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Original formation of benzyl benzoates by TDAE strategy

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Dedicated to the memory of Dr. Jean-Pierre Finet

Abstract

We report herein an original photoinduced electron transfer reaction between an aromatic aldehyde and TDAE in the presence of chloromethyl-dimethoxybenzenes. Thus, the reaction of 1-chloromethyl-2,5-dimethoxy-3,4,6-trimethylbenzene (**1**), dichlorides **4** and **5** with a series of aromatic aldehydes, in the presence of TDAE and under light catalysis, gave the corresponding benzyl benzoates.

Keywords: TDAE; Aromatic aldehydes; Benzyl benzoates; Electron transfer

Quinones are a large class of compounds with diverse biological activities. They are found in many animal and plant cells and are widely used as anticancer,[1] antibacterial[2] or antimalarial[3] drugs as well as fungicides.[4] Quinones represent a class of organic compounds possessing rich and fascinating chemistry. Many of them are important therapeutic agents, quite often they serve as auxiliaries in organic synthesis and in the dye industry.[5]

Electron transfer reactions are intensively studied in chemistry and the photochemical approach of reactions of this type has become familiar to most organic chemists as the result of a better understanding of primary processes.[6] Photoinduced electron transfer (PET) reactions between a carbonyl derivative considered as an acceptor and an amine considered as a donor have received considerable attention since the pioneering studies on photoreduction of aromatic ketones with tertiary amines.[7]

Tetrakis(dimethylamino)ethylene (TDAE) is a reducing agent, which reacts with halogenated derivatives to generate an anion under mild conditions via a single electron transfer (SET).[8] According to this strategy, we have recently developed many reactions between nitrobenzylic substrates and a series of electrophiles such as aldehydes, ketones, α-keto-esters, α-ketolactams and ketomalonates leading to the corresponding alcohol adducts.[9]

In our research program directed toward the development of original synthetic methods using TDAE methodology in medicinal chemistry and the preparation of new potentially bioactive compounds as anticancer agents,[9,10] we envisaged to prepare novel quinonic derivatives, from the reaction of dimethoxybenzene precursors and TDAE, in the presence of aldehydes. We report herein the preparation of 1-chloromethyl-2,5-dimethoxy-3,4,6-trimethylbenzene (**1**) and studied its reactivity with aromatic aldehydes in the presence of TDAE.

After the two-step synthesis of chloride **1** from 2,3,5-trimethyl-1,4-hydroquinone by methylation, using dimethylsulfate and chloromethylation according to Thomson

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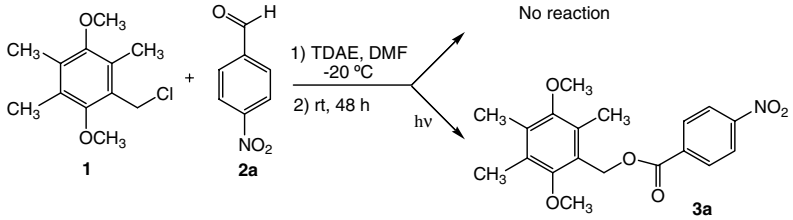


Scheme 1. Reaction of chloride **1** and aromatic aldehyde **2a**.

Table 1
Influence of experimental conditions in the reaction of **1** and **2a** in the presence of TDAE

Entry[a]	Solvent	TDAE (equiv)	Benzaldehyde **2a** (equiv)	Yield **3a** (%)
1	DMF	1	3	0
2	DMF[b]	0	3	0
3	DMF[b]	0.5	3	40
4	DMF[b]	1	3	57
5	DMF[b]	1.5	3	82
6	DMF[b]	3	3	—[c]
7	DMF[b]	1.5	1	40
8	DMF[b]	1.5	2	45
9	DMF[b]	1.5	4	45
10	THF[b]	1.5	3	64
11	CH_3CN[b]	1.5	3	50

[a] All the reactions are performed using 1 equiv of **1**.
[b] Under light irradiation.
[c] Only untractable tarry matters were formed.

procedure, a preliminary study in classical TDAE conditions was considered (Scheme 1).[11]

