Synthesis of 2-Alkylbenzimidazoles via TiO_2-Mediated Photocatalysis

Hongyu Wang, Richard E. Partch, and Yuzhuo Li*

Department of Chemistry, Clarkson University, Potsdam, New York 13699-5810

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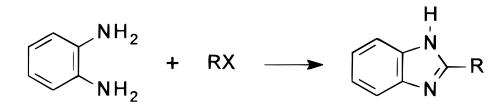
Introduction

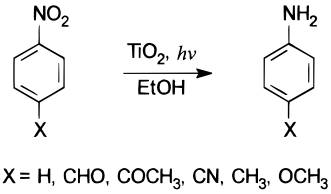
Benzimidazole and its derivatives have been the subject of much research due to their importance in various applications and its widespread biochemical significance.[1] For example, substituted 2-butylbenzimidazoles bearing a biphenylylmethyl moiety at the 1-position have been used as Angiotensin II receptor antagonists.[2] A number of benzimidazoles have been utilized to prevent the corrosion of iron and steel in acid media.[3] The classic study of the formation of 2-substituted benzimidazoles was conducted by Philips. In Philips' synthesis, *o*-phenylenediamine is used as a starting material that reacts with carbonyl-containing compounds, such as aldehydes, carboxylic acids, esters, or amides, to form benzimidazole products[4,5] (eq 1). Aqueous hydrochloric or polyphosphosphoric acid under reflux conditions is usually used to assist the final ring-closure step that involves dehydration.[5,6]



(1)

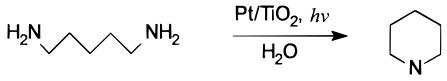
R = alkyl, aryl X = COOH, COOR', $CONH_2$

A variety of organic functional transformations mediated by irradiation semiconductors have been reported.[7] For example, it has been well established that a primary alcohol can be easily oxidized on the semiconductor surface to its corresponding aldehyde.[8] We have reported that irradiation of a primary alcoholic solution of a nitro compound with suspended TiO_2 particles gives an amino compound in a high yield as the reduced product and an aldehyde as the oxidized product (eq 2).[9] For simple oxidation or reduction needs, a photocatalyst does not offer an overall advantage over conventional chemical oxidizing or reducing agents and is no different from a high surface area electrode. For multistep synthesis, however, an illuminated semiconductor does offer a unique feature. The charge separation on a semiconductor particle creates a unique microenvironment that contains both a reduction center (conduction band electron) and an oxidation center (valence band electron hole). Intermediates generated from one site could be the substrates at another site. The integrated use of both reaction sites could complete a sophisticated multistep synthesis in "one pot". In addition, most semiconductor particles are inexpensive and nontoxic. The use of these nanoparticles could provide environmental benign alternatives for organic synthesis. It has been reported that, in an alcoholic solution of a primary amine, the alcohol can be photocatalytically oxidized to an aldehyde or ketone, which couples with the amine to form an imine. The imine is then reduced to a secondary amine.[10,11] Other examples include the photocatalytic conversion of 1,5-pentanediamine to piperidine on Pt/TiO_2 (eq 3). The transformation involves a single-electron transfer from one of the amino functional groups to the electron hole on the semiconductor and its subsequent hydrolysis to an aldehyde. The aldehyde terminal is then intramolecularly coupled with the remaining amino group to form an imine, which then reduces to the secondary amine on TiO_2.[12,13] Semiconductor particle-mediated syntheses of 1,2,4-triazolines and 2-phenylindazoles from azobenzene[14] and tetrahydroquinoline from nitrotoluene[15] also involve a combined redox scheme.



(2)

X = H, CHO, $COCH_3$, CN, CH_3, OCH_3



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The objective of this work was to investigate the feasibility of using this type of combined photocatalytic redox reactions for the synthesis of benzimidazoles via the reduction of an *o*-dinitro benzene and the oxidation of an alcohol. In this paper, the formation of benzimidazole on the surface of semiconductor particles is first described. The reaction mechanism and steps taken to validate the reaction mechanism are discussed.

