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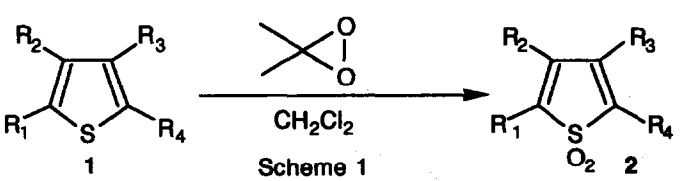
AN EXTREMELY EFFICIENT SYNTHESIS OF THIOPHENE 1,1-DIOXIDES. OXIDATION OF THIOPHENE DERIVATIVES WITH DIMETHYLDIOXIRANE

Yuji Miyahara* and Takahiko Inazu
Department of Chemistry, Faculty of Science, Kyushu University 33
Hakozaki, Higashi-ku, Fukuoka 812, Japan

Summary: Dimethyldioxirane was found to oxidize electron-rich thiophene derivatives, including sterically hindered thiophenophanes, to the corresponding thiophene 1,1-dioxides in excellent yields. Electron-withdrawing groups on a thiophene ring substantially retarded the oxidation, but dimethyldioxirane remained superior to other reagents.

Thiophene 1,1-dioxides have long been recognized as useful electron-deficient dienes in the Diels-Alder reactions with inverse electron demand,[1] or in [6+4]cycloadditions with aminofulvenes leading to azulenes.[2] Recently, their synthetic potential has also been revealed in facile ring opening reactions with alkyllithium compounds.[3] In multistep synthesis, however, several simple thiophene 1,1-dioxides have been utilized only as reagents,[4] mainly because of lack of efficient methods for oxidizing a thiophene ring in complex molecules to the corresponding 1,1-dioxide. For oxidation of sulfur atoms in resonance-stabilized thiophene rings strong oxidizing agents, such as hydrogen peroxide-acetic acid, perbenzoic acid, or, more commonly, *m*-chloroperbenzoic acid (MCPBA), are required and, under the strong reaction conditions, the resulting thiophene 1,1-dioxides can react further as dienes. The yields are, therefore, usually low to moderate, except for sterically or electronically stabilized thiophenes 1,1-dioxides.

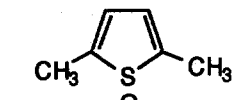
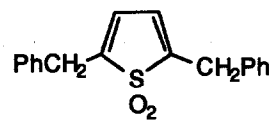
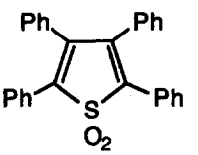
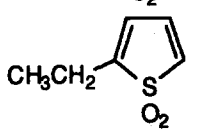
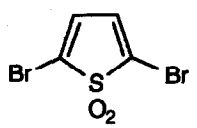
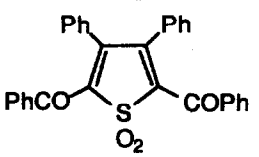
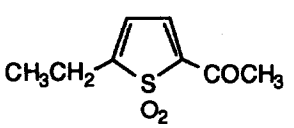
In the course of our studies on thiophenophanes,[5] we wanted to oxidize the thiophene rings in thiophenophanes to the corresponding thiophene 1,1-dioxides for further transformations to novel cyclophanes. As described below, all the MCPBA oxidations of [n.n]metacyclo(2,5)thiophenophanes **3** (n=3 and 4) as well as open chain 2,5-dimethyl- and 2,5-dibenzylthiophenes gave impure products in poor yields, even with the use of a variety of existing modifications.[6a] After additional unsatisfactory attempts of transition metal-catalyzed oxidations,[6b] we turned our attention to dimethyldioxirane, because recent rapidly developing dioxirane chemistry has demonstrated its remarkable reactivity and selectivity in transferring oxygen to an electron-rich center of substrates.[7] Although dimethyldioxirane oxidation of sulfides to the corresponding sulfoxides or sulfones have been studied in detail,[8] there appears to be no report on its application to thiophenes. Here we would like to report that dimethyldioxirane is a very strong and yet remarkably selective reagent for oxidation of thiophenes **1** to thiophene 1,1-dioxides **2** under neutral conditions (Scheme 1).



1 Scheme 1 **2**

Solutions of dimethyldioxirane can easily be prepared by oxidizing acetone with potassium caroate (Oxone [9]) in the presence of a base such as potassium bicarbonate and distilling dimethyldioxirane from the reaction mixture in the vapor of acetone at reduced pressure.[10] The oxidation with the reagent was carried out simply by adding the freshly prepared cold solution to a thiophene derivative in methylene chloride and stirred at room temperature. Since little overoxidation of the thiophene 1,1-dioxides formed was noticed[11], first an equivalent amount based on the reported average concentration of 0.08 mol/L[12] was added, followed by additional amounts of the solution

