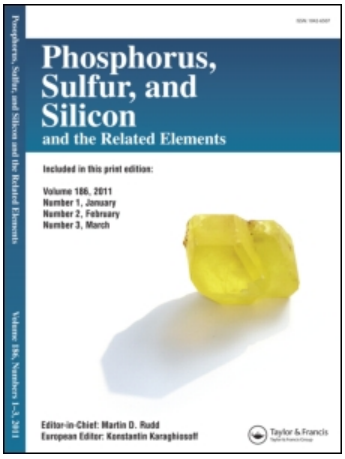

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A ONE-POT SYNTHESIS OF THIOPYRANE DERIVATIVES FROM KETENE S,S-ACETALS AND α,β-UNSATURATED NITRILES UNDER PTC CONDITIONS

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Some new functionally substituted thiopyranes and 1,3-dithiolanes were obtained in a one-pot reaction using phase transfer catalysis conditions (PTC) starting with some active methylene compounds, carbon disulphide or phenyl isothiocyanate and α,β-unsaturated nitriles. The structure of the new compounds was assigned.

Key words: Thiopyrane-2-thione derivatives; 1,3-dithiolane derivatives.

INTRODUCTION

The synthesis of ketoketene[1] or cyanoketene S,S-acetals[2] as well as heterocyclic ketene N,N-[3–9] or N,S-acetals[5,10–14] has become a subject of current interest since they have been used as versatile starting materials for the synthesis of a wide variety of heterocyclic systems. Recently, it has also been reported that dithiolate dianions or dithioic acids derived from reaction of 1,3-oxoalkane nitriles with CS_2 in the presence of a base can react on sulfur with a variety of electrophiles including allylic halides, propargyl halides, α-haloketones, α-halo esters, α-halo nitriles, α-haloamides and acrylonitrile.[15]

RESULTS AND DISCUSSION

In an extention of our recent studies on the application of cyanoketene s,s-acetals[16,17] or heterocyclic ketene N,O-acetals[18] in heterocyclic synthesis using (PTC) conditions. We report here the synthesis of some new thiopyrane derivatives starting with an active methylene compound, CS_2 and α,β-unsaturated nitriles in a one-pot reaction under PTC conditions [benzene/K_2CO_3/tetrabutylammonium bromide (TBAB)]. The reaction was carried out by stirring the reactants at different temperatures over different periods of time, cf. Table I. Thus, when an equimolar mixture of malononitrile, CS_2 and arylidenemalononitrile or arylidene ethyl cyanoacetate was stirred in K_2CO_3/benzene in the presence of the TBAB catalyst, 4-amino-6-aryl-3,5-dicyanothiopyrane-2-thione $\mathbf{1}_{a\text{-}e}$ or 4-amino-6-aryl-3-cyano-5-ethoxycarbonylthiopyrane-2-thione $\mathbf{2}_{a,b}$, were obtained, cf. Scheme 1. The reaction

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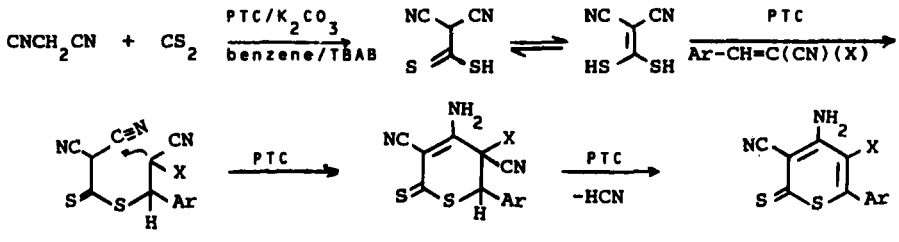


1a, Ar = *p*-$NO_2C_6H_4$, X = CN
1b, Ar = $CH{=}CHC_6H_5$, X = CN
1c, Ar = NHC_6H_5, X = CN
1d, Ar = *p*-$OCH_3C_6H_4$, X = CN
1e, Ar = C_6H_5, X = CN
2a, Ar = C_6H_5, X = CO_2Et
2b, Ar = *p*-$OCH_3C_6H_4$, X = CO_2Et

