cyclic enol ether bond. In the case of *n*-butyl-substituted derivatives, this reaction shows a remarkably high regioselectivity affording 1-*n*-butyl-9,9-diaryl-1,9-dihydro-10-oxa-1,3-diazaphenanthrene-2,4-diones **3b**−**d**. The 3-*n*-butyl derivative, whose occurrence would disturb the aimed hydrogen bond pattern, is not observed. The molecular structure has been evidenced by high-resolution ^1H and ^{13}C NMR spectroscopy. Furthermore, the 2,6-diacetamido pyridine (DAcP) adduct of **3c**, which is based on a complementary triple hydrogen bond pattern, was examined by X-ray structure analysis (Figure 1).

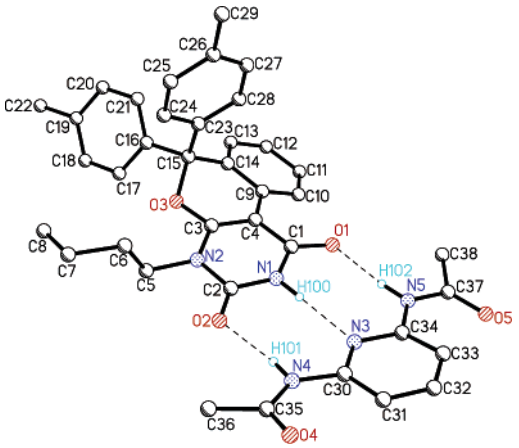

FIGURE 1. X-ray structure of the 1-*n*-butyl-9,9-bis(4-methylphenyl)-1,9-dihydro-10-oxa-1,3-diazaphenanthrene-2,4-dione/2,6-diacetamido pyridine adduct.

The complementary hydrogen bond pattern is also observed in $CDCl_3$ solution. From ^1H NMR titration, an equilibrium constant of $K_c = 1330 \pm 70$ L mol^{-1} (1:1 complex stoichiom-

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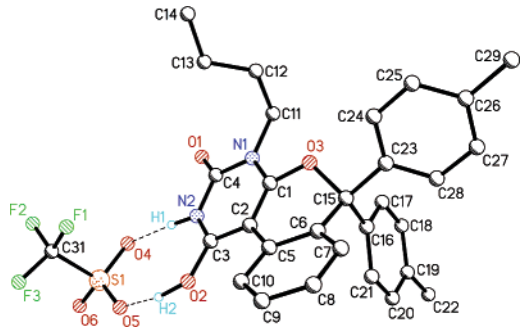


FIGURE 2. X-ray structure of the 1-*n*-butyl-9,9-bis(4-methylphenyl)-1,9-dihydro-10-oxa-1,3-diazaphenanthrene-2,4-dione/triflic acid adduct.

etry) for the **3c**/DAcP complex has been determined.[16] This complex formation seems to not be sufficient for generating the carbenium ion of this system which may be attributed to the high reactivity of the resulting tritylium ion.

Thus, a treatment with triflic acid (TfOH) has been carried out to generate the carbenium ion from the covalent precursor. If an equimolar amount of TfOH is used, a crystalline colorless product is obtained. Its X-ray structure analysis shows protonation at one of the carbonyl oxygen atoms of the barbituric acid moiety (Figure 2). However, this protonation is also not sufficient to generate the carbenium ion despite the increase of the central C−O bond distance (1.502 Å) compared to that of the solid **3c**/DAcP complex (1.491 Å).

The typical color and characteristic UV/vis absorption band of the triarylmethylium ions have been observed when an excess of acid has been added, but a stable crystalline salt was still not available. ^{1}H NMR investigations showed that a diprotonation of the barbituric acid moiety takes place leading to dicationic species.[17,18] Therefore, UV/vis spectra of the arylmethyl carbenium ions have been measured in 96% sulfuric acid,[19] in which color-stable solutions are obtained (Figure 3, Table 1).

The formation of the tritylium ions occurs similarly compared to that of nonsubstituted derivatives as shown by the established LFE (linear free energy) relationship of the UV/vis absorption energy (ν_{max}) as a function of the HAMMETT σ_p^+ substituent characteristics[20] (Figure 4). For comparison, Figure 4 also contains the value for **2a** in CH_2Cl_2.

Virtually, the protonated barbituric acid should serve as an electron-withdrawing substituent. Indeed, the sterical requirements are responsible for a strong twisting of the barbituric acid substituted phenyl ring. As the remaining two rings win planarity, the π-conjugation between them is improved causing the UV/vis absorption maxima of the corresponding carbenium ions to shift to a lower energy compared to the nonbarbituric acid substituted derivatives.

In fact, the results reported in this note on a new class of compounds show that aryl carbenium ions can be generated

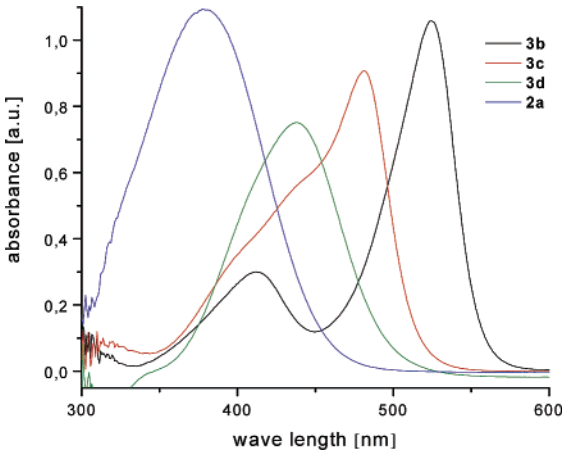


FIGURE 3. UV/vis spectra of **2a** and **3b**−**d** measured in 96% sulfuric acid.

