# A General Synthesis of Quinone Ammonium Salts

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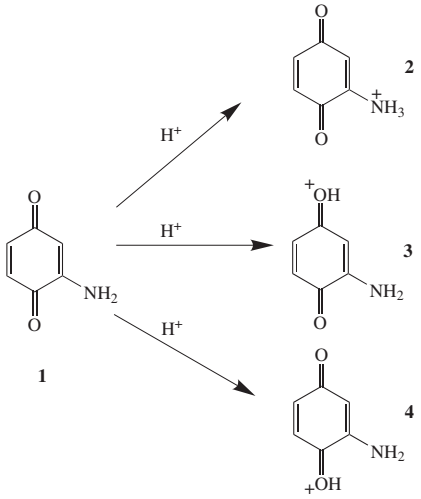
**Abstract:** A three-step procedure has been developed to convert substituted *p*-dimethoxybenzenes to quinone ammonium salts. Five examples of quinone ammonium salts have been prepared with this procedure. In the first step, the aromatic species is reacted with *N*-(hydroxymethyl)trifluoroacetamide and trifluoroacetic acid. The trifluoroacetamide product is then oxidatively demethylated and finally hydrolyzed to afford the quinone ammonium salt.

**Key words:** ammonium quinones, dimerizations, electrophilic aromatic substitutions, crystal structures, ammonium salts

We needed a series of variously substituted quinone ammonium salts to study charge-transfer phenomena between the quinones and redox partners mediated by noncovalent interactions formed by complexation of the ammonium salts to polyether macrocycles. In the literature, we were only able to uncover a single example of a discrete monocyclic quinone ammonium salt, which was synthesized by the oxidation of 6-hydroxydopamine (2,4,5-trihydroxyphenylethylammonium hydrobromide) with Frémy's salt to the corresponding quinone ammonium salt.[2] Our approach instead involves generation of a fully-substituted quinone that bears a protected amine group that can be hydrolyzed in a final step to generate the quinone ammonium salt. We report here five examples of quinone ammonium salts prepared using our approach.

Our initial attempts to make ammonium salts centered around the known species, 2-aminobenzoquinone **1**.[3] We successfully repeated, albeit in significantly lower yields than reported, the synthesis of this compound by oxidation of (trifluoroacetylamino)hydroquinone with phenyliodine diacetate followed by deprotection during chromatography on acidic alumina.

With quinone **1** in hand, we attempted to form an ammonium salt by protonation. However, we were unable to form a stable quinone ammonium salt species, since any treatment with acids caused reduction to hydroquinones, usually containing a nucleophile derived from the acid. This occurred even with weak acids, such as acetic acid, or non-nucleophilic acids, such as tetrafluoroboric. We interpreted these results to indicate that protonation occurs more readily at a quinone oxygen than on the amino group in this system leading to the undesired chemistry. This idea is consistent with restricted Hartree–Fock calculations we performed (Basis Set: 6-311G++) on 2-ammoniumbenzoquinone **2** and the two species formed by protonation of 2-aminobenzoquinone on either possible oxygen (Scheme 1).[4] According to this level of theory, the species **3** protonated at the carbonyl oxygen distal to the amino group is about 17.6 kcal/mol more stable than the ammoniumbenzoquinone **2**. Not surprisingly, the species protonated at the carbonyl oxygen proximal to the amino group **4** is predicted to be about 5.4 kcal/mol less stable than the ammonium salt.




**Scheme 1**

We also experienced similar difficulties with schemes that involved formation of readily prepared salts of 2-aminohydroquionone followed by attempted oxidations. Thus, we concluded that quinones/hydroquinones with an amino group directly attached are not robust and are prone to substitution at the position *para* to the amino group of the quinone nucleus. Accordingly, we turned our attention to preparing quinones in which (1) the ring positions are substituted, thus blocking the primary path of nucleophilic attack on the quinone nucleus, and (2) an insulating methylene group is present. This second factor would also ensure protonation on nitrogen rather than on a carbonyl oxygen, since the systems would no longer be vinylogous amides.

The overall methodology that we developed is illustrated in Scheme 2. We first performed an amidomethylation reaction [5] on a pentasubstituted benzene derivative, which has two methoxy groups in a *para* relationship. This reac-

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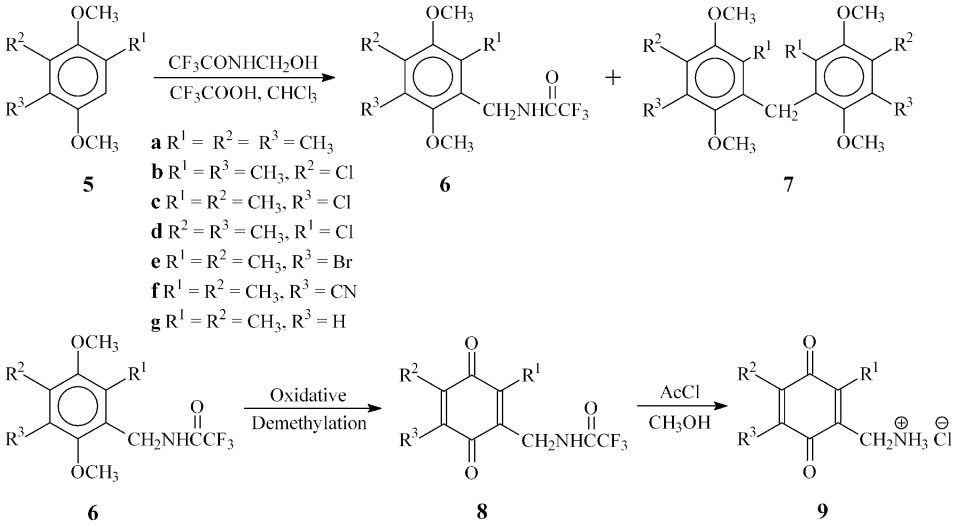


**Scheme 2**

tion produces the desired amidomethylation product **6**, as well as an interesting bisarylmethane side product **7**, with most of the substrates **5**. We then subjected **6** to an oxidative demethylation reaction to produce quinone amide **8** that can finally be hydrolyzed to the desired ammonium salt **9**. We now discuss the specific examples we studied.

To make the trimethyl-substituted quinone, we reacted known **5a** with *N*-(hydroxymethyl)trifluoroacetamide and trifluoroacetic acid in chloroform. This afforded the desired trifluoroacetamide product **6a** in 49% yield as well as the interesting dimeric by-product **7a** in 40% yield. We observe this by-product in most of the other reactions of this type that we have studied and have already communicated our results in this area which focused on the structures of the dimeric products.[6] Only a few other examples of dimeric products of this type are known from amidomethylations, and these were derived from more reactive aromatic substrates and under different reaction conditions.[5] In any case, the desired trifluoroacetamide product **6a** is easily separated by silica chromatography from the dimer **7a** and starting material (which co-elute under the conditions we explored). The ease of separation of the trifluoroacetamide products **6** was general for all of the cases we studied.

Trifluoroacetamide **6a** was then oxidatively demethylated with nitrogen dioxide[7] in a very facile reaction that afforded a 92% yield of **8a**. Finally, **8a** was hydrolyzed in methanolic hydrogen chloride in a quantitative fashion to give the chloride salt **9a**.

We next explored the same set of reactions with the three chlorodimethoxydimethylbenzene isomers **5b–d**. The preparation of substrates **5b–d** is described in the experimental section.[12–15] We decided to explore this chemistry on all three isomers since it was unclear if the substitution pattern would affect the chemistry. We were able to convert all three isomers **5b–d** to the quinone ammonium salts **9b–d**; however, there were some differences from the similar reactions with **5a**.

