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A CONVENIENT ONE-STEP PROCEDURE FOR THE SYNTHESIS OF KETENE O,S- AND KETENE S,S-ACETALS VIA THIOACYLATION OF MALONONITRILE

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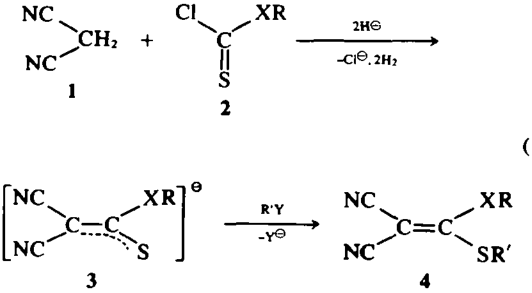
Abstract—Ketene O,S-acetals have been prepared by condensation of malononitrile **1** with chlorothionoformate esters **2** (X=O) in the presence of two equivalents of sodium hydride followed by alkylation of the intermediate thiolate anion **3**. In a similar manner a number of unsymmetrical ketene S,S-acetals were synthesised via thioacylation of **1** with chlorodithioformate esters **2** (X=S). The reaction of the ketene O,S-acetals with secondary amines was investigated.

The base-induced thioacylation of malonic acid derivatives with thionesters, dithioesters, aliphatic O,S-dithiocarbonates and trithiocarbonates has recently been investigated by Hartke.[1] In a preceding paper[2] we have shown that ketene S,N-acetals are conveniently synthesised by thiocarbamoylation[3] of active methylene compounds (using sodium hydride as the base) with thiocarbamoyl chlorides **2** (X=NR) or C-sulfonylthioformamides followed by alkylation of the intermediate thiolate anion. This communication deals with the facile synthesis of ketene O,S- and ketene S,S-acetals **4** by a similar procedure.

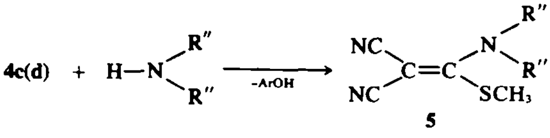


(1)

X = O, S Y = Cl, Br, J, FSO_3, CH_3OSO_3

Ketene O,S-*acetals*. The ketene O,S-acetals **4** (X=O) were prepared in a benzene-DMF solution according to (1) without isolation of the intermediate thiolate anion **3**. The low yield of **4b** (Table 1) is probably due to an ether cleavage induced by liberated iodine ions.[1] In agreement with this explanation high yields of **4c** and **4d** (R = aryl), where a similar cleavage is excluded, were obtained. However, only a very low yield of **4a** (R=R′=Me) was isolated even when methyl iodide was replaced by dimethyl sulfate (following the proposal of Hartke[1]) as the alkylating agent. Several other attempts to increase the yield of **4a** (variation of temperature, solvent and base) were unsuccessful. Thus disproportionation[4] of the chlorothionoformate to alkyl halide and carbonyl sulfide also seems to be of importance. A comparison of the UV spectra of **4c** and **4d** (Table 2) reveals that the conjugation of the benzene ring with the lone pair on oxygen in the latter is removed as a result of the steric hindrance of the two *ortho*-methyl substituents. In fact the absorption maxima of the $\pi \rightarrow \pi^*$ transition of **4a** and **4d** are found at the same wavelength.

Aliphatic ketene O,S-acetals are known to react with amines with the formation of ketene O,N-acetals.[5] As the pK_a-values diminish in the order ROH > RSH > ArOH it should be expected that **4c** and **4d** with amines yield the ketene S,N-acetals **5**.



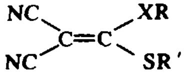
5

a: $R'' = CH_3$
b: $R'' = CH_2C_6H_5$

In fact a high yield of **5a** was obtained in the reaction of **4d** with dimethylamine. The corresponding reaction of **4c** with dibenzylamine similarly yields **5b**. Rather severe reaction conditions were necessary in this case, due to the bulky benzyl substituents.

Ketene S,S-*acetals*. The ketene S,S-acetals **4** (X=S) were prepared according to (1) as previously described for the ketene O,S-acetals by initial thioacylation of **1** with chlorodithioformate esters.

