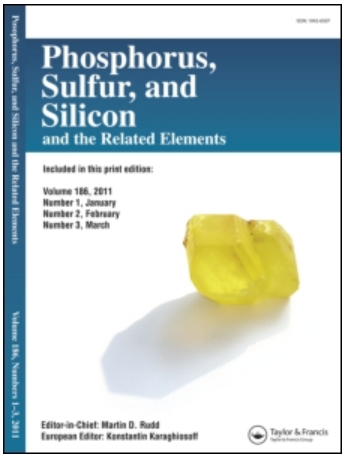


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# DIMETHYL METHYLPHOSPHONATE AS METHYLATING REAGENT

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# DIMETHYL METHYLPHOSPHONATE AS METHYLATING REAGENT

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The methylating properties of dimethyl methylphosphonate have been investigated. Aromatic mono- and polycarboxylic acids were converted into their methyl esters by heating with dimethyl methylphosphonate. Similarly phenols or amines gave their respective *O*- or *N*-methyl derivatives. The sodium salts of sulfinic acids also reacted yielding sulfones in high yield.



## INTRODUCTION

It has been reported that trimethyl phosphite[1] and trimethyl phosphate, respectively,[2] have been used successfully for a high yield esterification of carboxylic acids. In particular the phosphate ester seemed to be especially well suited for the preparation of sterically hindered carboxylic acid methyl esters. The extremely toxic properties of dimethyl sulfate, the classical reagent for methylations and esterifications, render the above mentioned phosphorus esters useful substitutes for such reactions. Further examples of their methylating properties were demonstrated by the *N*-methylation of thymine and of uracil which gave the *N*-methylated compounds in high yields.[3]

More recently attention has been focused upon similar methylating properties of dimethyl methylphosphonate (DMMP) (**1**). This was previously employed to methylate the nitrogen in heterocyclic compounds such as imidazole, pyrazole etc.,[4] simply by heating a solution of the respective heterocycle under reflux for a few hours.

Smooth methylation with DMMP is further attested by the recent disclosure of a patent[5] describing the *N*-methylation of aliphatic dimethylamino compounds in an aqueous dispersion of toluene with DMMP giving excellent yields of quaternary ammonium compounds, the counterion of which is the methyl methylphosphonate anion. This last example in particular demonstrated that *N*-methylation with this phosphorus ester can be performed even in a two phase system consisting of an aqueous layer and an organic solvent, under mild conditions, and free of any undesirable side reactions.

Dimethyl methylphosphonate is formed in considerable quantities as a by-product in Horner-Wittig reactions when carried out on large-scale industrial runs, and can be isolated during the work-up procedure of the reaction mixtures (see Experimental).

## RESULTS AND DISCUSSION

### *Methylation of carboxylic acids*

The use of DMMP led to fast and, usually, high yield methylation of aromatic mono- and polycarboxylic acids (Scheme 1). The esterification of such carboxylic acids, as 4,4′-stilbenedicarboxylic acid or 1,4-dioxino[2,3-b:5,6-b′]dipyridine-2,7-di carboxylic acid proved to be very cumbersome because of the low solubility of these acids in any organic media feasible for the methylation procedure.

$$R{-}COOH + CH_3{-}PO(OCH_3)_2 \rightarrow R{-}COOCH_3 + CH_3{-}PO(OH)OCH_3$$

SCHEME 1

Although esterification of sterically hindered aromatic acids could be achieved by refluxing with an alkylmethylphosphonate, DMMP failed to effect the formation of appreciable amounts of methyl esters under similar conditions.

However, when a slurry of an aromatic carboxylic acid in DMMP was stirred in the presence of one equivalent of a base such as triethylamine or morpholine (one equivalent of base per carboxyl group) at room temperature the triethylammonium salt was formed. These salts were usually soluble in the excess of DMMP used, as for example the triethylammonium salt of 4,4′-stilbenedicarboxylic

acid or of 1,4-naphthalenedicarboxylic acid. Heating the solution or the slurry of the ammonium salts (which were not isolated) to reflux caused rapid esterification and after work-up the esters could be isolated. Some of the very insoluble methyl esters (such as **2** and **6**) precipitated already from the solution at reaction temperature. The scope of this reaction is detailed in Table I.

