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AN EASY FORMATION OF DITHIOACETALS ON ALUMINA-KF UNDER MICROWAVE IRRADIATION. SYNTHESIS OF NEW POTENTIAL ANTIVIRAL PHOSPHONATES.

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Abstract: The preparation of dithioacetals by the reaction of methylene compounds with S-methyl methanesulfonothioate on Al_2O_3-KF is described. Microwave irradiation without solvent provides a powerful activation. Potential antiviral phosphonates are prepared.

We have previously described the oxidation of methylene compounds by tosylazide in the presence of alumina-KF as base[1], yielding diazocompounds. Pursuing the development of anionic oxidation of acidic carbon compounds absorbed on alumina-KF, we report herein the synthesis of dimethyl dithioacetals from acidic methylene compounds. Dimethyl dithioacetals are masked carbonyl compounds, which make them very interesting for synthetic purposes. They can also be prodrugs or analogs of biologically active ketones.

Many reagents were proposed by different authors for the sulfenation of carbanions[2]: symmetric sulfides[3], sulfenamides[4], thiolsulfonates[5] and sulfenyles halogenides[6]. We describe the use S-methyl methanesulfonothioate adsorbed on

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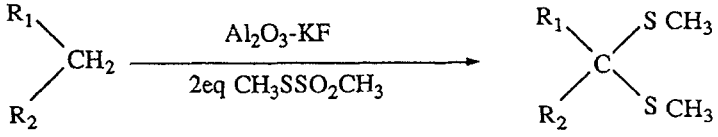
potassium fluoride on alumina for the bis-sulfenation of acidic methylene compounds.



We have also tried sulfenation[3] by methylsulfenyl chloride (2 eq.) in methylene chloride (0°C, 16h), which gave only poor yields (<50%). The reaction of S-methyl methanesulfonothioate (2 eq.) without solvent, and under microwave irradiation when necessary, gave better results (see table). Microwave irradiation without solvent is a new and powerful method for anionic or cationic activation, for which examples are given in ref. 7 et 8. In these conditions dimethyldisulfide did not react.

Due to their sensitivity to high temperature, microwave activation of the phosphonates is more delicate. It was not however necessary to activate tetraethylmethylenediphosphonate for it to react with S-methyl methanesulfonothioate on alumina-KF. The reaction was complete after one hour at room temperature, it yielded 95% of the tetraethyl di(methylthio)-methylenediphosphonate (7). It was possible to isolate the monomethylthio-diphosphonate after 5 Mn of reaction, this product was identified with that described by Masson et coll.[9]. Activation of the triethyl phosphonoacetate was necessary but afforded only 21% of the dimethylthio (5) and 46% of the monomethylthio compound (6). More intensive activation led to degradation of the products.

Many phosphonates or diphosphonates are of biological interest[10], and the di(methylthio)methylenediphosphonate is a new potential prodrug of carbonyldiphosphonate, a known antiviral[11]. The derivative obtained from triethyl

TABLE: Sulfenation with $CH_3SSO_2CH_3$ on Al_2O_3-KF

Product	R_1	R_2	Yield (%)
1	COOEt	COOEt	94[a]
2	COOEt	CN	91[a]
3	COOEt	C_6H_5	70[a]
4	COOEt	CH_3CO	85[a]
5	COOEt	$PO(OEt)_2$	21[b]
7	$PO(OEt)_2$	$PO(OEt)_2$	95[c]

a: Microwave irradiation (350 W, 2 Mn).
b: Microwave irradiation (140 W, 2 Mn).
c: Room temperature, 1 hour.

phosphonoacetate also is a new potential prodrug of the antiviral[1,2] phoshonooxoacetate.

The corresponding free phosphonic acids are obtained upon treatment by trimethylsilyl bromide. Biological tests on HIV are in progress at Rhône-Poulenc-Rorer.