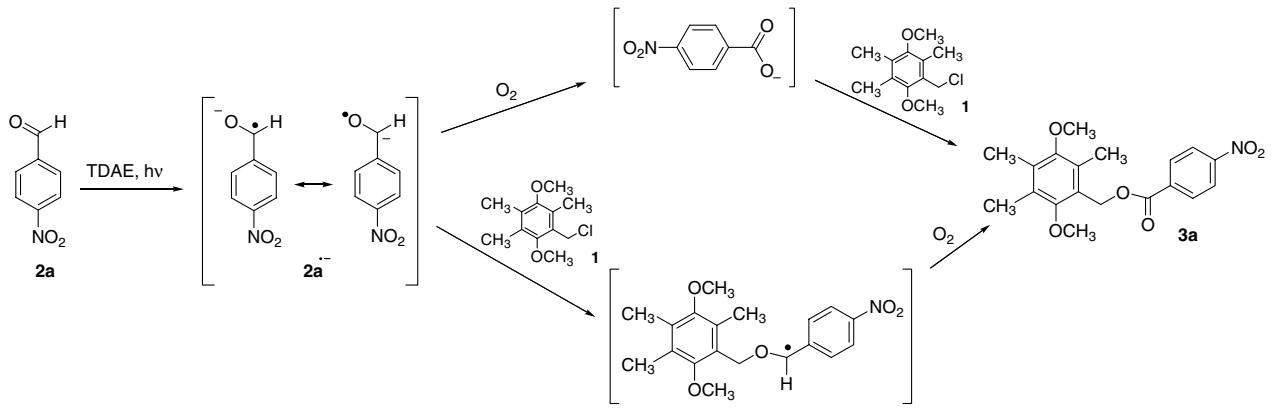
Treated under classical conditions,[9,10] that is, under inert atmosphere, with 3 equiv of 4-nitrobenzaldehyde **2a** in the presence of TDAE at −20 °C for 1 h, followed by 2 or 48 h at room temperature, chloride **1** was recovered unchanged. This result could be explained by the absence of reduction of chloride **1** due to its particularly high reduction potential ($E = -2.42$ V vs SCE).

The importance of light in electron transfer reactions, allowing to favor the reduction of chloride **1** or to realize an hypothetic photoinduced electron transfer between aromatic aldehyde as an acceptor and TDAE as donor, led us to investigate the impact of light on this reaction. The beneficial effect of light in TDAE mediated nucleophilic perfluoroalkylation of aldehydes and ketones has been previously demonstrated by one of us.[8a,f]

Under light irradiation and inert atmosphere, the reaction of chloride **1** with 4-nitrobenzaldehyde **2a** in the presence of TDAE at −20 °C for 1 h, followed by 48 h at room temperature furnishes the 2,5-dimethoxy-3,4,6-trimethylbenzyl 4-nitrobenzoate **3a** (Scheme 1). To optimize the formation of this unexpected ester derivative **3a**, we have studied the influence of solvent (DMF, THF, CH_3CN), the concentration of TDAE (0–3 equiv) and 4-nitrobenzaldehyde **2a** (1–4 equiv) as shown in Table 1.

This study shows the importance of DMF as the solvent and the sensitivity of this reaction to an excess of 4-nitrobenzaldehyde **2a** (3 equiv) and TDAE (1.5 equiv). The best yield (82%) was obtained under light irradiation and inert atmosphere, by using 3 equiv of 4-nitrobenzaldehyde **2a** and 1 equiv of chloride **1** in the presence of 1.5 equiv of TDAE at −20 °C for 1 h, followed by 48 h at room temperature and under light irradiation (Table 1, Entry 5). After 2 h only 42% of benzyl benzoate **3a** was isolated.

To explain the formation of this unexpected ester derivative **3a**, we have developed a mechanistic study. Firstly, contrary to the classical TDAE activation of chloride derivatives, which develops a red color, in this reaction an original green color appears when the TDAE and the 4-nitrobenzaldehyde **2a** get in contact. Thus, we have considered that the initiation step was a possible photoinduced electron transfer between TDAE and 4-nitrobenzaldehyde **2a**, we have replaced TDAE by a known electron donor used in many synthetic PET reactions, that is, triethylamine



Scheme 2. Mechanism formation of ester **3a**.

