Mild and Selective Oxygenation of Sulfides to Sulfoxides and Sulfones by Perfluoro-*cis*-2,3-dialkyloxaziridines

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Received December 6, 1993®

Sulfides are oxidized to sulfoxides by stoichiometric amounts of perfluoro-*cis*-2,3-dialkyloxaziridines **2**. The reactions proceed at −40 °C with nearly complete selectivity and very good yields. Sulfoxides are also oxidized easily by **2** under mild conditions to corresponding sulfones. The oxidation of some bioactive sulfides (promazine, albendazole, biotin, and others) is also reported.

Sulfoxide and sulfone groups are interesting moieties as their manifold reactivity allows several and different transformations to be performed efficiently.[1] Another reason of interest in these functionalities is that they are often involved in the metabolism/catabolism of sulfur-substituted natural compounds (amino acids, vitamins...), drugs, and other xenobiotics.[2]

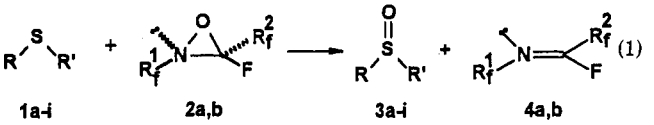
Both sulfoxides and sulfones are commonly prepared through oxidation of corresponding sulfides. A large number of electrophilic, nucleophilic, or one-electron transfer type oxidants have been employed for the oxygenation of sulfides, but few of them are highly chemoselective and able to stop at the sulfoxide level without resulting in significant overoxidation of sulfoxides to sulfones.[1]

Recently, we have reported that perfluoro-*cis*-2,3-dialkyloxaziridines **2a,b** are new, effective, neutral, and aprotic oxidizing agents. These versatile reagents oxidize secondary alcohols to the corresponding ketones,[3] alkenes to epoxides,[4] and are able to effect the hydroxylation of unactivated tertiary aliphatic C–H bonds at room temperature.[5]

In this paper we report the chemoselective oxidation of aliphatic and aromatic sulfides to sulfoxides and, in a separate series of reactions, the oxidation of sulfoxides to the corresponding sulfones. In order to prove the general usefulness of oxaziridines **2** in the oxidation of sulfides, some complex and bioactive compounds have been reacted. In some cases the substrates employed become a severe test of the selectivity and mildness of the oxygenating agents, inasmuch as they bear various functional groups susceptible to oxidation. In other cases the prepared sulfinyl drug derivatives are in themselves of interest as they are either active metabolites of the parent compound or probes for therapeutic monitoring in humans.

Results and Discussion

Sulfoxides **3a–i** have been obtained in high yields (Table 1) by treating the thioethers **1a–i** with an equimolecular amount of oxaziridines **2a,b** and stirring the reaction mixture at −40 °C for approximately 30 min (eq 1). The

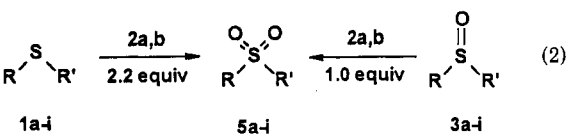


(1)

2a, 4a: $R_f^1 = n\text{-}C_4F_9$ $R_f^2 = n\text{-}C_3F_7$

2b, 4b: $R_f^1 = n\text{-}C_6F_{13}$ $R_f^2 = n\text{-}C_5F_{11}$

sulfones **5a–i** are formed when 2 equiv of oxaziridines **2** are employed for the oxygenation of the corresponding sulfides **1a–i**. Alternatively, the same products **5** have been obtained by reacting sulfoxides **3** with an equimolecular amount of the oxidizing species **2** (eq 2). Both routes afford sulfones **5** in high yields and best results are obtained when reactions are performed at −20–0 °C.



(2)

Similarly to what has already been observed in the oxidation of hydrocarbons,[5] alcohols,[3] and olefins,[4] azaalkenes (*Z*)-**4a,b** are the only "coproducts" formed in the reaction. As both oxaziridines **2** and azaalkenes **4** are quite volatile compounds,[6] the workup of oxidation reactions is particularly simple. In most cases, sulfoxides **3** and sulfones **5** have been isolated in nearly pure form and

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® Abstract published in *Advance ACS Abstracts*, April 1, 1994.