All three isomers **5b–d** successfully afforded the desired trifluoroacetamide upon reaction with *N*-(hydroxymethyl)trifluoroacetamide and trifluoroacetic acid in chloroform but with lower yields and under somewhat different reaction conditions than for **5a**. The oxidative demethylation reaction of **6b–d** with nitrogen dioxide gave only recovered starting material in this series, presumably due to the electron-withdrawing effect of the chlorine substituent. Therefore, the more reactive oxidant CAN was used for these cases.[8] The oxidative demethylation with CAN of **6b–d** worked well in each case (> 70% yield) to give the quinone amides **8b–d**. Hydrolysis of these quinones **8b–d** was performed in the same fashion as for **8a** to give the quinone ammonium salts **9b–d**, generally in nearly quantitative yields.

While we have fully characterized all compounds in the chloro series, we also attempted to grow suitable crystals of many of these materials for X-ray analysis. This proved successful for compounds **8c** and **9b** (Figures 1 and 2). These structures are in complete agreement with our assignments. Furthermore, the structure of **9b** is the first example of an X-ray structure of a quinone ammonium salt.

In order to synthesize a larger homologous series of compounds, we then prepared the bromo substrate **5e** and cyano substrate **5f** and subjected each to the amidomethylation reaction. The reaction proceeded in similar fashion to the chloro cases for **5e**: a separable mixture of desired trifluoroacetamide **6e**, the dimer **7e**, and 3,5-dibromo-1,4-dimethoxy-2,6-dimethylbenzene was obtained. We later found a better method to prepare **6e**: direct bromination of the unsubstituted adduct **6g**, which avoids the formation of the dibromo compound. The cyano substrate afforded very little if any of the desired amidomethylation product under our normal reaction conditions. Therefore, **6f** was prepared from the bromo

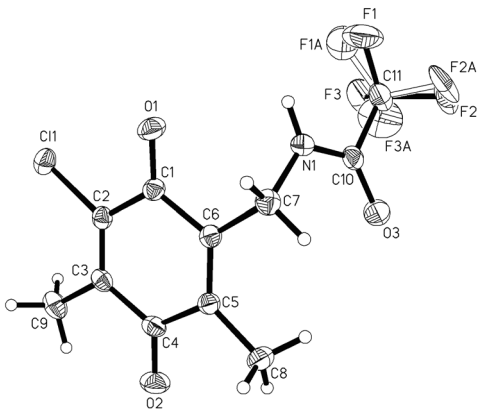


**Figure 1** General view of molecule **8c**. Fluorine atoms are disordered and occupy two different positions. The non-H atoms are shown with thermal ellipsoids drawn at the 30% probability level. H atoms are drawn as circles of arbitrary small radius for clarity.

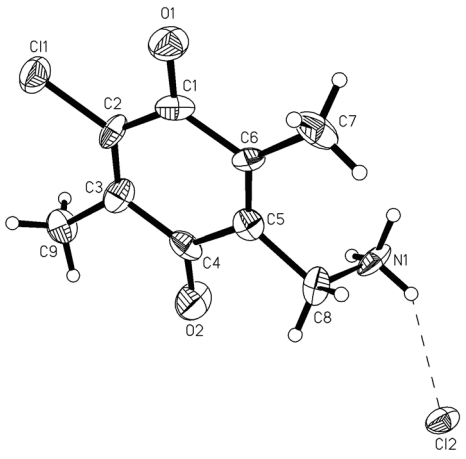


**Figure 2** General view of salt **9b**. Cation and anion are linked by N-H···Cl H-bond. The non-H atoms are shown with thermal ellipsoids drawn at the 30% probability level. H atoms are drawn as circles of arbitrary small radius for clarity.

compound **6e** using the Rosenmund–von Braun reaction.[9] Thus, reaction of **6e** with CuCN in DMF gave an 80% yield of **6f**.

We attempted oxidative demethylation of **6f** with CAN as described above. However, this reaction was slow and gave a mixture of products including some from oxidation of a methyl group. Therefore, we reacted **6f** in glacial acetic acid with concentrated nitric acid.[10] This reaction accomplished the necessary oxidative demethylation reaction without hydrolyzing either the amide or cyano groups giving **8f** in 95% yield. This oxidative demethylation procedure worked equally well with the bromo compound **6e** to give **8e**. Since all of our compounds **6** are not prone to aromatic nitration due to complete substitution, it seems likely that the nitric acid procedure would probably be the most convenient for all cases. The bromo compound **8e** was hydrolyzed with methanolic hydrogen chloride in quantitative yield as before to give the quinone ammonium salt **9e**. Unfortunately, attempted hydrolyses of the cyano derivative **8f** have only yielded complex reaction mixtures to date; we have attempted this reaction with methanolic hydrogen chloride, acetic acid, and the non-nucleophilic acid $HBF_4$ in MeOH. It seems likely that the extended conjugation provided by the cyano group induces greater reactivity for **8f** than in the other cases we examined.

In conclusion, we have developed a general procedure to produce quinone ammonium salts that we have utilized to produce such salts on gram scale. Our procedure has three steps: 1) the reaction of a pentasubstituted benzene derivative with *N*-(hydroxymethyl)trifluoroacetamide and trifluoroacetic acid; 2) the oxidative demethylation of the formed trifluoroacetamide with various reagents; and 3) the hydrolysis of the amide bond of the quinone amide formed in the second step. The yields of steps 2 and 3 are high in each case. The yield of step 1 is attenuated compared to those of the other steps, in part due to the formation of interesting dimeric side products **7**. This fact is partially ameliorated by the ease of purification of the trifluoroacetamides **6**. The synthesized quinone ammonium salts **9** are novel species with few similar compounds reported in the literature. We report here the first X-ray structure of such a species. These salts will be useful for studying charge-transfer reactions between the quinones[11] and suitable redox partners upon the preparation of supramolecular complexes formed by complexation of the ammonium moiety with substituted crown ethers.

Starting materials were commercially available unless otherwise noted. *N*-(Hydroxymethyl)trifluoroacetamide was purchased from Lancaster. MeOH was dried over 3 Å molecular sieves and DMF was dried over 4 Å molecular sieves. NMR spectra were taken on a Bruker AC300 spectrometer operating at 300 MHz for $^1$H NMR and 75 MHz for $^{13}$C NMR. TMS was used as internal reference for $^1$H NMR, and solvent peaks (77.00 for $CDCl_3$ or 39.5 for DMSO-$d_6$) were used as reference for $^{13}$C NMR spectra. Assignments were made using model compounds and coupled spectra. Assignments of similar peaks marked by *, †, §, ‡ are uncertain and could be interchanged. Melting points were determined on a Thomas-Hoover Uni-Melt, a Laboratory Products Mel-Temp II, or an Instec STC200B hot stage and are uncorrected.

**2-Chloro-3,6-dimethyl-4-methoxyphenol**

Anhyd MeOH (70 mL) was cooled in ice and stirred magnetically under nitrogen. AcCl (7.0 mL, 0.1 mole) was added slowly and carefully via syringe (caution – sputtering). The solution was stirred at 0 °C for 30 min and then 2,5-dimethyl-1,4-benzoquinone (*p*-xyloquinone) (1.36 g, 10 mmol) was added all at once as a solid, which then slowly dissolved. The cooling bath was removed and the solution was stirred overnight at r.t. The yellow solution was concentrated on a rotary evaporator and then dried under high vacuum to give the phenol (1.86 g, 100%) as a pink crystalline solid.

$^1$H NMR (DMSO-$d_6$): δ = 8.41 (s, 1 H, OH), 6.72 (s, 1 H, ArH), 3.71 (s, 3 H, $OCH_3$), 2.19 (s, 3 H, $ArCH_3$-3*), 2.14 (s, 3 H, $ArCH_3$-6*).