Table 2
Reaction of chloride **1** and aromatic aldehydes **2a–g**

Aromatic aldehyde	R	Ester derivative	Yield (%)
4-Nitrobenzaldehyde	4-NO_2	**3a**	82
4-Cyanobenzaldehyde	4-CN	**3b**	40
3-Nitrobenzaldehyde	3-NO_2	**3c**	40
2-Nitrobenzaldehyde	2-NO_2	**3d**	4
4-Bromobenzaldehyde	4-Br	**3e**	14
Benzaldehyde	4-H	**3f**	58
2,4-Dinitrobenzaldehyde	2-NO_2; 4-NO_2	**3g**	10

All the reactions are performed using 3 equiv of aromatic aldehydes **2a–g**, 1 equiv of chloride **1** and 1.5 equiv of TDAE in anhydrous DMF under light irradiation and inert atmosphere (N_2) at −20 °C for 1 h, followed by 48 h at room temperature.

(Et_3N).[12] With 4-nitrobenzaldehyde **2a**, the use of triethylamine and light catalysis furnished the corresponding ester although in lower yield, 37% versus 82% using TDAE; no reaction was observed in the absence of light catalysis. This result shows that the primary step is indeed an electron transfer between TDAE and the aldehyde, and that TDAE is a better electron donor than Et_3N.

An oxidation step proceeding via a possible radical mechanism seems to be probable to explain the final formation of ester derivative **3a**.[13] The use of freshly degassed DMF (N_2 bubbling for 2 h) in classical experimental conditions in the reaction of **1** with aldehyde **2a** decreases the yield of ester **3a** (33% vs 82%). These results suggest the possible role of molecular oxygen. This suggestion seems to be confirmed by the reaction of chloride **1**, aldehyde **2a** and Et_3N under atmospheric dioxygen, which gives an increase in yield (57% vs 37% under inert atmosphere). However, under similar conditions (under atmospheric dioxygen) the use of TDAE as electron donor did not permit us to isolate the expected ester **3a**, probably due to the instability of TDAE in the presence of dioxygen.[14]

To a better understanding of the formation of ester **3a**, we have considered a possible oxidation of benzaldehyde to a carboxylic species, which reacts with chloride **1**. This hypothesis seems confirm by the reaction of 4-nitrobenzoic acid and chloride **1** in the presence of TDAE which furnishes ester **3a** in 71% yield with or without light catalysis. No reaction was observed in the absence of TDAE. These two reactions show the basic properties of TDAE to form a carboxylate anion and the possibility of the latter to react with chloride **1**.

All these data led us to consider that under light catalysis, 4-nitrobenzaldehyde **2a** would be activated by TDAE to form a ketyl radical-anion followed by an oxidation step to form 4-nitrobenzoate anion, which reacts with substrate **1** (Scheme 2). However, the 4-nitrobenzoic acid was never isolated in all these reactions despite the modifications of the experimental protocol and the study of the reaction of 4-nitrobenzaldehyde **2a** and TDAE, which furnishes only resins. The absence of confirmation of 4-nitrobenzoic acid as an intermediate led us to propose an alternative pathway to explain the formation of ester **3a**. Moreover, it was not possible to trap the putative benzylic radical neither by methylacrylate[15] nor with TEMPO.[16]

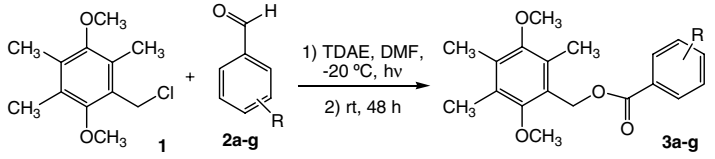
Table 3
Cyclic voltammetry study of benzaldehydes