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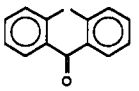
Table 1

sulfide	R	R^1	oxaziridine	sulfoxide 3 (yield, %)	sulfone 5 (yield, %)
1a	$C_6H_5CH_2$	CH_3	2b	95	96
1b	C_6H_5	CH_3	2a	97	95
1c	C_6H_5	CH_2CO_2H	2a	95	93
			2b	92	95
1d	C_6H_5	CH_2N_3	2a	95	93
1e	C_6H_5	CH_2Cl	2a	95	97
			2b	93	92
1f	C_6H_5	$CH_2Si(CH_3)_3$	2a	92	95
1g	CH_2=$CHCH_2$	CH_3	2a	90	92
1h	CH_2=CH	C_6H_5	2a	90	90
1i			2a	95	98

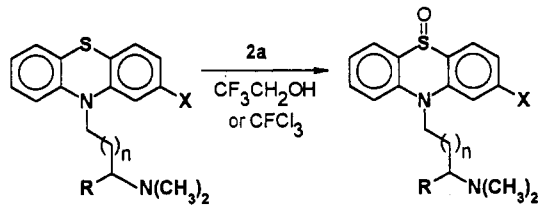
quantitative yields by simply removing the solvent, the "coproduct", and the excess reagent, if any, under reduced pressure.

It is interesting to observe that several of the obtained products are useful reagents in organic synthesis (for instance, the methyl phenyl sulfoxide (**3b**),[7] the methyl ester of phenysulfinyl acetic acid (**3c**),[8] the chloromethyl phenyl sulfoxide and sulfone (**3e** and **5e**, respectively),[9] the phenyl trimethylsilylmethyl sulfone (**5f**),[10] the phenyl vinyl sulfoxide and sulfone (**3h** and **5h**, respectively)).[11]

To further prove the synthetic usefulness of oxaziridines **2** for the selective oxygenation of the sulfide moiety, the oxidation of some polyfunctional compounds of biological interest has been studied. The hydrochlorides of promazine, chlorpromazine, and promethazine (**6a**, **6b**, and **6c**, respectively) are three typical neuroleptic drugs commonly employed in human therapy.[12] When these compounds have been treated with an equimolecular amount of the oxaziridine **2a** in trifluoroethanol solution, the corresponding sulfinyl products **7a–c** have been obtained in 90–94% isolated yields. The same reactions have been performed on the free bases **6d–f** and the corresponding sulfoxides **7d–f** are exclusively formed also in these cases (Scheme 1).

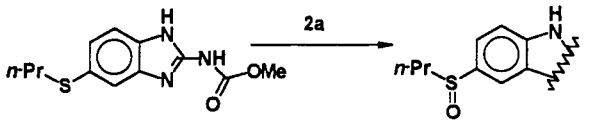
Albendazole **8** is a broad-spectrum anthelmintic drug routinely used for human treatment[13] and its sulfoxide **9**, the major active metabolite, is used for the therapeutic monitoring of the drug.[14] The reaction of **8** with equimolecular quantities of oxaziridine **2a** in trifluoroethanol solution gives the sulfoxide **9** in a few minutes and in high yields.

Scheme 1



6a-f **7a-f**

		R	X	n
6a	Promazine HCl	H	H	1
6b	Chlorpromazine HCl	H	Cl	1
6c	Promethazine HCl	CH_3	H	0
6d	Promazine	H	H	1
6e	Chlorpromazine	H	Cl	1
6f	Promethazine	CH_3	H	0



8 **9**

Under similar reaction conditions, the 4-nitrophenyl ester of (+)-biotin (vitamin H) (**10**) leads to the formation of biotin (+)-sulfoxide 4-nitrophenyl ester (**11**) (90% yield) in diastereoisomerically pure form (Scheme 2). The strict similarity of optical rotation and ^1H NMR data of the obtained product **11** with the corresponding values for biotin (+)-sulfoxide methyl ester[15] allowed the equatorial configuration to be assigned to the sulfoxide oxygen. The oxidation reaction occurred with nearly quantitative chemo- and diastereoselectivity, one single oxygen atom entering exclusively on the sulfur from the α-side of molecule, which is much less sterically hindered than the β-side.