$^{13}$C NMR (DMSO-$d_6$): δ = 150.4 (ArC-4), 144.4 (ArC-1), 123.7 (ArC-3), 122.5 (ArC-2), 121.4 (ArC-6), 111.8 (ArC-5), 56.0 ($OCH_3$), 16.9 ($ArCH_3$-6), 12.9 ($ArCH_3$-3).

**2-Chloro-1,4-dimethoxy-3,6-dimethylbenzene (5b)**

To a solution of 2-chloro-3,6-dimethyl-4-methoxyphenol (1.86 g, 10 mmol) in $CH_2Cl_2$ (30 mL) under nitrogen was added tetra-*n*-butylammonium bromide (TBAB) (0.97 g, 3 mmol, 0.3 equiv) and a solution of KOH (1.98 g, 30 mmol, 3 equiv) in water (30 mL). To the vigorously stirred mixture was added dimethyl sulfate (2.85 mL, 30 mmol, 3 equiv) in three portions (1 mL, 1 mL, and 0.85 mL) at 2 h intervals. After a further 3 h, 2 N aq NaOH (12 mL) was added and the mixture was stirred overnight. The layers were separated and the aqueous layer was washed with $CH_2Cl_2$ (2 × 20 mL). The combined organic layers were washed with water (2 × 20 mL), filtered through cotton, and concentrated on the rotary evaporator leaving an orange oil, which slowly crystallized. Chromatography on silica gel (40 g; hexanes–EtOAc, 25:1) gave **5b** (1.92 g, 96%) as a colorless oil, which crystallized slowly and was then recrystallized (EtOAc–hexane, 1:9); mp 48.5–49 °C. (This is not in agreement with the reported[16] value of 135–137 °C; however, the authors gave no spectral data. The only other report[17] of this compound did not include a melting point, but gave NMR data identical with our own.)

$^1$H NMR ($CDCl_3$): δ = 6.56 (s, 1 H, ArH), 3.79 (s, 3 H, $OCH_3$), 3.76 (s, 3 H, $OCH_3$), 2.29 (s, 3 H, $ArCH_3$-3*), 2.24 (s, 3 H, $ArCH_3$-6*).

$^{13}$C NMR ($CDCl_3$): δ =153.9 (ArC-4), 148.0 (ArC-1), 129.2 (ArC-6), 128.9 (ArC-2), 123.6 (ArC-3), 110.8 (ArC-5), 60.1 ($OCH_3$-1), 55.9 ($OCH_3$-4), 16.4 ($ArCH_3$-6), 12.8 ($ArCH_3$-3).

**3-Chloro-2,6-dimethyl-4-methoxyphenol**

This compound was prepared analogously to the method described for the 2-chloro-3,6-dimethyl isomer starting from 2,6-dimethyl-1,4-benzoquinone (*m*-xyloquinone). This isomer gave a lower yield due to significant side reactions not seen with the *p*- and *o*-isomers. By-products isolated from subsequent reactions indicated the presence of 3,5-dichloro-2,6-dimethyl-4-methoxyphenol, 3,4-dimethoxy-2,6-dimethylphenol, and a probable biphenyl reductive coupling product.[18]

$^1$H NMR ($CDCl_3$): δ = 6.60 (s, 1 H, ArH), 4.38 (br s, 1 H, OH), 3.83 (s, 3 H, $OCH_3$), 2.32 (s, 3 H, $ArCH_3$-2*), 2.24 (s, 3 H, $ArCH_3$-6*).

**3-Chloro-1,4-dimethoxy-2,6-dimethylbenzene (5c)**

O-Methylation of 3-chloro-2,6-dimethyl-4-methoxyphenol by the method described for **5b** after recrystallization from EtOAc–hexane (1:9) gave **5c** (50%; overall yield from quinone); mp 49.5–50.5 °C.

$^1$H NMR ($CDCl_3$): δ = 6.61, (s, 1 H, ArH), 3.85 (s, 3 H, $OCH_3$-4), 3.66 (s, 3 H, $OCH_3$-1), 2.33 (s, 3 H, $ArCH_3$-2), 2.28 (s, 3 H, $ArCH_3$-6).

$^{13}$C NMR ($CDCl_3$): δ =151.3 (ArC-4), 150.9 (ArC-1), 130.8 (ArC-2), 129.3 (ArC-6), 120.4 (ArC-3), 111.3 (ArC-5), 60.2 ($OCH_3$-1), 56.3 ($OCH_3$-4), 16.3 ($ArCH_3$-6), 13.6 ($ArCH_3$-2).

**2-Chloro-5,6-dimethyl-4-methoxyphenol**

This compound was prepared analogously to the method described for the 2-chloro-3,6-dimethyl isomer starting from 2,3-dimethyl-1,4-benzoquinone (*o*-xyloquinone); yield: 96%.[19]

$^1$H NMR ($CDCl_3$): δ = 6.66 (s, 1 H, ArH), 4.80 (br s, 1 H, OH), 3.74 (s, 3 H, $OCH_3$), 2.20 (s, 3 H, $ArCH_3$-6), 2.11 (s, 3 H, $ArCH_3$-5).

$^{13}$C NMR ($CDCl_3$): δ = 151.3 (ArC-4), 143.5 (ArC-1), 125.8 (ArC-6*), 125.4 (ArC-5), 115.8 (ArC-2), 108.3 (ArC-3), 56.1 ($OCH_3$), 12.7 ($ArCH_3$-6), 11.9 ($ArCH_3$-5).

**2-Chloro-1,4-dimethoxy-5,6-dimethylbenzene (5d)**

O-Methylation of 2-chloro-5,6-dimethyl-4-methoxyphenol by the method described for **5b** gave **5d** (79%) as an oil which would not crystallize. (The only other report[17] of this compound did not indicate whether the compound was liquid or solid, but gave NMR data identical with our own.)

$^1$H NMR ($CDCl_3$): δ = 6.71 (s, 1 H, ArH), 3.76 (s, 3 H, $OCH_3$-1*), 3.74 (s, 3 H, $OCH_3$-4*), 2.22 (s, 3 H, $ArCH_3$-6), 2.10 (s, 3 H, $ArCH_3$-5).

$^{13}$C NMR ($CDCl_3$): δ = 153.8 (ArC-4), 147.9 (ArC-1), 132.3 (ArC-6), 125.1 (ArC-5), 124.3 (ArC-2), 109.4 (ArC-3), 60.4 ($OCH_3$-1), 55.8 ($OCH_3$-4), 12.9 ($ArCH_3$-6), 11.9 ($ArCH_3$-5).

**3-Bromo-1,4-dimethoxy-2,6-dimethylbenzene (5e)**

1,4-Dimethoxy-2,6-dimethylbenzene **5g**[7a] was treated with bromine in $CCl_4$ according to the method described in the literature.[20] It was necessary to exclude light and to keep the reaction time under 1 h in order to avoid side-chain bromination. The product **5e** (74–82%) was obtained as white crystals; mp 50–52 °C (lit.[21] mp 53–54 °C).

$^1$H NMR ($CDCl_3$): δ = 6.59 (s, 1 H, ArH), 3.85 (s, 3 H, $OCH_3$-4), 3.66 (s, 3 H, $OCH_3$-1), 2.37 (s, 3 H, $ArCH_3$-2), 2.27 (s, 3 H, $ArCH_3$-6).

