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Dimethylmalonoyl peroxide – the neglected lowest homologue: simple synthesis and high reactivity

**Margarita A. Lapitskaya, Vera A. Vil', Elena D. Daeva,
Alexander O. Terent'ev and Kasimir K. Pivnitsky***

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 499 135 8824; e-mail: kpiv@mail.ru

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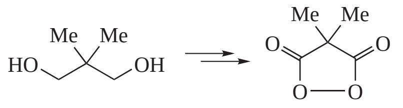
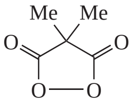
Easily available dimethylmalonoyl peroxide is proposed as a reactive alternative to the widely known spirocyclopropyl analogue for the use in the arene acyloxylation and other oxidative reactions.

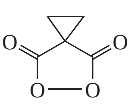


Five-membered cyclic diacylperoxides, malonoyl peroxides (MPOs), first synthesized in 1971,[1] became widely known in 2010 after discovery of their ability to perform heavy metal-free *cis*-hydroxylation of olefins[2] and other oxidative reactions.[3] The reactions of olefin *trans*-hydroxylation,[4] oxidative acyloxylation of aromatic[5] and β-dicarbonyl compounds,[6] arene dearomatization,[7] chemoselective sulfide oxidation into sulfoxides,[8] and generation of arynes[9] and permalonic acids[10] were developed for MPOs (and their competitors, unstable six-membered phthaloyl peroxides).

The majority of cited studies employed spirocyclopropyl MPO (CP-MPO) previously shown to be the most reactive spiroannelated MPO in the olefin *cis*-hydroxylation reaction.[2] Other MPOs were used as the reagents only rarely.[6,10,11] As for the lowest MPO homologue, dimethyl MPO[†] (Me-MPO), to the best of our knowledge, it was not mentioned in the literature over last three decades.



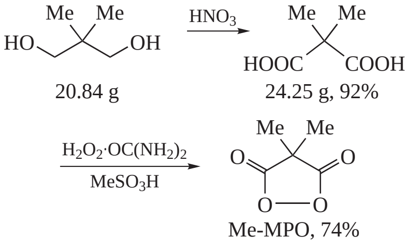
Me-MPO



CP-MPO

Such neglect of Me-MPO is possibly connected with its unordinary history. Its synthesis had been first described[12] in 1973, but the product was erroneously identified as dimer with tetraoxacyclodecane structure. However, one year earlier, Me-MPO (with correct, monomeric structure) had been utilized for generation of dimethyl-α-acetolactone,[13] and later it was used for oxidation of thiols and sulfides.[14] Neither synthesis nor properties of Me-MPO were presented in these publications.

Recently we have proved the monomeric structure of Me-MPO.[10(*b*)] Additionally we found that the rate of Me-MPO methanolysis is equal to that of most reactive spiroannelated MPOs and exceeds the rates for other dialkyl MPOs. Such a high reactivity of Me-MPO allows us to hope for possibility of its wide application. The good advantage of Me-MPO is its accessibility and record-low cost. The standard method of MPOs synthesis is the reaction of disubstituted malonic acids (or their diesters[15]) with hydrogen peroxide. According to Sigma-Aldrich website information, the price of dimethylmalonic acid (starting material for Me-MPO) is only *ca*. 2 times lower than the price of 1,1-cyclopropanedicarboxylic acid (starting material for CP-MPO). However, dimethylmalonic acid in multigram quantities can be quickly and easily prepared by the simplest, but little-known method[16] comprising HNO_3 oxidation of 2,2-dimethylpropane-1,3-diol, multi-tonnage intermediate of polyester plastics (Scheme 1).[‡] The conversion of dimethylmalonic acid into Me-MPO in the yields of 64[12] and 41%[10(*b*)] was reported. The reason for these relatively low yields could be a partial evaporation of Me-MPO with solvent during isolation due to its high volatility. The minimizing



Scheme 1

[†] Esters of monoalkylmalonic acids are C-oxidized with MPOs.[6] Therefore, mono- and non-substituted MPOs are not commonly accessible as they are unstable.

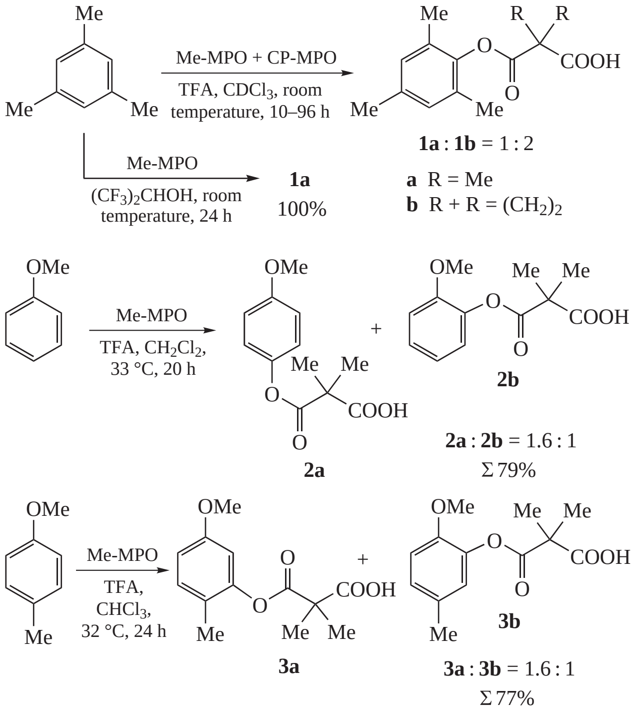
[‡] *Dimethylmalonic acid*. A portion of 2,2-dimethylpropane-1,3-diol (0.5–1 g) was added with stirring to 68% nitric acid (130 ml, 2 mol) in an open round bottom flask at 28 °C. After the appearance of brown fumes (1–2 min), the remaining diol (total 20.84 g, 0.2 mol) was added portionwise over 45 min with maintaining a temperature of the reaction mixture in the range of 28–35 °C (water bath). Thereafter the mixture was stirred for 1 h at 40 °C and left overnight at room temperature. From the resulting green suspension a white crystalline precipitate was separated by filtration and without washing dried in a vacuum dessicator over NaOH to give 20.45 g of the diacid. Additional crop (3.80 g) was similarly isolated from the mother liquor concentrated to a very small volume by evaporation at 40-45 °C. Total yield 24.25 g (92%), mp 200–203 °C (rapid heating, decomp.) (lit.,[16] mp 193 °C). ^{1}H NMR (200 or 300 MHz) δ: 1.55 ($CDCl_3$), 1.49 ($CDCl_3$–acetone-d_6, 5 : 1), 1.41 (acetone-d_6) (s, Me_2). No further purification was necessary.