Also, protected amino acids **12** and **14** have been nicely oxidized to corresponding sulfoxides **13** and **15** in high yields. For both methionine and cysteine derivatives **12** and **14** no overoxidation to sulfonyl products has been

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(8) Synthesis of cyclohexane-1,3-dione derivatives (Jaxa-Chamiec, A. A.; Sammes, P. G.; Kennewell, P. D. *J. Chem. Soc., Perkin Trans. 1* **1980**, 170) and of conjugated sulfoxides (Cass, Q. B.; Jaxa-Chamiec, A. A.; Sammes, P. G. *J. Chem. Soc., Chem. Commun.* **1981**, 1248); cycloalkylation reactions (Wilson, S. R.; Phillips, L. R.; Pelister, Y.; Huffmann, J. C. *J. Am. Chem. Soc.* **1979**, *101*, 7373).

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(10) Conversion of aldehydes and ketones to the corresponding vinyl sulfones (Ley, S. V.; Simpkins, N. S. *J. Chem. Soc., Chem. Commun.* **1983**, 1281).

(11) Acetylene and ethylene equivalents in Diels–Alder cycloadditions (Paquette, L. A.; Moerck. R. E.; Harirchian, B.; Magnus, P. D. *J. Am. Chem. Soc.* **1978**, *100*, 1597; Carr, V. C.; Paquette, L. A. *Org. Synth.* **1986**, *64*, 157).

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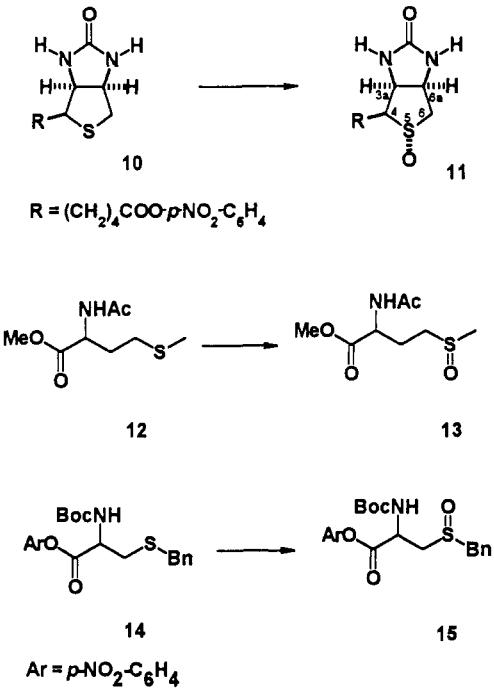
Scheme 2



observed, but the high chemoselectivity contrasts with the low diastereoselectivity of the processes. In fact, a nearly 1:1 mixture of the two products having opposite configuration at sulfur is formed in both cases.

Several general comments can be made on the above described reactions. Oxaziridines **2a,b** can be easily prepared from perfluoro tri-*n*-butyl and perfluoro tri-*n*-hexylamine, respectively.[6] They are stable liquids which can be stored for years and can be handled in the air with common glass or metal apparatuses. They behave in a similar way, the size of the perfluorinated chains having no effect on the oxidizing power. Both reagents oxidize selectively sulfides to corresponding sulfoxides in nearly quantitative yields if low reaction temperature (−40 °C) and equimolar amounts of oxidizing agent are employed. Alternatively, sulfones are obtained if higher temperatures (−20 °C to 0 °C) and stoichiometric ratios (2.2 equiv) are employed. This property is particularly remarkable as it is well known that a major difficulty encountered in the preparation of sulfoxides through oxidation of sulfides is the overoxidation to sulfones.[1] Both aprotic (halogenated hydrocarbons) and protic (trifluoroethanol, hexafluoro-2-propanol) solvents can be employed so that a wide range of substrates, with different polarity, can be oxidized in homogeneous solution. Adopted reaction conditions are notably mild. For instance, oxidants commonly used for these reactions (*m*-chloroperbenzoic acid, *tert*-butyl hydroperoxide, hydrogen peroxide in the presence of metal salts, iodosyl benzene, sodium metaperiodate)[1] require reaction temperatures higher than those needed by oxaziridines **2**. Some other reagents (e.g. ozone[16] and dioxiranes[17]) work at lower temperature, but usually they have to be prepared before use as a consequence of their limited shelf-life.