TABLE I

Esterification of aromatic carboxylic acids with dimethyl methylphosphonate (DMMP)

| | Methylesters | Yield % | mp °C |
|---|---|---|---|
| **2** | 4,4′-Stilbenedicarboxylic acid | 100 | 230–232 |
| **3** | 1,4-Naphthalenedicarboxylic acid | 99 | 66–67.5 |
| **4** | Terephthalic acid | 98 | 141–142 |
| **5** | 1,2,4,5-Benzenetetracarboxylic acid | 89 | 141–142 |
| **6** | Benzenehexacarboxylic acid | 74.2 | 118–119 |
| **7** | 4-Chloro-3-nitrobenzoic acid | 100 | 81–82 |
| **8** | 2,5-Thiophenedicarboxylic acid | 92.3 | 148.5–149 |
| **9** | 2,5-Dichloronicotinic acid | 85 | 56.5–58 |
| **10** | 4-Cyanobenzoic acid | 81.4 | 67–68 |
| **11** | 4-Hydroxybenzoic acid | 52 | 122–125 |
| **12** | 2-Hydroxybenzoic acid | 60 | oil[a] |
| **13** | 3-Carboxybenzaldehyde | 76 | 52 |
| **14** | 1,4-Dioxino[2,3-b:5,6-b]dipyridino-2,7-dicarboxylic acid | 85.4 | 330 |
| **15** | 2-Aminobenzoic acid | 46 | oil[a] |
| **16** | 4-Aminobenzoic acid | 70 | 81 |

[a] **12** and **15** were identified by g.c. with authentic samples of the methylesters.

It is noteworthy that esterification of amino acids such as **15** and **16** was accompanied by a concurrent *N*-methylation of the amino group. Further substituents on the aromatic ring, such as halogen, formyl, hydroxy, nitro or cyano groups, were uneffected by DMMP under the reaction conditions used for the esterification, although after extended reaction times the phenolic group was also methylated.

The reaction products were identified either by comparison of their melting points or infrared spectra with those of authentic specimens, or by elemental analysis and spectral data for unknown compounds.

Although the methylation procedure with DMMP at a reaction temperature of 130–180° was terminated within a period ranging from a few minutes to half an hour, the diethyl ethylphosphonate reacted only very sluggishly. Thus the esterification of 4,4′-stilbenedicarboxylic acid to the diethyl ester (**17**) in the presence of tributylamine required a reaction period of 2.5 hours at 200°.

### *Methylation of Phenols and Amines*

The direct methylation of phenol or its methyl homologues failed under the reaction conditions used above for esterification of carboxylic acids, however, it occurred rapidly with the chlorinated phenols (**19, 20**) and with *p*-nitrophenol (**18**). The addition of equivalent amounts of base was mandatory as otherwise no methylation could be observed over a reaction period of several hours.

Aniline yielded *N,N*-dimethylaniline (**21**), albeit in low yield, whereas chloro-(**23**) or nitro substituents (**22**) on the aromatic ring enhanced considerably the yields of *N,N*-dimethyl analogues (Table II).

TABLE II

Methylation of phenols and amines

| | Products | Yields | mp/bp |
|---|---|---|---|
| **18** | 4-Nitrophenyl methyl ether | 90 | 51.5–53.5 |
| **19** | 2,4-Dichlorophenyl methyl ether | 93 | 28–29 |
| **20** | 2,4,5-Trichlorophenyl methyl ether | 93 | 74–75 |
| **21** | *N,N*-Dimethylaniline | 47 | oil[a] |
| **22** | N,*N*-Dimethylamino-4-nitrobenzene | 77 | 163.5–164.5 |
| **23** | *N,N*-Dimethylamino-2,4-dichlorobenzene | 92 | oil[a] |

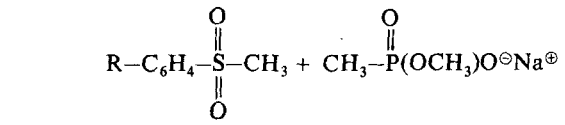
[a] **21** and **23** resp. were identified by g.c. with authentic samples.

### *Synthesis of Aromatic Methylsulfones*

Dimethyl methylphosphonate proved to be a superior methylating agent for the synthesis of phenyl methylsulfones, starting from the readily accessible alkali salts of phenylsulfinic acids.[6] The phenyl methylsulfones are usually prepared by heating the sodium salts of aromatic sulfinic acids either with dimethyl sulfate[7] or occasionally methyl halides have been used for this purpose.[7]

When the sodium salt of 4-chlorophenyl sulfinic acid[6] was heated to 170° for one hour with an excess of DMMP in the presence of one equivalent of sodium bicarbonate in an autoclave under autogenous pressure, 4-chlorophenyl methylsulfone was

formed in 93–95% yield and 99% purity (Scheme 2). The reaction could also be performed



$R = H, CH_3, Cl, NO_2$

SCHEME 2

in an open flask in the presence of triethylamine as base although the yield was slightly reduced while the purity of the product remained essentially the same. The reaction proceeded also in the absence of base, but the formation of by-products was considerably enhanced. Thus, heating the sodium salt of 4-chlorosulfinic acid with DMMP yielded 64% of **25**, which, however, contained 25% of a mixture of 4,4′-dichlorodiphenylsulfide and 4,4′-dichlorodiphenylsulfone, both identified by their nmr and mass spectra.