Experimental

Infrared spectra were recorded in KBr or between NaCl plates on a Perkin Elmer 684 IR spectrophotometer, absorptions are in cm^{-1}. Proton NMR spectra (PMR) were recorded in ppm downfield from internal Me_4Si on a Varian EM 360 instrument (60 MHz). ^{13}C NMR spectra were recorded in ppm downfield from internal Me_4Si on a Brucker WP 60, as were the ^{31}P NMR spectra, in ppm downfield from external H_3PO_4. Mass spectra (MS) were recorded on a Nermag

R10-10H spectrometer. Microwave irradiations were carried out with a commercial microwave oven Toshiba ER 7620 at 2450 MHz.

S-methyl methanesulfonothioate was prepared according to Laszlo and Marthy[13].

General procedure :

The acidic methylene compound (5 mmol) and S-methyl methanesulfonothioate (10 mmol) were adsorbed on Al_2O_3-KF (5 g or 8 g for the phosphonates) and were either irradiated under microwave in an open Erlenmeyer flask or left at room temperature. The reactions were monitored by TLC on silica gel (eluent dichloromethane: methanol = 99 : 3). The products were extracted with methylene chloride (3 x 20 ml). The solvent was distilled and the residue purified by chromatography (eluent dichloromethane: methanol = 99 : 1) or by Kugelrohr distillation (boiling points (Bp) are given in °C (mmHg)).

Ethyl di(methylthio)malonate (1)

Obtained from ethyl malonate; microwave irradiation (2450 MHz, 350 W, 2 Mn) ; yield 94 %.

Yellow liquid, Bp 75 (0.1) [lit[14] Bp 85 (0.2)] ; PMR ($CDCl_3$) δ : 1.30 (t, 6H, CH_3), 2.10 (s, 6 H, SCH_3), 4.35 (q, 4 H, OCH_2) ; IR(film) : 1750 (ν C=O).

Ethyl di(methylthio)cyanoacetate (2)

Prepared from ethyl cyanoacetate ; microwave irradiation (2450 MHz, 350 W, 2 Mn) ; yield 91%.

Pale yellow liquid ; Bp 135 (1.5) ; PMR ($CDCl_3$) δ : 1.25 (t, 6 H, CH_3), 2.25 (s, 6 H, SCH_3), 4.45 (q, 4 H, OCH_2) ; IR(film) : 2250 (ν CN), 1750 (ν C=O).

Ethyl α-di(methylthio)phenylacetate (3)

Obtained from ethyl phenylacetate ; microwave irradiation (2450 MHz, 350 W, 2 Mn) ; yield 70%.

Pale yellow liquid ; Bp 98 (0.1) [lit[14] Bp 134-136 (1.1)] ; PMR ($CDCl_3$) δ : 1.15 (t, 6 H, CH_3), 2.20 (s, 6 H, SCH_3), 4.35 (q, 4 H, OCH_2), 7.2 (s large, 5 H, H arom) ; IR(film) : 1750 (ν C=O), 1595 (ν C=C).

Ethyl α-di(methylthio)acetylacetate (4)

Prepared from acetylacetone ; microwave irradiation (2450 MHz, 350 W, 2 Mn) ; yield 85%.

Pale yellow liquid ; Bp 65 (0.2) [lit[14] Bp 107-109 (2)] ; PMR ($CDCl_3$) δ : 1.3 (t, 6 H, CH_3), 2.0 (s, 6 H, SCH_3), 2.3 (s, 3 H, CH_3CO), 4.45 (q, 4 H, OCH_2) ; IR(film) : 1730, 1700 (ν C=O).

Triethyl di(methylthio)phosphonoacetate (5)

Prepared from triethyl phosphonacetate ; microwave irradiation (2450 MHz, 140 W, 2 Mn) ; purified by chromatography ; yield 21%.