Table 2. Oxidation of Chloromethyl Phenyl Sulfoxide 1e to Corresponding Sulfoxide 3e

reagent	conditions	yield (%)	ref
H_2O_2–V_2O_2[a]	*tert*-BuOH, rt	73	18
H_2O_2–SeO_2	MeOH, rt	20	19
MCPBA	*b*	70	20
ozone	CH_2Cl_2, −78 °C	74	16
SO_2Cl_2	CH_2Cl_2, SiO_2–H_2O	82	21
2a or **2b**	$CFCl_3$–$CHCl_3$, −40 °C	>93	experimental

[a] Unsatisfactory results are obtained in the hydrogen peroxide–tungstate system. [b] Not described.

The presence of various nitrogen functionalities in the substrate molecule do not interfere with oxidation reactions. For instance, an amide group, an azido residue geminal to the sulfur moiety, or a tertiary amine, either in the free form or as its hydrochloride, all allow sulfoxides and sulfones to be formed in high yields. The same holds for the presence of various oxygen functionalities (ketone, carboxylic acid or ester...), olefinic double bonds (conjugated or isolated), and halogen atoms.

A comparison between the behavior of several oxidants in the formation of chloromethyl phenyl sulfoxide **3e** from corresponding sulfide **1e** is reported in Table 2. It clearly results how the employment of oxaziridines **2** allows higher yields to be obtained also in the synthesis of labile sulfoxides.

In general, oxaziridines can work as aminating or oxygenating agents depending on the substituent pattern on the ring. *N*-Sulfonyloxaziridines are well established and versatile oxidants,[22] their oxidizing ability being strictly related to the electron-withdrawing power of the sulfonyl residue. In these systems, chlorination[23] and fluorination[24] at a α-exocyclic position of the three-membered heterocyclic ring increase the rate of oxidation reactions. It has also been reported that *N*-phosphinoyloxaziridines oxidize alkenes to oxiranes and sulfides to sulfoxides.[25]

Simple *N*-alkyl- and -aryloxaziridines are poor oxidizing agents,[22] but their perfluorinated analogues have been shown to be involved in oxygen atom transfer reactions.[26,27] The strong electron-withdrawing ability of fluorine atoms and perfluorinated chains may account for this change in reactivity. The effect of perfluorination is so strong that the oxidizing power of perfluorinated oxaziridines **2** is definitively higher than that of *N*-sulfonyl oxaziridines as shown, among others,[3,5] by the mild conditions required for the synthesis of sulfones from sulfides when **2** are employed.

Finally, it is interesting to observe that while oxaziridines **2** are sufficiently reactive to perform the hydroxyfunctionalization of inactivated tertiary carbons,[5] at the same time they are mild enough to allow the selective and high-yield oxidation of sulfides to sulfoxides.

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Experimental Section

^1H and ^{19}F NMR spectra were recorded with a Bruker AC 250 or an IBM NR200AF instruments, using tetramethysilane and $CFCl_3$ as internal standards and $CDCl_3$ as solvent unless otherwise stated chemical shifts are reported in ppm. The IR spectra were recorded on a Perkin-Elmer Model 257 spectrophotometer. Frequencies are reported in cm^{-1}. Melting points are uncorrected and were obtained on a capillary apparatus. Flash chromatographies were performed with silica gel 60 (63–200 μm) and TLCs were run on silica gel 60 F_{254} plates (Merck). Commercially available reagent grade solvents were employed without purification. All reactions have been performed in glass apparatuses under a well-ventilated hood. Oxaziridines **2a,b** have a pungent odor; they have been handled carefully and no hazard has ever been experienced.