of solvent quantities in extractive isolation provided the yield of 74%.[§] As a result, the production of Me-MPO according to Scheme 1 is much simpler and cheaper than that for any other MPO.

Like the commonly used CP-MPO, Me-MPO melts on heating and evaporates or calmly decomposes. It is stable during several months of storage in a closed vessel at –20 °C. At room temperature and on contact with wet air, Me-MPO is gradually converted to dimethylmalonic acid. These properties make Me-MPO convenient and sufficiently safe laboratory reagent.

The reactivity of Me-MPO was evaluated in the arene acyloxylation reaction. Reaction with mesitylene under standard conditions, in hexafluoroisopropanol, proceeds smoothly, like the reaction with CP-MPO,[5] to give the quantitative yield of the acyloxylation product **1a** (Scheme 2). In this and some other cases, the high volatility of Me-MPO allowed one to use the simplest isolation procedure of products, an exhaustive vacuum evaporation of the reaction mixture.

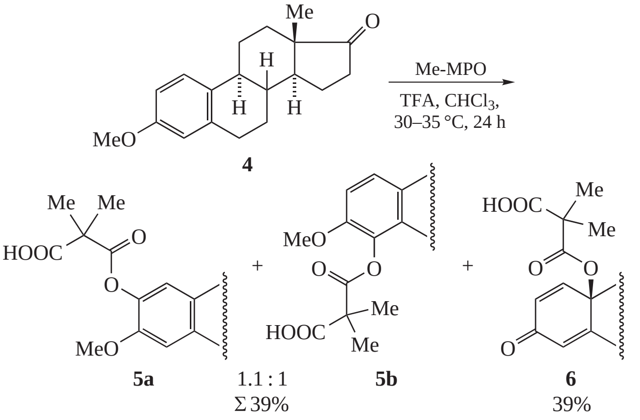
In the competitive experiment with an excess of 1 : 1 mixture of Me-MPO and CP-MPO in $CDCl_3$, without catalyst and with trifluoroacetic acid catalysis,[¶] corresponding products **1a** and **1b** were formed in the ratio 1 : 2 (for experimental details, see Online Supplementary Materials). Thus, in this reaction Me-MPO is only twice as less active than the most active CP-MPO. Previously we have found that Me-MPO is much more active than CP-MPO in methanolysis reaction.[10(*b*)]



Scheme 2

The acyloxylation of anisole and *p*-methylanisole with Me-MPO under modified conditions (see Scheme 2) occurs analogously to the reactions of these substrates with CP-MPO in HFIP, and regioisomeric products **2a**,**b** and **3a**,**b** in the same ratios and good yields were obtained.

Similar acyloxylation of steroid anisole, estrone methyl ether **4**, proceeded somewhat anomalously (Scheme 3). Along with normal regioisomeric *ortho*-substituted products **5a**,**b**, the same amount of *para*-product **6** was formed with dearomatization of the ring A. 10β-Configuration of a new asymmetric center in **6** was assigned by analogy with other numerous reactions of A-aromatic steroids at C[10].



Scheme 3

In conclusion, the properties shown above allow one to recommend Me-MPO as the most affordable alternative to other MPOs, including the most popular CP-MPO.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2018.09.018.

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[§] *Dimethylmalonoyl peroxide (Me-MPO).* Dimethylmalonic acid (1.98 g, 15 mmol) was added to a solution of $H_2O_2 \cdot OC(NH_2)_2$ (6.27 g of 90% purity, ~60 mmol) in methanesulfonic acid (12 ml), and the suspension was stirred at room temperature until a clear solution was formed (2.5 h), and this was left overnight. The solution was cooled to 0 °C in an ice bath, and CH_2Cl_2 (14 ml), $CHCl_3$ (2 ml, to improve layer separation), and then crushed ice (12 g) were added upon stirring. The bottom layer was separated, washed with water (4 ml) and dried with a minimal amount of a mixture of $MgSO_4$ + MgO (9 : 1). The extract was evaporated at 20–30 Torr on a rotary evaporator without a bath, with self-cooling caused by evaporation of solvents, to a volume of 2–3 ml, and the residue was diluted with hexane (2 ml). When product crystallization started, the suspension was similarly evaporated to dryness, and then kept for 10–15 s in the vacuum of the oil pump. The dry crystalline residue was Me-MPO, yield 1.322 g, mp 49–50 °C. The water layer was extracted with CH_2Cl_2 (12 ml), and additional crop of 114 mg was similarly isolated from the extract. The total yield was 74%. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.59 (s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.6 (Me), 39.0 (C), 174.6 (CO). No further purification was necessary.

[¶] Modified conditions of arene oxidation with MPO, in common solvents and with acid catalysis, will be published elsewhere.

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