Results and Discussion

Irradiation of a suspension of titanium dioxide in ethanol containing *o*-dinitrobenzene gave 2-methylbenzimidazole in 96% yield in 1 h (eq 4). In a control experiment, irradiation of an ethanolic solution of 1,2-dinitrobenzene alone led to no reaction product, indicating that TiO_2 was essential to the reaction. On the other

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(1) Pozharskii, A. F.; Garnovskii, A. D.; Simonov, A. M. *Russ. Chem. Rev.* **1966**, *35*(2), 122.
(2) Kubo, K.; Inada, Y.; Kohara, Y.; Sugiura, Y.; Ojima, M.; Itoh, K.; Furukawa, Y.; Nishikawa, K.; Naka, T. *J. Med. Chem.* **1993**, *36*, 1772.
(3) Raicheva, S. N.; Aleksiev, B. V.; Sokolova, E. I. *Corros. Sci.* **1993**, *34*(2), 343.
(4) Philips, M. A. *J. Chem. Soc.* **1928**, 2393.
(5) Hein, D. W.; Alheim, R. S.; Leavitt, J. J. *J. Am. Chem. Soc.* **1957**, *79*, 427.
(6) Alcalde, E.; Dinares, I.; Perez-Garcia, L.; Roca, T. *Synthesis* **1992**, *4*, 395.
(7) Bahnemann, D. W. *Photochem. Convers. Storage Sol. Energy, Proc. Int. Conf., 8th.* **1991**, 251.
(8) Hussein, F. H.; Pattenden, G.; Rudham, R.; Russell, J. J. *Tetrahedron Lett.* **1984**, *25*(31), 3363.
(9) Mahdavi, F.; Bruton, T. C.; Li, Y. *J. Org. Chem.* **1993**, *58*, 744.
(10) Ohtani, B.; Osaki, H.; Nishimoto, S.; Kagiya, T. *J. Am. Chem. Soc.* **1986**, *108*, 308.
(11) Ohtani, B.; Goto, Y.; Nishimoto, S.; Inui, T. *J. Chem. Soc., Faraday Trans.* **1996**, *92*(21), 4291−4295.
(12) Nishimoto, S.; Ohtani, B.; Yoshikawa, T.; Kagiya, T. *J. Am. Chem. Soc.* **1983**, *105*, 7180−7182.
(13) Ohtani, B.; Tsuru, S.; Nishimoto, S.; Kagiya, T. *J. Org. Chem.* **1990**, *55*, 5551−5553.
(14) Shibata, K.; Mimura, T.; Matsui, M.; Sugiura, T.; Minoura, H. *J. Chem. Soc., Chem. Commun.* **1988**, 1318−1320.
(15) Park, K. H.; Joo, H. S.; Ahn, K.; Jun, K. *Tetrahedron Lett.* **1995**, *36*(33), 5943−5946.

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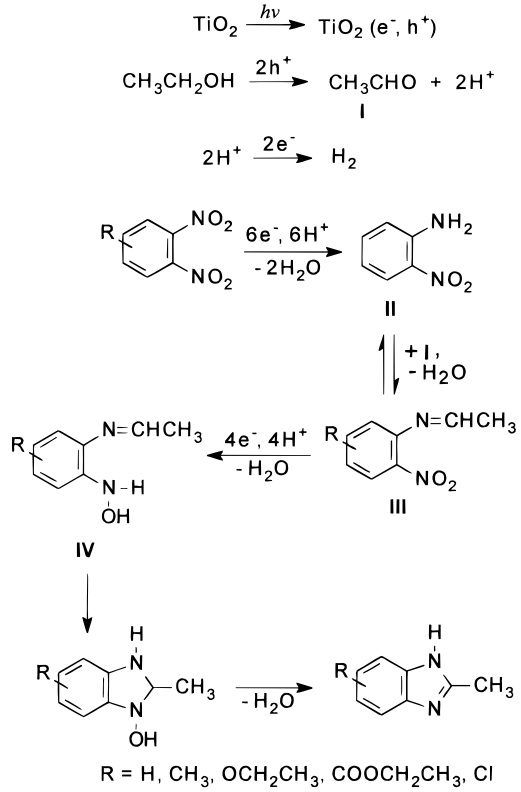
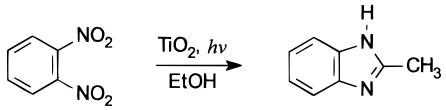


Figure 1. Photocatalytic formation of benzimidazole on TiO_2 particles.



(4)

hand, without irradiation under UV light, no reaction product was detected either.