Table 1. Preparation of ketene O,S- and ketene S,S-acetals



$\mathrm{(NC)_2C{=}C(XR)(SR')}$

4

	R	R′	X	Y	Reaction Temp °C	Yield %	M.p.° [B.p.°/mmHg]	Recryst from	Formula (Molecular weight)	Analysis Found (Calc), %			
										C	H	N	S
4a	CH_3	CH_3	O	CH_3OSO_3	0	4	49–50	sublimated (40°/10 mmHg]	$C_6H_6N_2OS$ (154·1)	46·74 (46·76)	3·91 (3·92)	18·02 (18·18)	21·09 (20·76)
4b	CH_2CH_3	CH_3	O	J	25	1	48–49	abs. ethanol	$C_7H_8N_2OS$ (168·2)	50·04 (50·00)	4·98 (4·80)	— (16·66)	— (19·02)
4c	C_6H_5	CH_3	O	J	0	82	55–56	petroleum (b.p. < 50) -ether 2 : 1	$C_{11}H_8N_2OS$ (216·2)	61·17 (61·11)	3·79 (3·73)	13·05 (12·96)	14·84 (14·80)
4d	2,6-$(CH_3)_2C_6H_3$	CH_3	O	J	60	77	132–133	abs. ethanol	$C_{13}H_{12}N_2OS$ (244·2)	63·86 (63·92)	4·92 (4·95)	11·36 (11·47)	— (13·10)
4e[a]	CH_3 CH_2CH_3	CH_2CH_3 CH_3	S	Br J	10 10	23 87	[123/0·2]		$C_7H_8N_2S_2$ (184·15)	45·71 (45·65)	4·47 (4·38)	15·14 (15·21)	34·37 (34·75)
4f[b]	CH_3	$CH_2C_6H_5$	S	Cl Br	45	43 87	[90/ ~ 10^{-4}]		$C_{12}H_{10}N_2S_2$ (246·2)	57·69 (58·59)	4·16 (4·09)	11·23 (11·38)	26·07 (25·99)
4g	C_6H_5	CH_3	S	FSO_3	0	79	60	petroleum (b.p. < 50)	$C_{11}H_8N_2S_2$ (232·2)	57·06 (56·90)	3·54 (3·47)	11·95 (12·07)	27·38 (27·56)
4h	4-$CH_3C_6H_4$	CH_3	S	J	50	83	65–66	cyclohexane	$C_{12}H_{10}N_2S_2$ (246·2)	58·65 (58·53)	4·15 (4·09)	11·68 (11·38)	— (25·99)
4i	C_6H_5	$CH_2C_6H_5$	S	Br	40	77	81–82	abs. ethanol	$C_{17}H_{12}N_2S_2$ (308·3)	66·07 (66·23)	4·02 (3·92)	9·13 (9·09)	20·46 (20·76)

[a] $n_D^{23·5}$ 1·6211
[b] $n_D^{24·5}$ 1·6566

Table 2. Spectral data of 4

	IR-Frequencies (KBr), cm^{-1}		UV-$\pi \rightarrow \pi^*$ Bands (EtOH)		^{1}H NMR (CDCl$_3$), δ, ppm
	$\nu_{C≡N}$	$\nu_{C=C}$	λ_{max}, nm	log ϵ	
4a	2215 2200	1530	296	4·01	2.58(3H, s, SCH_3); 4·37(3H, s, OCH_3)
4b	2215 2205	1525	297	4·06	1·50(3H, t, $CH_2C\underline{H}_3$); 2·53(3H, s, SCH_3); 4·70(2H, q, $OC\underline{H}_2CH_3$)
4c	2215 2205	1520	304	4·20	2·42(3H, s, SCH_3); 7·0–7·5(5H, m, arom. H)
4d	2212 2198	1510	296	4·12	2·22(6H, s, 2CH_3); 2·67(3H, s, SCH_3); 7·1–7·2(3H, m, arom. H)
4e	2212	1460	335	4·02	1·38(3H, t, $CH_2C\underline{H}_3$); 2·75(3H, s, SCH_3); 3·27(2H, q, $SC\underline{H}_2CH_3$)
4f	2215	1460	337	4·12	2·61(3H,s,SCH_3);4·40(2H,s,CH_2);7·33(5H,s,arom.H)
4g	2215 2208	1470	334	4·11	2·52(3H,s,SCH_3);7·48(5H,s,arom.H)
4h	2212 2200	1460	332	4·13	2·38(3H,s,4-CH_3);2·54(3H,s,SCH_3);7·3–7·5(4H,m,arom.H)
4i	2215 2207	1470	337	4·14	4·25(2H, s, $SC\underline{H}_2$); 7·2–7·5(10H, m, arom. H)

However, in this case high yields were obtained both with aliphatic and aromatic chlorodithioformate esters. While the yields were rather independent on the reaction temperature,[*] the use of strong alkylating agents was found advantageous (Table 1). Unsymmetrical ketene S,S-acetals have been prepared via monoalkylation of the mono-tetrabutylammonium salts obtained by condensation of active methylene compounds with carbon disulfide using tetrabutylammonium hydroxide as the base.[6] As dialkylation is difficult to avoid by this technique, the present method is a promising alternative for the preparation of unsymmetrical ketene S,S-acetals.