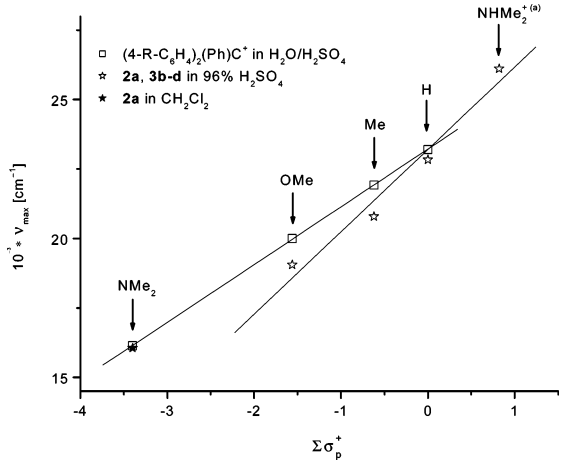
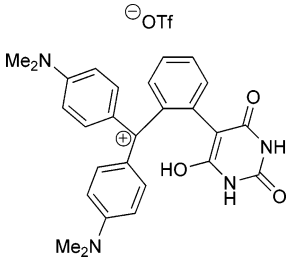


FIGURE 4. Correlation of the UV/vis absorption energy (cm^{-1}) as a function of σ_p^+ [20] of the triarylmethylium ions in 96% sulfuric acid. The square plots are UV/vis data from related 4,4′-disubstituted triarylmethylium ions without the *ortho*-barbituric acid substituent from refs 19a and 21. The σ_p^+ of NMe_3^+ has been used.

bearing barbituric acid substituents. The covalent precursors of these cations are obtained in a facile nucleophilic substitution reaction of 5-phenylbarbituric acids with benzophenones which involves two highly regioselective steps. The compounds have proved to possess the potential to bind via a complementary hydrogen bond pattern. In further work, we will show that those compounds react manifold with acids and bases forming various molecular and supramolecular structures.

Experimental Section

2-(6-Hydroxypyrimidin-2,4-dion-5-yl)-phenyl-bis(4-dimethylaminophenyl)-methylium triflate 2a. A solution of 1.541 g (5.74



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mmol) of 4,4′-bis(dimethylamino)benzophenone in 10 mL of dichloromethane is slowly treated with 1.00 mL (1.670 g, 5.92 mmol) of triflic anhydride. After stirring for 15 min, the deep blue solution is treated with 1.281 g (6.27 mmol) of 5-phenylbarbituric acid and the mixture is stirred for 48 h at room temperature. After addition of 10 mL of a 10% aqueous Na_2CO_3 solution, stirring continues for 1 h, whereat a dark precipitate forms. Precipitation is finished with toluene, and the solid is filtrated and washed with water and toluene. Recrystallization from acetone/toluene and drying in vacuo affords 1.079 g (31%) of **2a** as a green solid still containing traces of toluene (approximately 2 wt %).

Mp: 223 °C (decomp.). ^{1}H NMR (400 MHz, CD_3CN): δ [ppm] 3.28 (s, 12 H), 6.99 (m, 5 H), 7.18 (t, $^3J_{15,14} = 7.8$ Hz, $^3J_{15,16} = 7.8$ Hz, 1 H), 7.63 (d, $^3J_{16,15} = 7.8$ Hz, 1 H), 7.77 (m, 5 H). ^{13}C{^{1}H} NMR (101 MHz, CD_3CN): δ [ppm] 41.5, 88.6, 115.4, 123.7, 124.7, 126.2, 127.6, 131.7, 132.6, 138.0, 138.8, 152.0, 158.0, 162.6, 164.5. ^{19}F NMR (376 MHz, CD_3CN) δ [ppm] −78.0. IR (KBr): $\tilde{\nu}$ [cm^{-1}] 3073 w, 2929 m, 2867 m, 2815 w, 1692 w, 1586 vs, 1491 s, 1408 vs, 1372 vs, 1269 m, 1169 vs, 1030 m, 940 m, 909 m, 832 w, 723 m. UV/Vis (CH_2Cl_2): λ_{max} [nm] 423, 623. ESI-MS: *m*/*z* (%) 455.2 (4) [M]$^+$, 294.2 (100).

General Procedure for 1-*n*-Butyl-9,9-diaryl-1,9-dihydro-10-oxa-1,3-diazaphenanthren-2,4-diones 3b−d. A solution of 5.92 mmol of the appropriate benzophenone in 10 mL of dichloromethane is slowly treated with 1.00 mL (1.670 g, 5.92 mmol) of triflic anhydride. After stirring for 15 min, the deeply colored solution is treated with 1.51 g (5.8 mmol) of 1-*n*-butyl-5-phenyl barbituric acid and the mixture is stirred for 24 h at room temperature. After addition of 20 mL of a 10% aqueous Na_2CO_3 solution, stirring continues for 3 h, whereat the mixture decolorizes. The organic layer is separated and washed with water. By adding toluene, the product is precipitated and the solid is filtrated, recrystallized from $CHCl_3$/toluene, and dried at 115 °C.

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Supporting Information Available: General methods and full characterization data for compunds **2a** and **3b**−**d**. Crystallographic data for **3c**/DAcP and **3c**/TfOH adducts. Data of ^{1}H NMR titration of **3c** with DAcP. This material is available free of charge via the Internet at http://pubs.acs.org.

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