$^{13}$C NMR ($CDCl_3$): δ = 152.1 (ArC-4), 151.0 (ArC-1), 132.6 (ArC-2), 130.1 (ArC-6), 111.7 (ArC-3), 111.3 (ArC-5), 60.3 ($OCH_3$-1), 56.4 ($OCH_3$-4), 16.5 ($ArCH_3$-2), 16.3 ($ArCH_3$-6).

**2,5-Dimethoxy-4,6-dimethylbenzonitrile (5f)**

A stirred mixture of **5e** (0.99 g, 4.0 mmol), CuCN (1.07 g, 12.0 mmol, 3 equiv), and anhyd DMF (30 mL) was heated at 120 °C under nitrogen for 2.5 d. The brown-black solution was cooled and partitioned between water (100 mL) and $CH_2Cl_2$ (3 × 20 mL). Precipitated salts were filtered off. The solution was concentrated on a rotary evaporator and then dried at high-vacuum to give **5f** (0.59 g, 77%) as a greenish-brown solid.

$^1$H NMR ($CDCl_3$): δ = 6.60 (s, 1 H, ArH), 3.87 (s, 3 H, $OCH_3$-2), 3.67 (s, 3 H, $OCH_3$-5), 2.43 (s, 3 H, $ArCH_3$-6), 2.33 (s, 3 H, $ArCH_3$-4).

$^{13}$C NMR ($CDCl_3$): δ = 157.5 (ArC-2), 150.5 (ArC-5), 137.9 (ArC-6), 136.1 (ArC-4), 115.7 (CN), 110.9 (ArC-3), 100.7 (ArC-1), 60.2 ($OCH_3$-5), 56.0 ($OCH_3$-2), 17.0 ($ArCH_3$-4), 14.5 ($ArCH_3$-6).

**Amidomethylations[5]**

***N*-[(2,5-Dimethoxy-3,4,6-trimethylphenyl)methyl]-2,2,2-trifluoroacetamide (6a)**

A mixture of **5a** (1.8 g, 10 mmol),[7] *N*-(hydroxymethyl)trifluoroacetamide (1.43 g, 10 mmol), $CHCl_3$ (20 mL), and trifluoroacetic acid (10 mL) was refluxed with stirring under a drying tube filled with 4 Å molecular sieves for 3 d. The pale orange solution was cooled and concentrated on a rotary evaporator leaving a yellowish brown solid. Column chromatography on silica gel (hexanes–EtOAc, 10:1) gave two fractions, both as white crystalline solids; the first was the dimer, bis(2,5-dimethoxy-3,4,6-trimethylphenyl)methane **7a** (0.74 g, 40%), which was recrystallized from EtOH [mp 142–143 °C (lit.[22] 142–143 °C)]; the second fraction was product **6a** (1.51 g, 49%).

$^1$H NMR ($CDCl_3$): δ = 6.67 (br s, 1 H, NH), 4.56 (d, *J* = 5.5 Hz, 2 H, $ArCH_2$) 3.71 (s, 3 H, $OCH_3$-2*), 3.65 (s, 3 H, $OCH_3$-5*), 2.28 (s, 3 H, $ArCH_3$-6*), 2.21 (s, 3 H, $ArCH_3$-3*), 2.19 (s, 3 H, $ArCH_3$-4*).

$^{13}$C NMR ($CDCl_3$): δ = 156.7 (q, $J_{CF}$ = 36.7 Hz, CO), 153.6 (ArC-2*), 153.4 (ArC-5*), 131.8 (ArC-1), 128.5 (ArC-3*), 128.1 (ArC-4*), 125.4 (ArC-6), 115.9 (q, $J_{CF}$ = 287.7 Hz, $CF_3$), 61.0 ($OCH_3$-2), 60.2 ($OCH_3$-5), 36.6 ($ArCH_2$), 12.9 ($ArCH_3$-4*), 12.8 ($ArCH_3$-3*), 12.1 ($ArCH_3$-6).

***N*-[(4-Chloro-2,5-dimethoxy-3,6-dimethylphenyl)methyl]-2,2,2-trifluoroacetamide (6b)**

Amidomethylation of **5b** was carried out as for **5a**, except that the reaction time was extended to 7 d due to the deactivating effect of the halogen substituent. Only a trace amount of dimer was obtained under these conditions, and the desired product was obtained in 36% yield along with a considerable amount of unreacted starting

material. When the reaction was conducted in a sealed tube at 100 °C for 4 d, more dimer was obtained at the expense of starting material but the yield of adduct was only slightly higher at 40%.

**Bis(4-chloro-2,5-dimethoxy-3,6-dimethylphenyl)methane (7b)**
Mp 148.5–149.0 °C.[6a]

$^1$H NMR ($CDCl_3$): δ = 4.07 (s, 2 H, $CH_2$), 3.69 (s, 6 H, $OCH_3$-5), 3.49 (s, 6 H, $OCH_3$-2), 2.31 (s, 6 H, $ArCH_3$-3), 2.03 (s, 6 H, $ArCH_3$-6).

$^{13}$C NMR ($CDCl_3$): δ = 153.6 (ArC-2), 150.8 (ArC-5), 132.1 (ArC-1), 129.8 (ArC-6), 127.5 (ArC-3*), 126.7 (ArC-4*), 60.6 ($OCH_3$-2), 60.1 ($OCH_3$-5), 25.5 ($CH_2$), 13.8 ($ArCH_3$-3), 12.6 ($ArCH_3$-6).

**6b**
$^1$H NMR ($CDCl_3$): δ = 6.65 (br s, 1H, NH), 4.56 (d, *J* = 5.5 Hz, 2 H, $CH_2$), 3.77 (s, 3 H, $OCH_3$-5*), 3.74 (s, 3 H, $OCH_3$-2*), 2.32 (s, 6 H, $ArCH_3$-3,6).

$^{13}$C NMR ($CDCl_3$): δ = 156.7 (q, $J_{CF}$ = 38.1 Hz, C=O), 154.0 (ArC-2), 151.3 (ArC-5), 129.8 (ArC-4), 129.8 (ArC-1), 128.6 (ArC-3), 126.7 (ArC-6), 115.8 (q, $J_{CF}$ = 287.7 Hz, $CF_3$), 61.2 ($OCH_3$-2) 60.3 ($OCH_3$-5), 36.4 ($CH_2$), 13.8 ($ArCH_3$-3) 12.5 ($ArCH_3$-6).

***N*-[(3-Chloro-2,5-dimethoxy-4,6-dimethylphenyl)methyl]-2,2,2-trifluoroacetamide, 6c**
Amidomethylation of **5c** was carried out as described for **6b**, using a sealed tube. When the reaction was attempted in an open flask there was almost no reaction of any kind. The desired adduct was obtained in 22% yield along with a considerable amount of recovered starting material and dimer.

**Bis(3-chloro-2,5-dimethoxy-4,6-dimethylphenyl)methane (7c)**
Mp 114.6–115.5 °C.[6a]

$^1$H NMR ($CDCl_3$): δ = 4.11 (s, 2 H, $CH_2$), 3.60 (s, 6 H, $OCH_3$-5*), 3.57 (s, 6 H, $OCH_3$-2*), 2.31 (s, 6 H, $ArCH_3$-4), 2.06 (s, 6 H, $ArCH_3$-6).

$^{13}$C NMR ($CDCl_3$): δ = 153.5 (ArC-5), 151.0 (ArC-2), 132.3 (ArC-1), 129.7 (ArC-4), 128.5 (ArC-6), 126.0 (ArC-3), 60.4 ($OCH_3$-2*), 60.3 ($OCH_3$-5*), 26.1 ($CH_2$), 13.7 ($ArCH_3$-4), 12.5 ($ArCH_3$-6).