Table. Oxidation of Thiophene Derivatives by Dimethyldioxirane

Entry	Thiophene 1,1-Dioxide	Yield (%)	Appearance	Mp (°C)
1		93 52 (MCPBA)[a)]	colorless granules	88-89 89-90[a)]
2		93 50 (H_2O_2-HOAc) 48 (MCPBA)	colorless plates	94-94.5
3		99 100 (H_2O_2-HOAc)[b)]	yellow granules	282-283.5 265[b)]
4		0		
5		27 (31)[e)]	colorless prisms	126-128 (dec)
6		76 (93)[e)] 43 (H_2O_2-HOAc)[c)]	light yellow granules	246-248 (dec) 244-245 (dec)[c)]
7		53 0 (MCPBA)[d)]	pale yellow plates	120-121

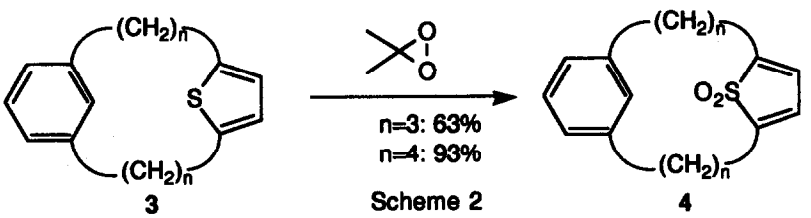
a) W. J. M. van Tilborg, *Synth. Commun.* **1976**, *6*, 583.
b) O. Hinsberg, *Ber. Dtsch. Chem. Ges.*, **1915**, *48*, 1611.
c) J. L. Melles and H. J. Backer, *Rec. Trav. Chim. Pays-Bas*, **1953**, *72*, 314.
d) R. T. Patterson, PhD Dissertation, Louisiana State University 1979.
e) The value in parentheses indicates the yield corrected for the recovered material.

judging from periodical monitoring of the reaction by thin layer chromatography (Merck #5554, UV detection). The reaction was fast for thiophenes with electron-donating groups and complete in several hours, while in the case of electron-deficient thiophenes the reaction was incomplete after two days at room temperature even with the use of excess of the reagent. Workup procedure is particularly simple. Removal of the solvents from the reaction mixture usually provided almost pure crystals, which were further purified by recrystallization. The results obtained for open chain thiophene derivatives with substituents of considerably different electronic characters are listed in Table 1.[13]

Electron-rich thiophenes with both of their 2-positions being substituted (entries 1, 2, and 3) were all oxidized rapidly and efficiently. When only one of the thiophene 2-positions was blocked as in 2-ethylthiophene (entry 4), although rapid oxidation took place as evidenced by TLC analysis, the desired thiophene 1,1-dioxide could not be isolated because of Diels-Alder dimerization and the ensuing side reactions upon concentration.[1,14]

For the oxidation of thiophenes deactivated by electron-withdrawing groups, longer reaction times and, because of the instability of dimethyldioxirane at room temperature,[8] much more than the stoichiometric amount of the reagent were required. Nevertheless, dimethyldioxirane was superior to MCPBA and hydrogen peroxide-acetic acid. For example, in contrast to a report which describes that 5-methyl-2-acetylthiophene or its less electron-withdrawing ethylene ketal derivative completely resists oxidation with MCPBA,[14] dimethyldioxirane provided the corresponding dioxide in moderate yield (entry 7). Furthermore, the oxidation of 3,4-diphenyl-2,5-dibenzoylthiophene with dimethyldioxirane gave a higher yield of the corresponding dioxide than the reaction with hydrogen peroxide-acetic acid (entry 6).[15]

We then applied this oxidation to thiophenophanes. A remarkably high yield (93%) was realized for dimethyldioxirane oxidation of [4.4]metacyclo(2,5)thiophenophane 3 (n=4) as compared to the MCPBA oxidation (40%) as shown in Scheme 2.[13]



3 Scheme 2 4

In conformationally rigid thiophenophane systems, after the first oxygen transfer from the less hindered side of the molecule, the second oxygen must be delivered from the more hindered side to the initially formed 1-monoxide, which is usually much more reactive and unstable as compared to the corresponding 1,1-dioxide.[16] This steric effect appeared to account for the slow MCPBA oxidation of 3 (n=3) and the resulting very low yields (at best 16%) of 4 (n=3). The small size as well as the high reactivity of dimethyldioxirane was expected to be advantageous and, in fact, a much improved yield (63%) of 4 (n=3) was obtained for the dimethyldioxirane oxidation.

Since the oxidation of thiophene derivatives has been carried out very efficiently, thiophene 1,1-dioxide derivatives can now be considered not just as starting materials or reagents but as intermediates in multistep syntheses. We are currently extending the application of this oxidation to a variety of other thiophenophanes and exploring the transformation of the resulting thiophenophane 1,1-dioxides to the corresponding cyclophanes[17] and cycloheptatrienophanes.[18]

References and Notes

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11. Excess of the reagent appeared only to increase formation of methylglyoxal and its condensation products.
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