EXPERIMENTAL

B.ps are uncorrected. M.ps were determined with a Büchi-apparatus (Dr. Tottoli). IR spectra were recorded on a Beckman IR-18A spectrophotometer and the UV spectra on a Bausch & Lomb Spectronic 505. NMR spectra were obtained with a Varian A-60 spectrometer using TMS as internal standard. All reactions were followed by TLC on Merck silica gel $HF_{254+366}$.

Materials. The chlorothionoformate esters **2** (X=O) and chlorodithioformate esters **2** (X=S) were prepared from thiophosgene by the methods described in the literature.[7] DMF and benzene were dried over 4 Å molecular sieves and sodium wire, respectively.

General procedure for the preparation of ketene O,S- *and ketene* S,S-*acetals* **4**. A solution of **1** (6·6 g, 0·1 mole) in 50 ml DMF was added dropwise with stirring during 30 min to a suspension of sodium hydride (4·8 g, 0·2 mole) in 150 ml benzene-DMF 2 : 1 at room temp. After additional stirring for 1 hr a soln of **2** (0·1 mole) in 100 ml benzene was added dropwise during 1 hr at 0–45° (Table 1, reaction temp). After stirring for another 1 hr the alkylating agent (0·11 mole) dissolved in 50 ml benzene was added at once and the soln after being stirred overnight at room temp was poured into 500 ml ice water and extracted with 200 ml benzene. The combined benzene layers were washed twice with 500 ml portions of NaCl-saturated water and dried over $CaSO_4$, and concentrated. The residue was digested with cold EtOH and finally purified by sublimation, recrystallization, or distillation (alternatively coloured impurities can easily be removed by filtration through silica gel by elution with chloroform).

Deviations from the general procedure. Compounds **4a** and **4b** were prepared under N_2. **4a** was purified by column chromatography on silica gel (eluent: petroleum (b.p. 60–80°)—acetone (80 + 20)) followed by sublimation at 40°C/10 mm Hg. In the preparation of **4f** via alkylation with benzyl chloride the two symmetrical ketene S,S-acetals, *i.e.* bis(methylthio) methylene malononitrile and bis(benzylthio) methylene malononitrile were formed as byproducts. **4f** was obtained in a pure condition from the mixture by column chromatography on silica gel (eluent: petroleum (b.p. 60–80°)—ether (50 + 50)).

Reaction of **4d** *with dimethylamine.* To a soln of **4d**

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[*] The thioacylation of 1 with chlorothionoformate esters and chlorodithioformate esters was found to be a rather fast and exothermic reaction contrary to the thiocarbamoylation of 1.

(1·23 g, 5 mmole) in 20 ml alcohol, dimethylamine (0·51 g, 5 mmole) as a 40% soln in water was added at room temp. After 1 hr, the mixture was diluted with 150 ml water and extracted with 100 ml chloroform. The chloroform layer was washed with 100 ml 1N NaOH and dried over $CaSO_4$. Evaporation of the solvent and recrystallization from cyclohexane yields 0·60 g (72%) (dimethylamino-methylthio) methylene malononitrile **5a** m.p. 76° (lit.[8] 76–77°).

Reaction of **4c** *with dibenzylamine.* A mixture of **4c** (4·32 g, 20 mmole) and dibenzylamine (3·94 g, 20 mmole) dissolved in 75 ml dioxane was heated to 75° for 24 hr. The solvent was removed *in vacuo* and the residue taken up in 150 ml ether. The ether soln was washed twice with portions of 1N NaOH (2 × 75 ml) and dried over 4 Å molecular sieves. Evaporation of the solvent and recrystallization from EtOH yielded 2·26 g (35%) **5b**, m.p. 118° (lit.[2] m.p. 118°).

REFERENCES

[1] K. Hartke and F. Meissner, *Tetrahedron* **28**, 875 (1972), and refs cited

[2] N. H. Nilsson and J. Sandström, *Synthesis* to be published

[3] N. H. Nilsson, A. Senning, S. Karlsson and J. Sandström, *Synthesis* 314 (1972)

[4] A. Berthoud and D. Porret, *Helv. Chim. Acta* **16**, 939 (1933)

[5] D. Borrmann, *Methoden der Org. Chem.* p. 431 (Houben–Weyl) **7/4** (1968)

[6] L. Dalgaard, H. Kolind-Andersen, and S.-O. Lawesson, *Tetrahedron* **29**, 2077 (1973)

[7] M. Bögemann, S. Petersen, O.-E. Schultz and H. Söll, *Methoden der Org. Chem.* p. 807, 808 (Houben-Weyl) **9** (1955)

[8] Takeshi Nakai, Makoto Okawara, *Bull. Chem. Soc. Japan* **43**, 3528 (1970)