A mechanism for the production of benzimidazole is proposed as illustrated in Figure 1. First, the solvent ethanol is oxidized to aldehyde **I** while the dinitro compound is reduced to 2-nitroaniline, **II**. The condensation between aldehyde **I** and the amino group of **II** forms an imine, **III**. At room temperature and in the presence of a considerable amount of water, **III** is in equilibrium with the aniline and aldehyde. However, the further reduction of **III** into hydroxylamine, **IV**, pushes the equilibrium away from **III**. The nitrogen atom in the hydroxylamine group attacks the imino carbon to close the ring. Further dehydration leads to a benzimidazole. The stiochiometry of the overall reaction demands a 10-electron reduction for each dinitro compound and a two-electron hole oxidation for each ethanol. In addition, some conduction band electrons are also used to reduce surface protons. As a consequence, therefore, some residual acetaldehydes are found in a postreaction analysis of the suspension. As all protons generated from oxidation are consumed in the reduction of nitro compounds or into hydrogen, no protons should be accumulated during the reaction. It is consistent with our observation that the pH of the suspension remained relatively constant throughout the reaction. The surface hydroxyl groups are likely to serve as a cache-buffer zone for the generated protons before being used in the reduction sequences.

A number of experiments were conducted to verify the reaction mechanism. For the involvement of the solvent,

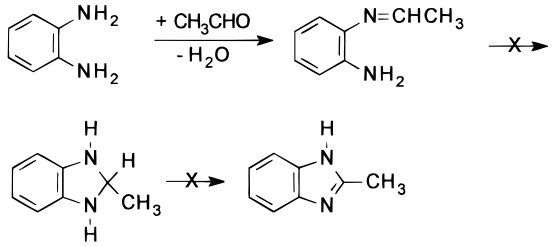
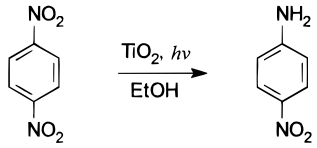


Figure 2. *o*-Diaminobenzene under photocatalytic condition.

the photocatalyzed reaction of a 3,4-dinitrotoluene in ethanol with intentionally added 1-propanal successfully gave 2-ethyl-6-methylbenzimidazole as the product. This result provided supporting evidence for the involvement of an aldehyde in the formation of benzimidazole. According to the proposed mechanism, the reductions of the two nitro groups are not simultaneous. A time-dependent study of the photocatalytic reaction of *o*-dinitrobenzene showed that 2-nitroaniline was an intermediate. In addition, irradiation of a suspension of TiO_2 containing 2-nitroaniline instead of *o*-dinitrobenzene produced benzimidazole as well. This is consistent with the fact that 2-nitroaniline was found in the formation of benzimidazole as a transient product.

Irradiation of an alcoholic solution of *p*-dinitrobenzene gave a high yield of *p*-diaminobenzene as the only product via a *p*-aminonitrobenzene intermediate (eq 5). The

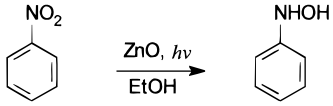


(5)

p-aminonitrobenzene intermediate can be isolated in a high yield if the irradiation time is carefully controlled. This is consistent with the fact that a ring-closure reaction is needed to drive the condensation between an aniline and an aldehyde toward the imine as shown in Figure 1.

Irradiation of *o*-phenylenediamine in ethanol in the presence of TiO_2 failed to produce 2-methylbenzimidazole. Although monoanil and dianil might have been formed in this reaction mixture, they could not proceed further to form benzimidazole compounds (Figure 2) as in the Philips synthesis,[4,16] due to the lack of oxidizing reagents. Although the electron hole in the valence band is often used in the oxidation of organic functional groups, the monoanil or dianil clearly cannot compete efficiently with the alcohol solvent. This result indicated that the second nitro group is not reduced all the way to an amino group in the pathway to benzimidazole.

We have previously demonstrated that irradiation of nitrobenzene with TiO_2 gives a high yield of aniline while the same reaction using ZnO particles instead generates hydroxylamine as the final product (eq 6).[9,17] Irradiation



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of *o*-nitroaniline in ethanol with ZnO for ca. 1 h gave 2-methylbenzimidazole. In this case, ethanol solvent

(16) Latif, N.; Mishriky, N.; Assad, F. N. *Recl.: J. R. Neth. Chem. Soc.* **1983**, *102*(2), 73.