General Procedure for the Preparation of Sulfoxides (3a–i) with Oxaziridines 2a,b. Azidomethyl Phenyl Sulfoxide (3d). To a solution of azidomethyl phenyl sulfide (**1d**) (184 mg, 1.1 mmol) in chloroform (2 mL) was added dropwise a solution of oxaziridine **2a** (500 mg, 1.1 mmol) in $CFCl_3$ (5 mL) at −40 °C and under nitrogen. After stirring the reaction mixture for 30 min at the same temperature, the starting compound had disappeared and a lower R_f product was formed (TLC analyses). ^{19}F NMR of crude reaction mixture showed that the azaalkene (*Z*)-**4a** was the only formed coproduct. Volatiles were removed under reduced pressure to give 192 mg (96% yield) of almost pure **3d**. An analytically pure sample was obtained through flash chromatography: mp 49–52 °C (isopropyl ether); IR (Nujol) 2098, 1312, 1141; ^1H NMR 4.0 and 4.3 (AB system, CH_2N_3, 1H each), 7.6–7.7 (m, ArH, 5H); MS *m/z* (ra %) 182 (25), 165 (3), 125 (100). Anal. Calcd for $C_7H_7N_3OS$: C, 46.39; H, 3.89; N, 23.19. Found: C, 46.66; H, 4.09; N, 22.86.

Benzyl methyl sulfoxide (**3a**), methyl phenyl sulfoxide (**3b**), and phenyl vinyl sulfoxide (**3h**) were identified through comparison of isolated products with authentic samples (purchased from Lancaster (**3a**) and Aldrich (**3b,h**).

Phenylsulfinyl acetic acid (**3c**),[28] chloromethyl phenyl sulfoxide (**3e**),[16] phenyl trimethylsilylmethyl sulfoxide (**3f**),[29] allyl methyl sulfoxide (**3g**),[30] and thioxanthone sulfoxide (**3i**)[31] were identified through comparison of their spectral and physical data with those reported in the literature.

General Procedure for the Preparation of Sulfones (5a–i). Azidomethyl Phenyl Sulfone (5d). To a solution of azidomethyl phenyl sulfoxide (**3d**) (0.50 g, 2.7 mmol) in chloroform (5 mL) at −20 °C under nitrogen was added dropwise a solution of oxaziridine **2a** (1.47 g, 3.24 mmol) in $CFCl_3$ (2 mL). After stirring for 15 min at −20 °C the volatile materials were removed under reduced pressure to give 0.50 g (93% yield) of almost pure **5d**: mp 56–57 °C (*n*-hexane/isopropyl ether); IR (nujol) 2119, 1034; ^1H NMR 4.32 (s, 2H), 7.6–8.0 (m, ArH, 5H). Anal. Calcd for $C_7H_7N_3O_2S$: C, 42.63; H, 3.58; N, 21.31. Found: C, 42.82; H, 3.52; N, 21.06.

Benzyl methyl sulfone (**5a**), methyl phenyl sulfone (**5b**), (phenylsulfonyl)acetic acid (**5c**), phenyl trimethylsilylmethyl sulfone (**5f**), and phenyl vinyl sulfone (**5h**) were identified through comparison with authentic samples (purchased from Lancaster (**5a–c**) and Aldrich (**5f,h**).

Chloromethyl phenyl sulfone (**5e**),[9] allyl methyl sulfone (**5g**),[30] and thioxanthone sulfone (**5i**)[31] showed spectral and physical data identical to those reported in the literature.

General Procedure for the Preparation of (Aminoalkyl)-phenothiazine Sulfoxides (7a–f). A solution of oxaziridine **2a** (700 mg, 1.56 mmol) in trifluoroethanol (15 mL) was added dropwise at −40 °C to a stirred solution of the appropriate (aminoalkyl)phenothiazine hydrochloride **6a–c** (1.56 mmol) in the same solvent (25 mL). After stirring for 30 min, the volatile materials were removed under reduced pressure. ^1H NMR of the crude products showed that no more starting material **6** was present and that hydrochlorides of promazine sulfoxide (**7a**), chlorpromazine sulfoxide (**7b**), and promethazine sulfoxide (**7c**) were formed cleanly. Analytically pure samples were obtained through flash chromatography (90–94% yields, eluting system, chloroform/ethanol 8:2). Physical and spectral data were in agreement with those reported in the literature.[32]

The reactions on free bases **6d–f** of (aminoalkyl)phenothiazines **6a–c** were performed in a similar manner and corresponding sulfoxides **7d–f** were formed in >90% yield.