The reaction of sodium salts of other phenylsulfinic acids[6] in the presence of triethylamine as base gave also good yield of sulfones (**24, 26, 27,** Table III), the purity of which was found in all cases to be above 96% (by gas chromatography).

The sulfones exhibited characteristic absorption bands in the infrared spectrum at 1300–1305 $cm^{-1}$ and 1150 $cm^{-1}$ for compounds with substituents such as H, $CH_3$ and Cl, and bands at 1358 $cm^{-1}$ and 1162 $cm^{-1}$ for a sulfone carrying a 3-nitrophenyl substituent.

This methylation method is particularly advantageous in that it avoids cumbersome and time consuming purification procedures and permits the use of crude hydrated sodium salts of sulfinic acids.

The intermolecular mechanism of the rearrangement of sulfinic esters into sulfones has been amply demonstrated.[8] Here it would appear that the highly ionizing character of the solvent and the availability of protons strongly favored the rearrangement.

## EXPERIMENTAL

### *Chemicals*

Dimethyl methylphosphonate used was of commercial quality and contained 92% of dimethyl methyl phosponate, 2.3% of trimethyl phosphate and 5.7% of dimethyl phosphite (by gas chromatography) and was used as such. Control runs were made with DMMP prepared according to the literature procedure,[8] and gave no detectable difference in reaction products from the results obtained with the commercial DMMP.

Diethyl ethylphosphonate was prepared according to the literature.[10]

Some of the acids used for the preparation of methylesters were not commercially available and were prepared according to known procedures: 4,4′-stilbenedicarboxylic acid,[11] 1,4-naphthalenedicarboxylic acid,[12] 2.6-dichloronicotinic acid,[13] 2,5-thiophenedicarboxylic acid[14] and 1,4-dioxino[2,3-b:5,6-b]dipyridino-2,7-dicarboxylic acid.[15]

### *General procedure*

Melting points are uncorrected. Ir spectra were recorded with a Perking Elmer Infracord 157 spectrometer.

The general procedures for the methylation of the different types of compounds are outlined by the examples given below.

### *Terephthalic Acid Dimethyl Ester* (**4**)

To a stirred suspension of 33.2 g (0.2 mole) of terephthalic acid in 150 ml of DMMP was added 41.4 g (0.41 mole) of triethylamine. The mixture was heated to 170° over a period of 25 min. (during which time the excess of triethylamine distilled). The mixture was cooled to 80° and 500 ml of water added followed by 32 ml of conc. ammonium hydroxide. Filtration and

TABLE III

Phenyl methylsulfones

| | Substituent | Base | Yield | mp °C | Formula | Analysis (%) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Calculated | | | Found | | |
| | | | | | | C | H | S | C | H | S |
| **24** | H | $Et_3N$ | 72.8 | 83–85 | $C_7H_8SO_2$ | 53.82 | 5.16 | 20.53 | 53.71 | 5.28 | 20.64 |
| **25** | 4-Cl | $NaHCO_3$ | 95.3 | 94–95 | $C_7H_7ClSO_2$ | 44.10 | 3.70 | 16.82 | 44.15 | 3.64 | 16.98 |
| | | $Et_3N$ | 91.6 | 94–95 | | | | | | | |
| **26** | 4-$CH_3$ | $Et_3N$ | 80.9 | 95–96 | $C_8H_{10}SO_2$ | 56.44 | 5.92 | 18.89 | 56.89 | 5.83 | 19.05 |
| **27** | 3-$NO_2$ | $Et_3N$ | 100 | 138–9 | $C_7H_7NSO_4$ | 41.78 | 3.51 | 15.94 | 41.82 | 3.58 | 16.25 |

subsequent washing with 1 l of water yielded 38.0 g (97.9%) of product, mp 141.5–142°. The infrared spectrum of an authentic sample was superimposable to the one prepared above.

*4-Formylbenzoic Acid Methyl Ester* (**13**)

The stirred suspension of 7.5 g (0.05 mole) of 4-formylbenzoic acid in 37.5 ml of DMMP and 5.05 g (0.05 mole) of triethylamine was heated under reflux for a period of 10 min. The cooled solution was added to 350 ml of water, 4.2 ml of conc. ammonium hydroxide and 100 g of sodium chloride added. The solution was extracted with 3 × 300 ml portions of ether. The work-up yielded 6.23 g (76%) of product, mp 50–52°. The infrared spectrum of a known sample was superimposable with that of the above prepared specimen.