Table 1. Synthesis of Benzimidazoles via TiO_2-Mediated Photocatalysis

reactant/solvent	product	GC/MS *m/z* (%)	^{1}H NMR (CCl_3−*d*)δ, *J* (Hz)	yield (%)
1,2-dinitrobenzene/ethanol	2-methylbenzimidazole	132.0 (100)	2.6 (s, 3H); 6.77−7.6 (m,4H)	96
1,2-dinitrobenzene/1-propanol	2-ethylbenzimidazole	146.0 (70)	1.46 (t, 3H, *J* = 7.5); 2.94−3.03 (q, 2H, *J* = 7.5); 7.21−7.58 (m, 4H)	92
3,4-dinitrotoluene/ethanol	2,6-dimethylbenzimidazole	146.0 (90)	2.43 (s, 3H); 2.53 (s, 3H); 6.33 (br, 1H); 7.01−7.43 (m, 3H)	95
3,4-dinitrotoluene/1-propanol	2-ethyl-6-methylbenzimidazole	160.0 (67)	1.41 (t, 3H, *J* = 7.5); 2.44 (s, 3H); 2.91−3.01 (q, 2H, *J* = 7.5); 7.01−7.45 (m, 3H), 8.55 (br, 1H)	97
4-ethoxy-2-nitroaniline/ethanol	5-ethoxy-2-methylbenzimidazole	176.0 (100)	1.40 (t, 3H, *J* = 5.0); 2.60 (s, 3H); 3.96−4.05 (q, 2H, *J* = 7.5); 6.83−7.44 (m, 3H)	94
4-ehtoxy-2-nitroaniline/1-propanol	5-ethoxy-2-ethylbenzimidazole	190.0 (62)	1.37−1.43 (m, 6H); 2.90−2.99 (q, 2H, *J* = 7.5); 3.77−4.04 (q, 2H, *J* = 7.5); 6.82−7.44 (m, 3H)	96
1-chloro-3,4-dinitrobenzene/ethanol	6-chloro-2-methylbenzimidazole	166 (100)	2.63 (s, 3H); 7.16−7.52 (m, 3H)	89
1-chloro-3,4-dinitrobenzene/1-propanol	6-chloro-2-ethylbenzimidazole	180 (54)	1.43 (t, 3H, *J* = 7.5); 2.93−2.99 (q, 2H, *J* = 7.5); 7.16−7.52 (m, 3H)	84
ethyl 3,4-dinitrobenzoate/ethanol	6-(ethoxycarbonyl)-2-methyl-benzimidazole	204 (43)	1.40 (t, 3H, *J* = 7.5); 2.67 (s, 3H); 4.35−4.43 (q, 2H, *J* = 7.5); 7.53−8.28 (m, 3H)	78
ethyl 3,4-dinitrobenzoate/1-propanol	6-(ethoxycarbonyl)-2-ethyl-benzimidazole	218 (69)	1.37−1.48 (m, 6H); 2.97−3.02 (q, 2H, *J* = 7.5); 4.35−4.43 (q, 2H, *J* = 7.5); 7.53−8.29 (m, 3H)	70

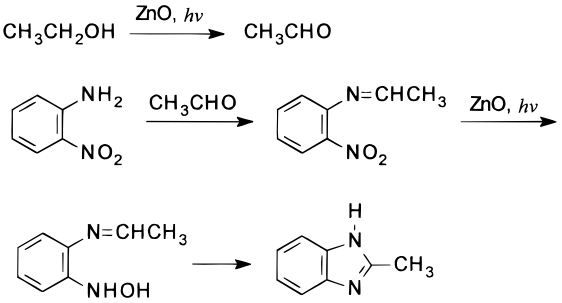

Figure 3. Irradiation of *o*-nitroaniline with ZnO.