Albendazole Sulfoxide (9). Following a procedure similar to that described above, the sulfoxide **9** has been isolated in pure form after flash chromatography (93% yield) (eluting system, chloroform/methanol 95:5). The identity of compound **9** has been established by comparison with an authentic sample (^1H NMR and mass spectra).[33]

Biotin (+)-Sulfoxide 4-Nitrophenyl Ester (11). Oxidation of (+)-biotin 4-nitrophenyl ester (**10**) was performed following a procedure similar to that described above. The (+)-sulfoxide **11** was isolated in 90% yield: eluting system for flash chromatography, chloroform/methanol 85:15; mp 181–84 °C; $[\alpha]_D^{20}$ +95° (*c* = 0.3, EtOH); IR (nujol) 1010, 1740; ^1H NMR ($CDCl_3/CD_3OD$ 3:1) 1.6–1.7 (m, CH_2CH, 2H), 1.8–2.0 (m, $(CH_2)_2$, 4H), 2.70 (t, CH_2CO, 2H), 3.09 (dd, H-6, ^3J = 6 Hz, ^2J = 13 Hz, 1H), 3.14 (m, H-4, 1H), 3.48 (dd, H-6, ^3J = 2.6 Hz, ^2J = 13 Hz, 1H), 4.63 (dd, H-3a, ^3J = 5.2, 8.8 Hz, 1H), 4.72 (m, H-6a, 1H), 7.34 and 8.30 (d each, CH ArH, 2H each). Anal. Calcd for $C_{16}H_{19}N_3O_6S$: C, 50.39; H, 5.02; N, 11.02. Found: C, 50.59; H, 5.31; N, 10.69.

***N*-Acetyl-D,L-Methionine Sulfoxide Methyl Ester (13).** To a solution of *N*-acetyl-D,L-methionine methyl ester (**12**) (1.0 g, 4.87 mmol) in trifluoroethanol (10.0 mL) was added dropwise a solution of oxaziridine **2a** (2.41 g, 5.36 mmol) in the same solvent (5.0 mL) at −40 °C under nitrogen. The reaction mixture was stirred for 30 min at the same temperature. The solvent was removed in vacuo and the crude product was flash chromatographed (eluting system, chloroform/methanol/ethyl acetate 4:2:4) to give 0.95 g (88% yield) of pure *N*-acetyl-D,L-methionine sulfoxide methyl ester (**13**) as a 1:1 mixture of the two diastereoisomers: ^1H NMR 2.03 and 2.04 (s each, CH_3CO for the two diast, 3H), 2.1–2.4 (m, CH_2CHN, 2H), 2.61 and 2.62 (s each, CH_3SO of the two diast, 3H), 3.77 (s, CH_3O, 3H), 4.69 (m, CHN, 1H). Anal. Calcd for: $C_8H_{15}NO_4S$: C, 43.43; H, 6.83; N, 6.33. Found: C, 43.30; H, 7.04; N, 6.01.

***N*-BOC-*S*-Bn-Cysteine 4-Nitrophenyl Ester (15).** A procedure similar to that described above was employed using $CFCl_3/CHCl_3$ (1:1) as solvent mixture. The volatiles were removed from the crude reaction mixture under reduced pressure, the residue was washed with perfluoro-tri-*n*-butylamine to give the *N*-BOC-*S*-Bn-cysteine 4-nitrophenyl ester (**15**) in nearly pure form as a 1:1 mixture of the two diastereoisomers (87% yield): ^1H NMR 1.44 (s, $(CH_3)_3$, 9H), 3.23 (dd, H_a-SO, ^2J = 12 Hz, ^3J = 4 Hz, 1H), 3.40 (dd, H_b-SO, ^3J = 8.0 Hz, 1H), 3.34 (m, CH_2SO of the other diast, 2H), 4.17 (m, CH_2Ph, 2H), 4.88 (m, CHN, 1H), 4.93 (m, CHN of the other diast, 1H), 7.2–7.5 and 8.30 (m, CH Ar, 9H). Anal. Calcd for: $C_{21}H_{24}N_2O_7S$: C, 56.24; H, 5.39; N, 6.24. Found: C, 56.35; H, 5.60; N, 5.95.

Acknowledgment. V.M. and G.R. gratefully acknowledge financial support from Progetto Finalizzato Chimica Fine II; D.D.D. acknowledges financial support from Ausimont SPA and the National Science Foundation.

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