**6c**
$^1$H NMR ($CDCl_3$): δ = 6.63 (br s, 1 H, NH), 4.58 (d, *J* = 5.9 Hz, 2 H, $CH_2$), 3.87 (s, 3 H, $OCH_3$-2), 3.67 (s, 3 H, $OCH_3$-5), 2.34 (s, 3 H, $ArCH_3$-4*), 2.30 (s, 3 H, $ArCH_3$-6*).

$^{13}$C NMR ($CDCl_3$): δ = 156.7 (q, $J_{CF}$ = 36.7 Hz, C=O), 153.8 (ArC-5), 151.4 (ArC-2), 131.6 (ArC-4), 129.7 (ArC-1), 126.9 (ArC-6), 126.2 (ArC-3), 115.8 (q, $J_{CF}$ = 287.7 Hz, $CF_3$), 61.0 ($OCH_3$-2), 60.3 ($OCH_3$-5), 36.5 ($CH_2$), 13.7 ($ArCH_3$-4), 12.2 ($ArCH_3$-6).

***N*-[(6-Chloro-2,5-dimethoxy-3,4-dimethylphenyl)methyl]-2,2,2-trifluoroacetamide (6d)**
Amidomethylation of **5d** was carried out as described for **6b**, except a 50% excess of *N*-(hydroxymethyl)trifluoroacetamide was used in an open flask protected by a drying tube. Only a minor amount of dimer was formed; the desired adduct was formed in 36% yield (45% based on unrecovered starting material).

**Bis(6-chloro-2,5-dimethoxy-3,4-dimethylphenyl)methane (7d)**
Mp 141–142.2 °C.[6a]

$^1$H NMR ($CDCl_3$): δ = 4.34 (s, 2 H, $CH_2$), 3.74 (s, 6 H, $OCH_3$-5), 3.38 (s, 6 H, $OCH_3$-2), 2.20 (s, 6 H, $ArCH_3$-4*), 2.13 (s, 6 H, $ArCH_3$-3*).

$^{13}$C NMR ($CDCl_3$): δ = 153.9 (ArC-2), 150.5 (ArC-5), 130.2 (ArC-1), 129.9 (ArC-4*), 129.1 (ArC-3*), 126.2 (ArC-6), 60.5 ($OCH_3$-2), 60.1 ($OCH_3$-5), 27.7 ($CH_2$), 13.0 ($ArCH_3$-3,4).

**6d**
$^1$H NMR ($CDCl_3$): δ = 6.71 (br s, 1 H, NH), 4.73 (d, *J* = 5.5 Hz, 2 H, $CH_2$), 3.77 (s, 3 H, $OCH_3$-5*), 3.73 (s, 3 H, $OCH_3$-2*), 2.24 (s, 3 H, $ArCH_3$-3*), 2.20 (s, 3 H, $ArCH_3$-4*).

$^{13}$C NMR ($CDCl_3$): δ = 156.6 (q, $J_{CF}$ = 37.1 Hz, C=O), 153.8 (ArC-2), 150.9 (ArC-5), 133.5 (ArC-4*), 130.4 (ArC-3*), 125.7 (ArC-6), 125.0 (ArC-1), 115.8 (q, $J_{CF}$ = 288.1 Hz, $CF_3$), 61.5 ($OCH_3$-2), 60.4 ($OCH_3$-5), 36.8 ($CH_2$), 13.2 ($ArCH_3$-4*), 12.9 ($ArCH_3$-3*).

***N*-[(3-Bromo-2,5-dimethoxy-4,6-dimethylphenyl)methyl]-2,2,2-trifluoroacetamide (6e)**
Amidomethylation of **5e** was carried out in a sealed tube at 100 °C for 4 d as described for **6c**. The usual dimer **7e** was obtained in 34% yield, 3,5-dibromo-1,4-dimethoxy 2,6-dimethylbenzene[23] was obtained in 14% yield, the desired adduct **6e** was obtained in 33% yield, and the debrominated adduct **6g** in 12% yield. A better method for the preparation of this compound is via bromination of the unsubstituted adduct **6g**, vide infra, which eliminates formation of the dibromo compound. To a stirred solution of **6g** (0.65 g, 2.2 mmol) in $CCl_4$ (15 mL) under nitrogen was added rapidly dropwise bromine (124 μL, 2.4 mmol, 10% excess) in $CCl_4$ (15 mL). The flask was wrapped in a black cloth and stirred in the dark for 2.5 d. The orange solution was poured into water (30 mL), the layers were separated, and the organic layer was washed successively with aq $Na_2S_2O_3$ (10%, 10 mL), sat. aq $NaHCO_3$ (10 mL), and water (15 mL). The residue was filtered through cotton, concentrated on a rotary evaporator, and then dried under high vacuum to give the product **6e** (0.82 g) as a beige solid (still containing 5% unbrominated starting material but otherwise pure; there was no evidence of side-chain bromination in this case).

**Bis(3-bromo-2,5-dimethoxy-4,6-dimethylphenyl)methane (7e)**
$^1$H NMR ($CDCl_3$): δ = 4.16 (s, 2 H, $CH_2$), 3.63 (s, 6 H, $OCH_3$-5*), 3.58 (s, 6 H, $OCH_3$-2*), 2.35 (s, 6 H, $ArCH_3$-4), 1.99 (s, 6 H, $ArCH_3$-6).

$^{13}$C NMR ($CDCl_3$): δ = 153.6 (ArC-5), 151.8 (ArC-2), 132.3 (ArC-1), 130.5 (ArC-6), 130.3 (ArC-4), 117.7 (ArC-3), 60.6 ($OCH_3$-2*), 60.2 ($OCH_3$-5*), 26.5 ($CH_2$), 16.6 ($ArCH_3$-4), 12.5 ($ArCH_3$-6).

**6e**
$^1$H NMR ($CDCl_3$): δ = 6.64 (br s, 1 H, NH), 4.60 (d, *J* = 5.5 Hz, 2 H, $CH_2$), 3.85 (s, 3 H, $OCH_3$-2), 3.67 (s, 3 H, $OCH_3$-5), 2.38 (s, 3 H, $ArCH_3$-4), 2.29 (s, 3 H, $ArCH_3$-6).

$^{13}$C NMR ($CDCl_3$): δ = 156.8 (q, $J_{CF}$ = 37.1 Hz, C=O), 154.0 (ArC-2), 152.5 (ArC-5), 133.6 (ArC-4), 130.5 (ArC-1), 127.2 (ArC-6), 117.8 (ArC-3), 115.8 (q, $J_{CF}$ = 287.7 Hz, $CF_3$), 61.2 ($OCH_3$-2), 60.4 $OCH_3$-5), 36.8 ($CH_2$), 16.8 ($ArCH_3$-4), 12.4 ($ArCH_3$-6).

***N*-[(3-Cyano-2,5-dimethoxy-4,6-dimethylphenyl)methyl]-2,2,2-trifluoroacetamide (6f)**
Attempted amidomethylation of **5f** was carried out as described for **6d**, using a 50% excess of *N*-(hydroxymethyl)trifluoroacetamide in an open flask. There was very little product formation; however, when a sealed tube was employed dimer formation with loss of the cyano substituent occurred (cf. **7g**). When $H_2SO_4$ was employed as a catalyst it led to the destruction of **5f**. Instead, bromo adduct **6e** underwent the Rosenmund–von Braun reaction.[9] A stirred mixture of **6e** (0.5 g, 1.35 mmol), CuCN (0.36 g, 4.05 mmol, 3 equiv), and anhyd DMF (10 mL) was heated at 120 °C under nitrogen. After 2.5 d the brown-black mixture was cooled, additional CuCN (0.36 g, 4.05 mmol, 3 equiv) and anhyd DMF (5 mL) was added and the resulting solution was heated at 120 °C for another 2 d. The suspension was cooled and partitioned between water (25 mL) and $CH_2Cl_2$ (3 × 15 mL). Precipitated salts were removed by filtration through Celite. The organic layer was filtered through cotton, concentrated on a rotary evaporator, and then dried under high vacuum to give 0.38 g

(89%) of a pale orange solid, which was purified by column chromatography on silica gel (hexanes–EtOAc, 4:1). A small amount (10%) of a mixture of unreacted **6e**, the corresponding debrominated material **6g**, and the biaryl Ullmann coupling product were obtained along with the desired product **6f** (0.34 g, 80%) as pale yellow, fine fibrous needles.