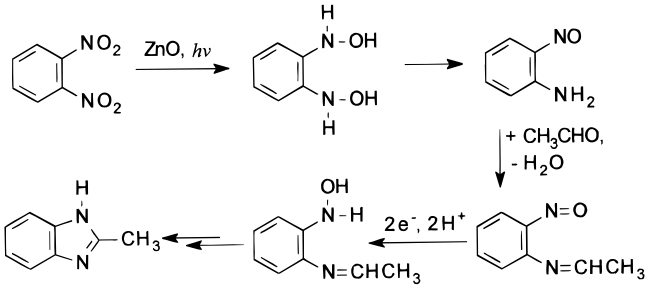

Figure 4. Involvement of *o*-nitrosoaniline.

could still be oxidized to aldehyde by ZnO particles, and the nitro group of *o*-nitroaniline was reduced only to hydroxylamine after condensation of the amino group with aldehyde. This result confirmed that, after the formation of **III**, it is not necessary for the second nitro group to be reduced into an amino group (Figure 3). When *o*-dinitrobenzene was used, 2-methylbenzimidazole was also found on the irradiated ZnO particles. This seems to be inconsistent with the reaction mechanism illustrated in Figure 1 since it is the amino group that is required for the first step, and only hydroxylamine can be formed on ZnO particles. A possible explanation is that the *o*-(dihydroxylamino)benzene from *o*-dinitrobenzene may undergo an intramolecular redox reaction in which one hydroxylamino group is oxidized into a nitroso group while the other is reduced into an amino group. The generated *o*-nitrosoaniline is then converted to 2-methylbenzimidazole as shown in Figure 4.

Irradiation of substituted dinitrobenzenes in the presence of alcohol solvents gave the corresponding substituted benzimidazoles in high yields (Table 1). The products were isolated and purified via thin-layer chromatography. The structure of each product was confirmed with its mass and ^{1}H NMR spectra (Table 1). The reaction product and reaction rate were strongly solvent dependent. When ethanol was used as a solvent, 2-methylbenzimidazole compounds were formed, whereas 2-ethylbenzimidazole compounds were produced when 1-propanol was used. When a secondary alcohol such as 2-propanol was used as a solvent, no benzimidazole compounds were obtained. The oxidation of 2-propanol generated acetone instead of acetaldehyde. Compared with acetaldehyde, acetone is much less apt, due to the steric effect, to undergo condensation with nitroaniline to form an imine. For the same reason, with a bulky primary alcohol such as 1-butanol, the reaction was also slow. The condensation reaction between the amino compound and the aldehyde is clearly the rate-limiting step of the entire reaction. Therefore, the larger the alcohol the slower the reaction proceeds. Methanol, however, is an exception. The reactions using methanol as a solvent were slower than those using ethanol as a solvent. For formaldehyde, the formation of hemiacetal with solvent was predominant. The amount of free formaldehyde was, therefore, small.

The substitutents on the benzene ring also have a significant impact on the reaction kinetics. Electron-withdrawing groups that lower the electron density on a nitro group facilitate the conversion of the nitro group into an amino group. The electron-withdrawing groups also reduce the nucleophilicity of the resulting aniline, hence lowering the reactivity for the condensation with an aldehyde. The overall quantum efficiency, therefore, depends upon the balance of these two effects. Preliminary results reveal that 3,4-dinitrotoluene has a higher overall quantum efficiency than *o*-dinitrobenzene, which in turn has a higher quantum efficiency than a reactant

(17) Li, Y.; Wang, L. Photoinduced Organic Functional Group Transformations on Semiconductor Particles. In *Nanocrystalline Semiconductor Materials*; Kamat, P.; Meisel, D., Eds.; Elsevier: New York, 1996.

bearing an electron-withdrawing group, such as 1-chloro-3,4-dinitrobenzene. A time-dependent study for the irradiation of a TiO_2 suspension containing 1-chloro-3,4-dinitrobenzene revealed that the benzimidazole was undetectable until all the starting material was completely converted into its nitroaniline intermediate. The reaction of 3,4-dinitrobenzene gave a similar result. These results indicated that the first reaction step, in which the reactant was converted into an amine intermediate, was faster than the second step, in which the nitroaniline intermediate was converted into a benzimidazole product. This is consistent with the fact that a dinitrobenzene compound is already electron deficient enough and the basicity of nitroaniline or aniline is not very high.

Conclusion

Substituted benzimidaloes have been prepared via a semiconductor-mediated photocatalytic process in which the reduction product of an *o*-dinitrobenzene and the oxidation product of an alcoholic solvent are coupled. Although the coupled reactive intermediate can be easily hydrolyzed via an equilibrium with water, the ring-closure reaction pushes the reaction further to the final benzimidazole product. The utilization of both oxidation and reduction aspects of the semiconductor charge separation is proven to be useful.