Colourless liquid ; PMR (CCl_4) δ : 1.30 (t, J = 7 Hz, 9 H, C-CH_3), 2.15 & 2.20 (s, 6 H, SCH_3), 4.17 (d q, $J^1 = J^2 = 7$ Hz, 4 H, $POCH_2$), 4.20 (q, J = 7 Hz, 2 H, $COCH_2$) ; ^{13}C NMR ($CDCl_3$) δ : 14.07 ($COC\underline{C}H_3$), 15.9 (d, J^4_{PC} = 4.6 Hz, $S\underline{C}H_3$), 16.4 (d, J^4_{PC} = 5.9 Hz, $POC\underline{C}H_3$), 45.3 (d, J_{PC} = 142 Hz, PC), 61.8 ($CO\underline{C}H_2$), 63.5 (d, J^3_{POC} = 6.8 Hz, $POCH_2$), 166.8 (C=O) ; ^{31}P NMR ($CDCl_3$) δ : 14.3 ; IR(film) : 1720 (ν C=O), 1250 (ν P=O), 1020 (C-O-P), 660 (C-S). MS *m/z* (rel. intens.) : 316 (M^+, 2.6), 269 (36.7), 242 (11.2), 223 (16), 43 (100).

Tetraethyl methylthiophosphonoacetate (6)

Prepared from triethyl phosphonacetate ; microwave irradiation 2450 MHz, 140 W, 2 Mn) ; purified by chromatography ; yield 46%.

Colourless liquid ; PMR (CCl_4) δ : 1.35 (t, J = 7 Hz, 9 H, C-CH_3), 2.15 & 2.30 (s, 3 H, SCH_3), 3.4 (d, J = 20 Hz, 1 H, PCH), 4.13 (d q, $J^1 = J^2 = 7$ Hz, 4 H, $POCH_2$), 4.17 (q, J = 7 Hz, 2 H, $COCH_2$) ; ^{13}C NMR ($CDCl_3$) δ : 13.9 ($COC\underline{C}H_3$), 14.05 (SCH_3), 16.4 (d, J^4_{PC} = 5.6 Hz, $POC\underline{C}H_3$), 61.9 (d, J_{PC} = 144 Hz, PC), 62.7 ($CO\underline{C}H_2$), 63.5 (d, J^3_{PC} = 7 Hz, $POCH_2$), 166.2 (C=O) ; ^{31}P NMR ($CDCl_3$) δ : 16.6 ; IR(film) 1730 (ν C=O), 1250 (ν P=O), 1020 (C-O-P), 665 (C-S). MS *m/z* (rel. intens.) : 270 (M^+, 21.3), 224 (100), 197 (60), 169 (10.1), 152 (12.5).

Tetraethyl di(methylthio)methylenediphosphonate (7)

Prepared from tetraethyl methylenediphosphonate ; no microwave irradiation, one hour reaction at room temperature ; purified by chromatography ; yield 95%.

Colourless liquid ; PMR (CCl_4) δ : 1.30 (t, J = 7 Hz, 9 H, C-CH_3), 2.15 & 2.20 (s, 6 H, SCH_3), 4.17 (d q, $J^1 = J^2 = 7$ Hz, 4 H, $POCH_2$), 4.20 (q, J = 7 Hz, 2 H, $COCH_2$) ; ^{13}C NMR ($CDCl_3$) δ : 13.9 (t, J^4_{PC} = 2.5 Hz, SCH_3), 16.5 (t, J^4_{PC} = 2.9 Hz, $OCCH_3$), 52.5 (t, J_{CP} = 139 Hz, PCP), 64.6 (t, J^3_{PC} = 3.7 Hz, $POCH_2$) ; ^{31}P NMR ($CDCl_3$) δ : 15.9; IR(film) : 1250 (ν P=O), 1020 (C-O-P), 660 (C-S). MS *m/z* (rel. intens.) : 380 (M^+, 6.8), 333 (34.5), 288 (12), 243 (2.5), 152 (100).

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