**6f**

$^1$H NMR ($CDCl_3$): δ = 6.67 (br s, 1 H, NH), 4.55 (d, *J* = 5.9 Hz, 2 H, $CH_2$), 4.05 (s, 3 H, $OCH_3$-2), 3.68 (s, 3 H, $OCH_3$-5), 2.46 (s, 3 H, $ArCH_3$-4), 2.38 (s, 3 H, $ArCH_3$-6).

$^{13}$C NMR ($CDCl_3$): δ = 156.8 (q, $J_{CF}$ = 37.1 Hz, C=O), 157.7 (ArC-2), 153.2 (ArC-5), 138.2 (ArC-6), 136.5 (ArC-4), 127.2 (ArC-1), 115.7 (q, $J_{CF}$ = 288.1 Hz, $CF_3$), 115.2 (CN), 105.1 (ArC-3), 62.4 ($OCH_3$-2), 60.3 ($OCH_3$-5), 35.8 ($CH_2$), 14.6 ($ArCH_3$-4), 12.9 ($ArCH_3$-6).

***N*-[(2,5-Dimethoxy-4,6-dimethylphenyl)methyl]-2,2,2-trifluoroacetamide (6g)**

Amidomethylation of 1,4-dimethoxy-2,6-dimethylbenzene **5g**[7a] was carried out as for **6a**, except that the reaction time was decreased to 2 d. Column chromatography on silica gel (hexanes–EtOAc, 10:1) gave dimer **7g** (20%), the corresponding trimer (5%), and the desired adduct **6g** (65%) as a white solid.

**Bis(2,5-dimethoxy-4,6-dimethylphenyl)methane (7g)**

$^1$H NMR ($CDCl_3$): δ = 6.49, (s, 2 H, ArH), 4.00 (s, 2 H, $CH_2$), 3.66 (s, 6 H, $OCH_3$-2), 3.59 (s, 6 H, $OCH_3$-5), 2.25 (s, 6 H, $ArCH_3$-4), 2.08 (s, 6 H, $ArCH_3$-6).

$^{13}$C NMR ($CDCl_3$): δ = 153.8 (ArC-2), 150.8 (ArC-5), 131.4 (ArC-1), 127.8 (ArC-4), 127.4 (ArC-6), 110.7 (ArC-3), 60.0 ($OCH_3$-5), 55.8 ($OCH_3$-2), 24.0 ($CH_2$), 16.3 ($ArCH_3$-4), 12.0 ($ArCH_3$-6).

**1,3-Bis[(2,5-dimethoxy-4,6-dimethylphenyl)methyl]-2,5-dimethoxy-4,6-dimethylbenzene (trimer)**

$^1$H NMR ($CDCl_3$): δ = 6.54 (s, 2 H, ArH), 4.13 (s, 4 H, $CH_2$), 3.77 (s, 6 H, $OCH_3$-2′), 3.58 (s, 6 H, $OCH_3$-5′), 3.55 (s, 3 H, $OCH_3$-5), 3.45 (s, 3 H, $OCH_3$-2), 2.27 (s, 6 H, $ArCH_3$-4′), 1.93 (s, 6 H, $ArCH_3$-6′*), 1.89 (s, 6 H, $ArCH_3$-4,6*).

$^{13}$C NMR ($CDCl_3$): δ = 153.5 (2 C, ArC-2′*), 153.4 (2 C, ArC-2,5*), 150.9 (2 C, ArC-5′), 131.5 (2 C, ArC-1′[†]), 131.1 (2 C, ArC-1,3[†]), 128.5 (2 C, ArC-4,6[§]), 128.0 (2 C, ArC-4′), 127.1 (2 C, ArC-6′[§]), 110.3 (2 C, ArC-3′), 61.1 ($OCH_3$-5), 60.0 (3 C, $OCH_3$-2,5′), 55.7 (2 C, $OCH_3$-2′), 24.2 (2 C, $CH_2$), 16.3 (2 C, $ArCH_3$-4′), 12.3 (2 C, $ArCH_3$-4,6[‡]),12.0 (2 C, $ArCH_3$-6′[‡]).

**6g**

$^1$H NMR ($CDCl_3$): δ = 6.80 (br s, 1 H, NH), 6.59 (s, 1 H, ArH), 4.54 (d, *J* = 5.9 Hz, 2 H, $CH_2$), 3.83 (s, 3 H, $OCH_3$-2), 3.65 (s, 3 H, $OCH_3$-5), 2.33 (s, 3 H, $ArCH_3$-4*), 2.30 (s, 3 H, $ArCH_3$-6*).

$^{13}$C NMR ($CDCl_3$): δ = 156.6 (q, $J_{CF}$ = 36.7 Hz, C=O) 154.0 (ArC-2), 150.8 (ArC-5), 131.6 (ArC-4), 131.2 (ArC-1), 121.1 (ArC-6), 110.3 (ArC-3), 115.9 (q, $J_{CF}$ = 287.7 Hz, $CF_3$), 60.1 ($OCH_3$-5), 55.6 ($OCH_3$-2), 36.1 ($CH_2$), 16.5 ($ArCH_3$-4), 12.1 ($ArCH_3$-6).

**Oxidative Demethylations[7,8,10]**

**2-{[(2,2,2-Trifluoroacetyl)amino]methyl}-3,5,6-trimethyl-2,5-cyclohexadiene-1,4-dione (8a)**

A solution of **6a** (1.21 g, 3.95 mmol) in $CH_2Cl_2$ (85 mL) was cooled to –10 °C in an ice-salt bath and nitrogen dioxide was bubbled through the solution for 10 min. Stirring was continued for a further 10 min at –10 °C and then for 1 h at r.t., during which time the color changed from green to yellow-brown. The mixture was concentrated and column chromatography of the crude product on silica gel (20 g, hexanes–EtOAc, 8:1) gave the quinone **8a** (1.0 g, 92%) as a viscous yellow-orange oil.

$^1$H NMR ($CDCl_3$): δ = 7.02 (br s, 1 H, NH), 4.39 (d, *J* = 6.25 Hz, 2 H, $CH_2$), 2.22 (s, 3 H, $CH_3$-3), 2.04 (m, 3 H, $CH_3$-5*), 2.03 (m, 3 H, $CH_3$-6*).

$^{13}$C NMR ($CDCl_3$): δ = 187.5 (C-1), 187.0 (C-4), 157.0 (q, $J_{CF}$ = 37.4 Hz, $CF_3CO$), 143.4 (C-2), 141.7, (C-5*), 140.3 (C-6*), 136.7 (C-3), 115.6 (q, $J_{CF}$ = 287.4 Hz, $CF_3$), 36.1 ($CH_2$), 12.4 ($CH_3$-3*), 12.1 ($CH_3$-5*), 11.9 ($CH_3$-6*).