Experimental Section

Materials. 3,4-Dinitrotoluene, 1,2-dinitrobenzene, 1-chloro-3,4-dinitrobenzene, and 4-ethoxy-2-nitroaniline were obtained from Aldrich. *o*-Nitroaniline and trioxane were obtained from Eastman Kodak. 3,4-Dinitrobenzoic acid was obtained from Lancaster. Titanium dioxide (P-25) was obtained as a gift from Degussa Corp. All reagents were used upon receipt without further purification. 3,4-Dinitro-1-ethoxycarbobenzene was prepared from 3,4-dinitrobenzoic acid by reacting with ethanol under acidic condition. GC−MS spectra were obtained on a Hewlett-Packard Model 5890 series II gas chromatograph with a Model 5917A mass spectrometer. ^{1}H NMR spectra were obtained on a Bruker AC250 250 MHz spectrometer. All products were identified by GC−MS and confirmed by ^{1}H NMR and MS. Photolysis experiments were conducted with a Rayonet photochemical reactor equipped with 350 nm bulbs or a homemade flow photochemical reactor that was built based on setups described in the literature.[17−20] The photon flux in the homemade photochemical reactor was ca. 1.9×10^{17} quanta/min·cm^2 or ca. 2.6×10^{18} quanta/min·cm^2 in a Rayonet photochemical reactor.

General Procedure for Irradiation with TiO_2. Analytical Scale. In a 5 mL shell vial equipped with a magnetic stir bar were mixed 2.0 mL of a 0.005 M alcoholic solution of a reactant and 2.0 mL of a TiO_2 suspension (1.0 g/L) in the same solvent. The vial was sealed with a rubber septum and purged with nitrogen for 5 min. The mixture was irradiated while stirring in a Rayonet photochemical reactor for a specific duration (typically 15−30 min). After the irradiation, the mixture was filtered with a 0.2 μm HPLC syringe filter to remove TiO_2 particles. The resulting solution was injected into the GC−MS for analysis.

Yield Determination. The experimental procedure was basically the same as that of the analytical scale with the following modifications. A 20.0 mL sample was placed in a shell vial. After the irradiation and filtration, the solvent was removed with a rota-evaporator. The resulting reaction mixture was dried on a vacuum line before being dissolved in CCl_3D for ^{1}H NMR analysis. A known amount of trioxane was added as an internal standard. The yield was determined on the basis of the integrated area ratio between a product peak and the peak from trioxane.

Small Preparative Scale. The reaction chamber has an outside tube with a 33.0 mm inner diameter and an inside tube with a 28.0 mm inner diameter. Both are 400 mm long. The suspension of the semiconductor particles with an organic substrate in solvent is pumped through the jackets of the reaction chambers during the irradiation. A typical flow rate is ca. 20 mL/min. After the reaction, the suspension is filtered and the semiconductor particles can be reused. This type of batch-flow reactor can handle up to ca. several liters of reaction mixture. In a typical run, a 100 mL three-neck round-bottom flask equipped with a magnetic stir bar was employed as a reservoir for the reaction mixtures. A reaction suspension was prepared by mixing 100.0 mL of 0.01 M reactant solution and 100.0 mL of 1.0 g/L TiO_2 suspension. The suspension was pumped through the flow reactor. The reaction mixture was first purged with nitrogen for 30 min and then irradiated for 4 h. After the irradiation, the mixture was filtered to remove TiO_2 particles. The solvent was then removed with a rota-evaporator. For a photochemical flow reactor with immobilized TiO_2, a similar workup procedure was employed. The resulting oily mixture was placed on a TLC plate (SIL G-200 UV_{254}, 20 mm × 20 mm) for separation using chloroform as the eluent. After the separation, the components were analyzed and characterized with ^{1}H NMR and GC−MS.

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Supporting Information Available: ^{1}H NMR spectra of new compounds *in lieu* of combustion analysis (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO970253J

(18) Matthews, R. W. AU Patent B 76028, 1987.
(19) Turchi, C. S.; Mehos, M. S. *Chemical Oxidation: Technologies for Nineties*; 2nd International Symposium, Vanderbilt University, Nashville, TN, Feb 19−21, 1992.
(20) Hofstadler, K.; Bauer, R.; Novalic, S.; Heisier, G. *Environ. Sci. Technol.* **1994**, *28*, 670−674.