*1,4-Dioxino[2,3-b:5,6-b']dipyridine-2,7-dicarboxylic acid Dimethyl Ester* (**14**)

A stirred suspension of 27.4 g (0.1 mole) of 1,4-dioxino [2,3-b:5,6-b'] dicarboxylic acid (**15**) in 150 ml of DMMP and 21.1 g (0.21 mole) of triethylamine was heated over 50 min to 167°, while part of the triethylamine slowly distilled off over a descending condenser. A reflux condenser was then attached to the reaction flask and the mixture heated under reflux for a further 10 min. After cooling there was added 500 ml of water followed by 30 ml of conc. aqueous ammonium hydroxide. The precipitate was filtered, washed with 1.5 l of water and dried at 100° yielding 25.8 g (85.4%) of product. An analytical sample was prepared by recrystallization from 30 ml of nitrobenzene, m.p. > 330°. IR(KBr): $\nu$1718 ($COOCH_3$) $cm^{-1}$. Anal. Calcd. for $C_{14}H_{10}N_2O$ (302.24): C, 55.63; H, 3.33; N, 9.26%. Found: C, 55.61; H, 3.21; N, 9.32%.

*4-N-Methylaminobenzoic Acid Methyl Ester* (**16**)

A solution of 27.4 g (0.2 mole) of 4-aminobenzoic acid in 150 ml of DMMP and 20.2 g (0.2 mole) of triethylamine was heated to 170° within a period of 10 min. Excess of triethylamine and other volatile products were distilled, the descending condenser was replaced by a reflux condenser, the temp. increased to 182° and maintained for a period of 5 min. The cold reaction mixture was poured into 1200 ml of water and 35 ml of conc. ammonium hydroxide. The crystalline product was filtered and washed with 500 ml of water, mp 81° (ligroin); IR(KBr): $\nu$3350 (NH), 1690 ($COOCH_3$) $cm^{-1}$.

Anal. Calcd. for $C_9H_{11}NO_2$ (165.18): C, 65.44; H, 6.71; N, 8.48%. Found: C, 65.80; H, 703; N, 8.65%.

*4,4'-Stilbenedicarboxylic Acid Diethyl Ester* (**17**)

A suspension of 13.4 g (0.05 mole) of 4,4'-stilbenedicarboxylic acid in 40 ml of diethyl ethylphosphonate and 20.3 g (0.11 mole) of tributylamine was stirred and heated at 190° for a period of 2.5 hours. The cold solution was added to a mixture of 500 ml of water and 15 ml of conc. hydrochloric acid, the crystals filtered, washed with water and dried. The crude product (14.2 g) was recrystallized from 420 ml of ethanol yielding 9.6 g (59%), mp 129–130° (lit.: 130°)[11].

*4-Nitrophenyl Methyl Ether* (**18**)

A solution of 13.9 g (0.1 mole) of 4-nitrophenol in 75 ml of DMMP and 10.1 g (0.1 mole) of triethylamine was heated under reflux for 3.5 hours. The cooled solution was poured into 500 ml of water and 10 ml of concd. aqueous ammonium hydroxide added (pH: 7.2). The precipitated crystals were filtered, washed with water and dissolved in 200 ml of ether. The ether solution was dried over sodium sulfate and after filtration evaporated to dryness yielding 13.8 g (90%) of product, mp 51.5–53.5°.

*N,N-Dimethylamino-4-nitrobenzene* (**22**)

A solution of 82.8 g (0.6 mole) of 4-nitroaniline in 150 ml of DMMP was heated under reflux for a period of 2.5 hr. The reaction mixture was added to 1 l of water and 100 ml of aqueous ammonium hydroxide. The suspension was stirred for 1.5 hours, the crystals filtered, washed with water and dried at 70°/12 torr, yielding 76.4 g (76%). A sample was recrystallized from acetic acid, mp 163–165°.

*4-Chlorophenyl Methylsulfone*

A. A suspension of 102.0 g (0.375 mole) of 4-chlorophenylsulfinic acid sodium salt (74.5% active substance), 36.2 g (0.43 mole) of sodium bicarbonate in 150 ml of DMMP was placed in a steel autoclave and heated at 170° for a period of one hour. After cooling 150 ml of water was added and the crystalline suspension added to 1 l of water and the mixture stirred for 2 hr. The crystals were filtered, washed with 1 l of water and dried at 55°/30 torr yielding 68.1 g (95.3%) of product.

B. The sodium salt of 4-chlorophenylsulfinic acid was dried at 100°/12 torr and contained 92% of active material.

A suspension of 27.0 g (0.125 mole) of dry 4-chlorophenylsulfinic acid sodium salt in 50 ml of DMMP and 12.6 g (0.125 mole) of triethylamine was heated at 152–155° for a period of 10 minutes. The product was isolated by the same procedure as described under A).

*4-Tolymethylsulfone* (**26**)

A suspension of 22.7 g (0.125 mole) of *p*-toluenesulfinic acid sodium salt in 50 ml of DMMP and 12.6 g (0.125 mol) of triethylamine was heated at 167° during a period of 45 min. Then the temperature was increased to 172° for an additional 30 min. The product was isolated as described above yielding 17.2 g.

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