**5-Chloro-3,6-dimethyl-2-{[(2,2,2-trifluoroacetyl)amino]methyl}-2,5-cyclohexadiene-1,4-dione (8b)**

A solution of CAN (9.85 g, 18 mmol, 3 equiv) in water (18 mL) was added rapidly dropwise to a stirred solution of **6b** (1.95 g, 6 mmol) in MeCN (60 mL). A transient blue-black color was occasionally observed during the addition. After stirring overnight at r.t., the orange reaction mixture was partitioned between water (100 mL) and $CHCl_3$ (3 × 20 mL). The organic layer was filtered through cotton, concentrated under reduced pressure, and dried under high vacuum. The crude product was purified by column chromatography on silica gel (40 g; hexanes–EtOAc, 4:1) to give the quinone **8b** (1.32 g, 74%) as an orange solid.

$^1$H NMR ($CDCl_3$): δ = 7.00 (br s, 1 H, NH), 4.41 (d, *J* = 6.3 Hz, 2 H, $CH_2$), 2.30 (s, 3 H, $CH_3$-3), 2.20 (s, 3 H, $CH_3$-6).

$^{13}$C NMR ($CDCl_3$): δ = 185.1 (C-1), 179.3 (C-4), 157.0 (q, $J_{CF}$ = 37.4 Hz, $CF_3CO$), 143.8 (C-2), 141.9 (C-6*), 141.2 (C-5*), 137.4 (C-3), 115.6 (q, $J_{CF}$ = 287.7 Hz, $CF_3$), 36.1 ($CH_2$), 13.4 ($CH_3$-6), 12.6 ($CH_3$-3).

**6-Chloro-3,5-dimethyl-2-{[(2,2,2-trifluoroacetyl)amino]methyl}-2,5-cyclohexadiene-1,4-dione (8c)**

Oxidative demethylation of **6c** was carried out with CAN as for **8b**. The desired quinone **8c** (71%) was obtained as a yellow solid, and was recrystallized from EtOH.

Mp 109–110 °C.

$^1$H NMR ($CDCl_3$): δ = 6.91 (br s, 1 H, NH), 4.41 (d, *J* = 6.6 Hz, 2 H, $CH_2$), 2.27 (s, 3 H, $CH_3$-3), 2.20 (s, 3 H, $CH_3$-5).

$^{13}$C NMR ($CDCl_3$): δ = 184.6 (C-4), 180.0 (C-1), 157.2 (q, $J_{CF}$ = 37.4 Hz, $CF_3CO$), 144.5 (C-2), 143.3 (C-5), 139.9 (C-6), 137.0 (C-3), 115.6 (q, $J_{CF}$ = 287.4 Hz, $CF_3$), 36.3 ($CH_2$), 14.0 ($CH_3$-5), 12.6 ($CH_3$-3).

**3-Chloro-5,6-dimethyl-2-{[(2,2,2-trifluoroacetyl)amino]methyl}-2,5-cyclohexadiene-1,4-dione (8d)**

Oxidative demethylation of **6d** was carried out with CAN as for **8b** except that the reaction time was extended to 2 d. In this case small amounts of nitrooxymethyl by-products from side-chain oxidation[24] were also formed. The desired quinone **8d** (77%) was obtained as an orange crystalline solid.

$^1$H NMR ($CDCl_3$): δ = 7.00 (br s, 1 H, NH), 4.59 (d, *J* = 6.25 Hz, 2 H, $CH_2$), 2.12 (q, *J* = 1.1 Hz, 3 H, $CH_3$-5*), 2.08 (q, *J* = 1.1 Hz, 3 H, $CH_3$-6*).

$^{13}$C NMR ($CDCl_3$): δ = 184.9 (C-1), 179.0 (C-4), 156.9 (q, $J_{CF}$ = 37.4 Hz, $CF_3CO$), 142.4 (C-3), 141.7 (C-5*), 141.3 (C-6*), 137.7 (C-2), 115.6 (q, $J_{CF}$ = 287.7 Hz, $CF_3$), 36.9 ($CH_2$), 12.9 ($CH_3$-5*), 12.4 ($CH_3$-6*).

**6-Bromo-3,5-dimethyl-2-{[(2,2,2-trifluoroacetyl)amino]methyl}-2,5-cyclohexadiene-1,4-dione (8e)**

Oxidative demethylation of **6e** was carried out with $HNO_3$ as described below for **8f**, column chromatography on silica gel (hexanes–EtOAc, 5:1) gave the quinone **8e** (81%) as a yellow solid.

$^1$H NMR ($CDCl_3$): δ = 7.04 (br s, 1 H, NH), 4.44 (d, *J* = 6.25 Hz, 2 H, $CH_2$), 2.29 (s, 3 H, $CH_3$-3*), 2.26 (s, 3 H, $CH_3$-5*).

$^{13}$C NMR ($CDCl_3$): δ = 184.0 (C-4), 180.0 (C-1), 157.2 (q, $J_{CF}$ = 37.4 Hz, $CF_3CO$), 147.1 (C-5), 144.3 (C-2), 137.0 (C-3), 135.0 (C-6), 115.6 (q, $J_{CF}$ = 287.7 Hz, $CF_3$), 36.6 ($CH_2$), 17.3 ($CH_3$-5), 12.6 ($CH_3$-3.

**6-Cyano-3,5-dimethyl-2-{[(2,2,2-trifluoroacetyl)amino]methyl}-2,5-cyclohexadiene-1,4-dione (8f)**

Oxidative demethylation of **6f** was attempted with CAN as for **8b** but the reaction was very slow and gave a mixture of products including side-chain oxidation. Concentrated $HNO_3$,[10] however, worked selectively without hydrolyzing either the nitrile or the trifluoroacetamide. To a stirred suspension of **6f** (0.58 g, 1.8 mmol) in glacial acetic acid (10 mL) under nitrogen was added rapidly dropwise concentrated $HNO_3$ (10 mL) at r.t. All solid dissolved during the course of the $HNO_3$ addition. The solution became bright yellow within 5 min. After stirring overnight the solution was poured into water (100 mL) and extracted repeatedly with $CHCl_3$ (4 × 15 mL). The organic layers were combined and washed with dil aq $NaHCO_3$ (15 mL) and then with water (15 mL). The organic layer was filtered through cotton, concentrated under reduced pressure, and dried under high vacuum to give essentially pure quinone **8f** (0.49 g, 95%) as a yellow solid.

$^1$H NMR ($CDCl_3$): δ = 7.12 (br t, 1 H, NH), 4.42 (d, $J$ = 6.25 Hz, 2 H, $CH_2$), 2.40 (s, 3 H, $CH_3$-5), 2.32 (s, 3 H, $CH_3$-3).

$^{13}$C NMR ($CDCl_3$): δ = 184.6 (C-4), 180.8 (C-1), 157.3 (q, $J_{CF}$ = 37.8 Hz, $CF_3CO$), 155.0 (C-5), 145.7 (C-2), 137.4 (C-3), 119.7 (C-6), 115.5 (q, $J_{CF}$ = 287.4 Hz, $CF_3$), 111.6 (CN), 36.0 ($CH_2$), 16.2 ($CH_3$-5), 12.7 ($CH_3$-3).

**Hydrolyses**

**2-(Aminomethyl)-3,5,6-trimethyl-2,5-cyclohexadiene-1,4-dione Hydrochloride (9a)**

Anhyd MeOH (35 mL) was cooled on ice and stirred magnetically under nitrogen. AcCl (4.0 mL, 56 mmol) was added slowly and carefully via syringe (caution – sputtering). The solution was stirred at 0 °C for 30 min and then **8a** (1.25 g, 4.5 mmol) was added as a solution in MeOH (5 mL). The cooling bath was removed and the solution was stirred for 6 d at r.t. The yellow solution was then concentrated on the rotary evaporator and dried under high vacuum to give the quinone ammonium salt **9a** (0.98 g, 100%) as an orange solid.