Aromatic aldehyde	E_{pc1} (V vs SCE)	E_{pc2} (V vs SCE)	Yield **3** (%)
4-Nitrobenzaldehyde	−0.87	−1.43	82
4-Cyanobenzaldehyde	−1.35	−2.40	40
3-Nitrobenzaldehyde	−0.97	−2.21	40
4-Bromobenzaldehyde	−1.76		14
Benzaldehyde	−1.95		58
2,4-Dinitrobenzaldehyde	−0.52	−0.99	10
4-Chlorobenzaldehyde	−2.30		0

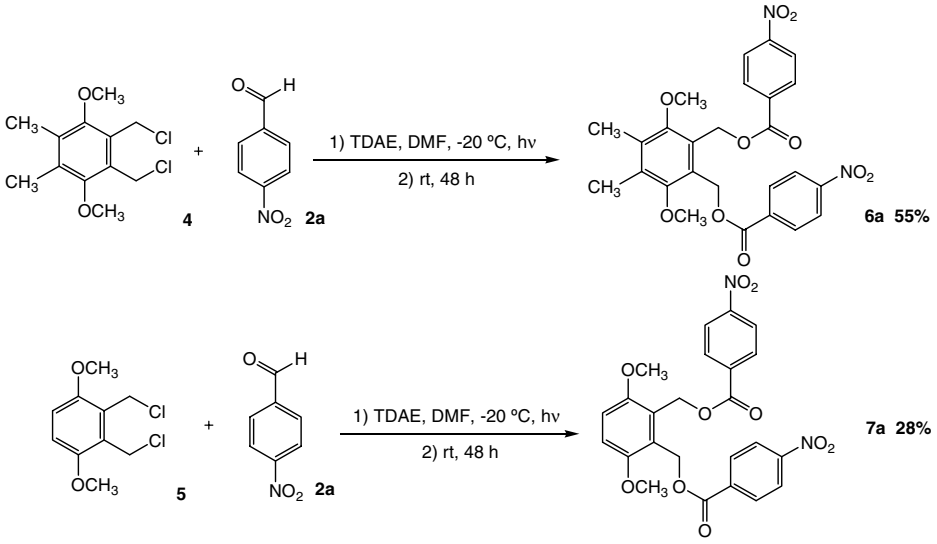
This reactivity has been generalized with various aromatic aldehydes but this reaction was only observed with aromatic aldehydes presented in Table 2 (Scheme 3).[17] No reactivity has been observed with other aromatic aldehydes (4-chloro, 4-fluoro, 4-trifluoromethyl, 2-bromo, etc.).

To determine if the aldehydes may act or not as electron transfer reagents, some of them have been studied by cyclic voltammetry in DMF as a solvent with NBu_4PF_6 as a supporting electrolyte (Table 3). Aromatic aldehydes **2a**, **2c**, and **2f** were the easiest to reduce in the series, and they usually gave two reduction steps; the first one was attributed to the formation of a stable ketyl radical anion ($E_{pc1} = -0.52$ to -0.87 V vs SCE) and the second one ($E_{pc2} = -0.99$ to -2.21 V vs SCE) to the formation of a stable dianion. 4-Cyanobenzaldehyde **2b** was also a good electron acceptor giving a stable radical anion close to −1.35 V versus SCE. Other aldehydes **2d**, **2e**, and **2g** gave only one irreversible reduction step (unstable radical anion; $E_{pc1} = -1.76$ to -2.30 V vs SCE) with 4-chlorobenzaldehyde being the most difficult ($E_{pc1} = -2.30$ V vs SCE). Yields of the benzoate derivatives **3** seem to be correlated to the ability of these aldehydes to form stable radical anions at relatively low reduction potentials, with the exception of aldehydes **2e** and **2f**.