$^1$H NMR (DMSO-$d_6$): δ = 8.23 (s, 3 H, $NH_3$), 3.84 (br s, 2 H, $CH_2$), 2.10 (s, 3 H, $CH_3$-3), 2.00 (s, 6 H, $CH_3$-5,6).

$^{13}$C NMR (DMSO-$d_6$): δ = 186.5 (C-4), 185.4 (C-1), 144.4 (C-2), 140.7 (C-5*), 140.2 (C-6*), 135.4 (C-3), 33.6 ($CH_2$), 12.4 ($CH_3$-5*), 12.3 ($CH_3$-6*), 12.1 ($CH_3$-3).

**2-(Aminomethyl)-5-chloro-3,6-dimethyl-2,5-cyclohexadiene-1,4-dione Hydrochloride (9b)**

Hydrolysis of **8b** was carried out as for **9a**, except the reaction time was extended to 8 d at r.t., to give the ammonium salt **9b** (quantitatively) as a yellow-orange solid, which was recrystallized from EtOH. $^1$H NMR (DMSO-$d_6$): δ = 8.27 (s, 3 H, $NH_3$), 3.88 (br s, 2 H, $CH_2$), 2.17 (s, 3 H, $CH_3$-3), 2.15 (s, 3 H, $CH_3$-6).

$^{13}$C NMR (DMSO-$d_6$): δ = 183.2 (C-1), 179.0 (C-4), 144.6 (C-2), 142.0 (C-6), 139.3 (C-5), 135.9 (C-3), 33.7 ($CH_2$), 13.7 ($CH_3$-6*), 12.9 ($CH_3$-3*).

**2-(Aminomethyl)-6-chloro-3,5-dimethyl-2,5-cyclohexadiene-1,4-dione Hydrochloride (9c)**

Hydrolysis of **8c** was carried out as for **9a**, except the reaction time was extended to 7 d at r.t., to give the ammonium salt **9c** (quantitatively) as an orange solid.

$^1$H NMR (DMSO-$d_6$): δ = 8.41 (br s, 3 H, $NH_3$), 3.86 (br s, 2 H, $CH_2$), 2.13 (s, 3 H, $CH_3$-3*), 2.12 (s, 3 H, $CH_3$-5*).

$^{13}$C NMR (DMSO-$d_6$): δ = 184.3 (C-4), 178.0 (C-1), 145.5 (C-2), 142.7 (C-5), 138.9 (C-6), 135.5 (C-3), 33.8 ($CH_2$), 14.0 ($CH_3$-5), 12.9 ($CH_3$-3).

**2-(Aminomethyl)-3-chloro-5,6-dimethyl-2,5-cyclohexadiene-1,4-dione Hydrochloride (9d)**

Hydrolysis of **8d** was carried out as for **9a**, except the reaction time was extended to 8 d at r.t., to give the ammonium salt **9d** (91%) as an orange solid.

$^1$H NMR (DMSO-$d_6$): δ = 8.53 (br s, 3 H, $NH_3$), 3.94 (s, 2 H, $CH_2$), 2.05 (s, 3 H, $CH_3$-5*), 2.04 (s, 3 H, $CH_3$-6*).

$^{13}$C NMR (DMSO-$d_6$): δ = 183.3 (C-1), 178.8 (C-4), 142.1 (C-3), 141.1 (C-5*), 140.7 (C-6*), 137.1 (C-2), 34.9 ($CH_2$), 12.7 ($CH_3$-5*), 12.4 ($CH_3$-6*).

**2-(Aminomethyl)-6-bromo-3,5-dimethyl-2,5-cyclohexadiene-1,4-dione Hydrochloride (9e)**

Hydrolysis of **8e** was carried out as for **9a**, except the reaction time was extended to 6 d at r.t., to give the ammonium salt **9e** (81%) as a dull yellow solid, along with a small amount of starting material [removed by extraction with $Et_2O$ (2 × 5 mL)].

$^1$H NMR (DMSO-$d_6$): δ = 8.29 (br s, 3 H, $NH_3$), 3.87 (br s, 2 H, $CH_2$), 2.15 (s, 3 H, $CH_3$-3*), 2.12 (s, 3 H, $CH_3$-5*).

$^{13}$C NMR (DMSO-$d_6$): δ = 183.8 (C-4), 178.2 (C-1), 146.4 (C-5), 145.5 (C-2), 135.3 (C-3), 134.4 (C-6), 34.3 ($CH_2$), 17.3 ($CH_3$-5), 12.9 ($CH_3$-3).

**2-(Aminomethyl)-6-cyano-3,5-dimethyl-2,5-cyclohexadiene-1,4-dione Hydrochloride (9f)**

When hydrolysis of **8f** was carried out with AcCl in MeOH in the usual way a hydroquinone reduction product was obtained, apparently involving substitution of the methyl group *ortho* to the nitrile. Attempted use of weaker solution of AcOH in MeOH or non-nucleophilic tetrafluoroboric acid in MeOH resulted in intractable mixtures, at least partially due to the difficulty of removing excess acid.

**X-Ray Crystal Analysis of 8c and 9b**

Crystal data for **8c**: $C_{11}H_9ClF_3NO_3$, monoclinic, space group $P2_1/n$, $a$ = 12.283(3), $b$ = 5.214(1), $c$ = 19.630(4) Å, $\beta$ = 102.35(3)°, V = 1228.1(4) Å$^3$, Z = 4, $D_c$ = 1.599 gcm$^{-3}$, μ(MoKα) = 0.35 mm$^{-1}$, F(000) = 600, T = 22 °C.

Crystal data for **9b**: $C_9H_{11}Cl_2NO_2$, triclinic, space group P–1, $a$ = 5.819(1), $b$ = 6.443(1), $c$ = 14.493(3) Å, $\alpha$ = 95.66(3)°, $\beta$ = 90.43(3)°, $\gamma$ = 95.98(3)°, V = 537.7(2) Å$^3$, Z = 2, $D_c$ = 1.458 gcm$^{-3}$, (MoKα) = 0.577 mm$^{-1}$, F(000) = 244, T = 22 °C.

Data collection: Single crystals of **8c** and **9b** were obtained by slow evaporation of their ethanol solutions. Suitable yellow crystals of **8c** and **9b** with approximate dimensions 0.50 × 0.30 × 0.20 mm and 0.30 × 0.20 × 0.10 mm, respectively, were found. Diffraction data for both compounds were collected on an Enraf-Nonius CAD4 diffractometer with graphite-monochromatized, MoKα radiation ($2\theta_{max}$ = 52°, 2496 reflections measured for **8c** and $2\theta_{max}$ = 49°, 1696 reflections measured for **9b**). Three standard reflections measured after every 97 reflections showed no decay for **8c** or **9b**. For intensities and background, the individual reflection profiles were analyzed.

Structure Refinement: The structures were solved by direct methods. It was found that the fluorine atoms of trifluoromethyl group in **8c** are disordered and occupy two different positions with a ratio of 2:1, as is normal for such a group.[25,26] Refinement was done by full-matrix least-squares, first isotropically and then anisotropically, for all non-H atoms using SHELXTL97.[27] Hydrogen atoms in all structures were placed in geometrically calculated positions and introduced in the refinements using the riding approximation. The final

difference map showed no unusual features, with no significant peaks above the general background ($R1 = 0.0450$, $wR2 = 0.1404$ for **8c** and $R1 = 0.0856$, $wR2 = 0.2181$ for **9b**). Crystal data for **8c** and **9b** have been deposited with the Cambridge Cyrstallographic Data Center (CCDC 253437 and 253438).

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