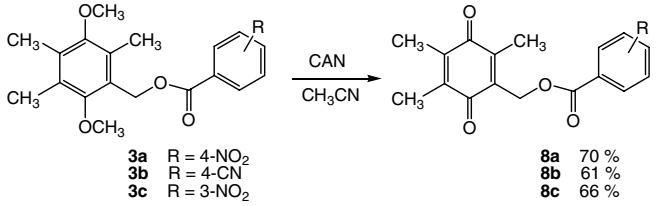
To generalize this original reactivity to other dimethoxybenzene derivatives, we have prepared two new dichloride derivatives **4** and **5**[18] ($E = -2.41$ V vs SCE for **4** and −2.17 V vs SCE for **5**) and studied their reactivity in the same experimental conditions (under light catalysis) pre-



Scheme 3. Reaction of chloride **1** and aromatic aldehydes **2a–g** under light irradiation.



Scheme 4. Reaction of dichlorides **4**, **5** and aromatic aldehyde **2a** under light catalysis.



Scheme 5. Preparation of benzoquinones **8a**–**c** by oxidation of the corresponding dimethoxybenzene derivatives **3a**–**c**.

sented with 4-nitrobenzaldehyde **2a**. The dichlorides **4** and **5** furnished the corresponding diester derivatives **6a** or **7a** in, respectively, 55% and 28% yields (Scheme 4).[19] Finally the obtained dimethoxybenzene, **3a**–**c** were oxidized into the corresponding benzoquinones **8a**–**c** using Cerium Ammonium Nitrate (CAN) in acetonitrile (Scheme 5).[20]

In conclusion, we have presented herein a photoinduced electron transfer reaction between an aromatic aldehyde and TDAE and its original application in dimethoxybenzene series leading to unexpected ester derivatives. This reactivity has been generalized to other dimethoxybenzene dichlorides and some products have been oxidized to the corresponding benzoquinones. The mechanistic study seems to indicate a TDAE-light activation of the benzaldehyde derivatives to form ketyl radical anion via a photoinduced electron transfer followed by an oxidation step. However, further experiments are necessary to confirm the oxidation step and the proposed mechanism. The generalization of the reaction of dichlorides with other benzaldehydes is under active investigation.

Acknowledgments

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17. General procedure for the reaction of 1-(chloromethyl)-2,5-dimethoxy-3,4,6-trimethylbenzene **1** and aromatic aldehydes **2a**–**g**, using TDAE. Into a two-necked flask equipped with a silica gel drying tube and a nitrogen inlet was added, under nitrogen and irradiated by fluorescent lamps (2×60 W) at -20 °C, 8 mL of anhydrous DMF solution of 1-(chloromethyl)-2,5-dimethoxy-3,4,6-trimethyl-benzene **1** (0.4 g, 1.74 mmol) and aromatic aldehydes **2a**–**g** (5.22 mmol). The solution was stirred and maintained at this temperature for 30 min and then was added dropwise (via a syringe) the TDAE (0.39 g, 2.61 mmol). A green color immediately developed with the formation of a white fine precipitate. The solution was vigorously stirred at -20 °C for 1 h and then warmed up to room temperature for 48 h under light irradiation. After this time TLC analysis (dichloromethane) clearly showed that compound **1** was totally consumed. The black-green turbid solution was filtered (to remove the octamethyl-oxamidinium dichloride) and hydrolyzed with 80 mL of H_2O. The aqueous solution was extracted with chloroform (3×40 mL) and the combined organic layers were washed with H_2O (3×40 mL) and dried over $MgSO_4$. Evaporation of the solvent left black oil as crude product. Purification by silica gel chromatography (dichloromethane) and recrystallization from ethanol gave the corresponding esters. New products: Compound **3a**: yellow solid; mp 131 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.22 (s, 3H); 2.24 (s, 3H); 2.31 (s, 3H); 3.68 (s, 3H); 3.72 (s, 3H); 5.50 (s, 2H); 8.20 (d, $J = 9.2$ Hz, 2H); 8.23 (d, $J = 9.2$ Hz, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.1 (CH_3); 12.7 (CH_3); 13.1 (CH_3); 60.2 (OCH_3); 60.9 (CH_2); 62.0 (OCH_3); 123.5 ($2 \times$ CH); 124.4 (C); 128.6 (C); 129.5 (C); 130.7 ($2 \times$ CH); 132.6 (C); 135.6 (C); 150.5 (C); 153.2 (C); 154.2 (C); 164.7 (C). Anal. Calcd for $C_{19}H_{21}NO_6$: C, 63.50; H, 5.89; N, 3.90. Found: C, 63.23; H, 5.57; N, 4.01. Compound **3b**: white solid; mp 147 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.21 (s, 3H); 2.24 (s, 3H); 2.29 (s, 3H); 3.68 (s, 3H); 3.71 (s, 3H); 5.48 (s, 2H); 7.71 (d, $J = 8.6$ Hz, 2H); 8.11 (d, $J = 8.6$ Hz, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.2 (CH_3); 12.7 (CH_3); 13.1 (CH_3); 60.2 (OCH_3); 60.8 (CH_2); 62.0 (OCH_3); 116.4 (C); 117.9 (C); 124.5 (C); 128.6 (C); 129.5 (C); 130.1 ($2 \times$ CH); 132.2 ($2 \times$ CH); 132.6 (C); 134.1 (C); 153.2 (C); 154.2 (C); 165.0 (C). Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.83; H, 6.19; N, 4.10. Compound **3c**: yellow solid; mp 98 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.22 (s, 3H); 2.25 (s, 3H); 2.31 (s, 3H); 3.69 (s, 3H); 3.73 (s, 3H); 5.51 (s, 2H); 7.62 (m, 1H); 8.37 (m, 2H); 8.82 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.1 (CH_3); 12.7 (CH_3); 13.0 (CH_3); 60.2 (OCH_3); 60.9 (CH_2); 62.0 (OCH_3); 124.4 (C); 124.6 (CH); 127.3 (CH); 128.6 (C); 129.5 (C); 129.6 (CH); 132.0 (C); 132.6 (C); 135.3 (CH); 153.2 (C); 154.2 (C); 164.5 (C); the C-nitro was not observed in this experiment. Anal. Calcd for $C_{19}H_{21}NO_6$: C, 63.50; H, 5.89; N, 3.90. Found: C, 63.34; H, 6.06; N, 3.89. Compound **3d**: white solid; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.22 (s, 3H); 2.24 (s, 3H); 2.31 (s, 3H); 3.68 (s, 3H); 3.72 (s, 3H); 5.50 (s, 2H); 7.75 (m, 2H); 8.20 (m, 2H). Compound **3e**: white solid; mp 109 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.21 (s, 3H); 2.24 (s, 3H); 2.29 (s, 3H); 3.68 (s, 3H); 3.71 (s, 3H); 5.43 (s, 2H); 7.54 (d, $J = 8.6$ Hz, 2H); 7.88 (d, $J = 8.6$ Hz, 2H). Compound **3f**: white solid; mp 70 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.22 (s, 3H); 2.24 (s, 3H); 2.31 (s, 3H); 3.68 (s, 3H); 3.72 (s, 3H); 5.45 (s, 2H); 7.42 (m, 2H); 7.54 (m, 1H); 8.03 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 11.9 (CH_3); 12.6 (CH_3); 12.9 (CH_3); 59.6 (CH_2); 60.0 (OCH_3); 61.8 (OCH_3); 125.0 (C); 128.1 (C); 129.0 ($2 \times$ CH); 129.2 (C); 129.3 ($2 \times$ CH); 129.8 (C); 131.8 (C); 133.5 (CH); 152.8 (C); 153.8 (C); 165.9 (C). Anal. Calcd for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05. Found: C, 72.51; H, 7.26. Compound **3g**: brown solid; mp 106 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.16 (s, 3H); 2.21 (s, 3H); 2.24 (s, 3H); 3.75 (s, 3H); 3.81 (s, 3H); 5.44 (s, 2H); 6.79 (s, 1H); 8.23 (d, $J = 9.2$ Hz, 2H).
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19. Compound **6a**: white solid; mp 196 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.29 (s, 6H); 3.77 (s, 6H); 5.57 (s, 4H); 8.06 (m, 8H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.2 ($2 \times CH_3$); 60.1 ($2 \times CH_2$); 62.0 ($2 \times OCH_3$); 123.5 ($4 \times$ CH); 126.1 ($2 \times$ C); 130.6 ($4 \times$ CH); 133.6 ($2 \times$ C); 135.2 ($2 \times$ C); 150.5 ($2 \times$ C); 154.6 ($2 \times$ C); 164.3 ($2 \times$ C). Anal. Calcd for $C_{26}H_{24}N_2O_{10}$: C, 59.54; H, 4.61; N, 5.34. Found: C, 59.38; H, 4.56; N, 5.26. Compound **7a**: yellow solid; mp 238 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.85 (s, 6H); 5.45 (s, 4H); 7.02 (s, 2H); 8.25 (m, 8H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 56.3 ($2 \times OCH_3$); 62.9 ($2 \times CH_2$); 113.3 ($2 \times$ CH); 123.5 ($4 \times$ CH); 124.8 ($2 \times$ C); 130.8 ($4 \times$ CH); 135.7 ($2 \times$ C); 150.6 ($2 \times$ C); 151.7 ($2 \times$ C); 164.6 ($2 \times$ C). Anal. Calcd for $C_{24}H_{20}N_2O_{10}$: C, 58.07; H, 4.06; N, 5.64. Found: C, 58.36; H, 4.28; N, 5.01.
20. *General procedure for the oxidation*: To a solution of benzyl benzoate (0.10 g, 27 mmol) in acetonitrile (1 mL) was added dropwise a mixture of CAN (0.40 g, 67.5 mmol) in water (0.5 mL). The reaction mixture was stirred for 12 h at room temperature and was quenched with water (30 mL). The aqueous solution was extracted with dichloromethane (3×20 mL), and the combined organic layers were dried over $MgSO_4$ and the solvent was removed under vacuum. Purification by silica gel chromatography (dichloromethane) and recrystallization from diethylether gave the corresponding benzoquinones. Compound **8a**: orange solid; mp 97 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.07 (s, 6H); 2.20 (s, 3H); 5.33 (s, 2H); 8.16 (d, $J = 9.1$ Hz, 2H); 8.27 (d, $J = 9.1$ Hz, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.4 (CH_3); 12.5 (CH_3); 12.6 (CH_3); 58.6 (CH_2); 123.6 ($2 \times$ CH); 130.9 ($2 \times$ CH); 135.0 (C); 136.1 (C); 140.8 (C); 141.3 (C); 145.2 (C); 150.7 (C); 164.3 (C); 185.6 (C); 187.2 (C). Anal. Calcd for $C_{17}H_{15}NO_6$: C, 62.00; H, 4.59; N, 4.25. Found: C, 61.70; H, 4.89; N, 4.26. Compound **8b**: orange solid; mp 125 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.06 (s, 6H); 2.18 (s, 3H); 5.30 (s, 2H); 7.72 (d, $J = 8.6$ Hz, 2H); 8.09 (d, $J = 8.6$ Hz, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.4 (CH_3); 12.5 (CH_3); 12.6 (CH_3); 58.5 (CH_2); 116.7 (C); 117.8 (C); 127.5 (C); 130.2 ($2 \times$ CH); 132.2 ($2 \times$ CH); 133.5 (C); 136.2 (C); 140.8 (C); 141.3 (C); 145.2 (C); 164.5 (C); 185.6 (C). Anal. Calcd for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.50. Found: C, 69.32; H, 4.94; N, 4.50. Compound **8c**: yellow solid; mp 182 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.06 (s, 6H); 2.18 (s, 3H); 5.28 (s, 2H); 7.45 (m, 3H); 7.98 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.4 ($2 \times CH_3$); 12.5 (CH_3); 57.7 (CH_2); 128.4 ($2 \times$ CH); 129.7 ($2 \times$ CH); 133.2 (C); 136.8 (C); 140.8 (C); 141.1 (C); 144.9 (C); 166.2 (C); 185.7 (C); 187.4 (C); the C-nitro was not observed in this experiment. Anal. Calcd for $C_{17}H_{15}NO_6$: C, 62.00; H, 4.59; N, 4.25. Found: C, 61.86; H, 4.35; N, 4.18.