SCHEME 1

TABLE I

Compound No.	T (°C)	t (h)	Yield (%)	M.p[a] Cryst.Solv.	Mol.Form[b] Mol.Wt.
1a	50	7	25	218-2220 (Ethanol)	$C_{13}H_6N_4S_2$ (282.32)
1b	60	11	58	194-195 (Methanol)	$C_{15}H_9N_3S_2$ (295.36)
1c*	75	7	70	>300 (benzene)	$C_{13}H_9N_4S_2Cl$ (320.79)
1d*	65	12	48	>300 (benzene)	$C_{14}H_{10}N_3S_2Cl$ (289.80)
1e*	50	10	36	>300 (benzene)	$C_{13}H_8N_3S_2Cl$ (305.78)
2a*	70	8	25	>300 (benzene)	$C_{15}H_{13}N_2S_2Cl$ (320.84)
2b	70	12	32	212 (Ethanol)	$C_{16}H_{14}N_2S_2O_3$ (346.40)
3a	75	48	45	290 (Methanol)	$C_{19}H_{20}N_2S_2O_5$ (420.48)
3b	75	48	10	>300 (Ethanol)	$C_{16}H_{13}NS_2O_4$ (347.39)
4	60	13	14	>300 (Ethanol)	$C_{16}H_{13}NS_2O_4$ (347.39)
5	70	11	71	165-166 (benzene)	$C_{20}H_{14}N_4SO$ (358.40)
6	75	9	39	142-145 (Ethanol)	$C_{22}H_{19}N_3SO_3$ (405.44)
7	50	7	43	220[d]	$C_{17}H_{12}N_4S_2O_3$

* Separated as HCl salt.

TABLE I

(*continued*)

Compound	IR (KBr)[c] ν Cm^{-1}	^{1}H-nmr (DMSO-d_6)[d] δ ppm
1a	3470,3380(NH_2), 2225,2220 (CN)	8.40-7.60(m,4H,arom.), 7.20 (br,2H,NH_2).
1b	3390,3285(NH_2), 2230,2220 (CN)	8.10(s,2H,CH=CH styryl), 7.70-7.20(m,5H,arom), 6.50 (br,2H,NH_2).
1c	3370,3275(NH_2), 3190(NH), 2225,2220(CN).	9.50(br,3H,NH_2.HCl), 9.20 (br,1H,NH), 8.40-7.30(m,5H, arom.).
1d	3325,3230(NH_2), 2215,2210 (CN).	9.70(br,3H,NH_2.HCl), 8.20-7.10(m,4H,arom.), 4.30(s, 3H,OCH_3).
1e	3290,3190(NH_2), 2225,2220 (CN)	9.70(br,3H,NH_2.HCl), 8.10-7.60(m,5H,arom.)
2a	3320,3235(NH_2), 2225,2215 (CN), 1710(C=O ester)	9.30(br,3H,NH_2.HCl), 8.20-7.30(m,4H,arom.), 5.40-4.20 (m,5H,CH_2 + OCH_3), 1.30-0.80(t,3H,CH_3)
2b	3217(NH), 2228,2225(CN) 1690(C=O ester).	8.25-7.00(m,4H,arom.), 4.80 (s,2H,NH_2), 4.00-3.20(m,5H, CH_2 + OCH_3), 1.30-0.80(t, 3H,CH_3)
3a	3302,3200(NH_2), 2210(CN), 1731,1710(C=O ester)	8.40-7.60(m,4H,arom.), 6.20 -6.00(br,2H,NH_2), 4.60-4.10 (m,7H,2CH_2+OCH_3), 3.20(s,1H ,CH), 1.60-1.20(t,6H,2CH_3)
3b	3421(OH), 2215(CN), 1710 (C=O ester)	8.30-6.90(m,4H,arom.), 4.60 -4.10(m,3H,OH + CH_2), 3.90 (s,3H, OCH_3), 1.50-1.30(t, 3H,CH_3)
4	3428(OH), 2220(CN), 1715 (C=O ester)	8.20-7.10(m,4H,arom.), 4.50 -4.00(m,3H,OH + CH_2), 3.80 (s,3H,OCH_3), 1.40-0.90(t, 3H,CH_3)
5	3427,3320(NH_2), 2215,2210 (CN)	8.10-7.20(m,9H,arom.), 5.60 (br,2H,NH_2), 4.40(s,3H, OCH_3)
6	3350,3245(NH_2), 2225(CN), 1680(C=O ester)	7.70-7.10(m,9H,arom.), 6.50 (br,2H,NH_2), 4.70-4.00(m,5H ,CH_2 + OCH_3), 1.60-1.10(m, 3H,CH_3)
7	3320,3215(NH_2), 2225(CN)	8.50-7.20(m,10H,arom.+ pyridyl + =CH), 6.40(s,2H,NH_2), 2.70(s,1H,CH)

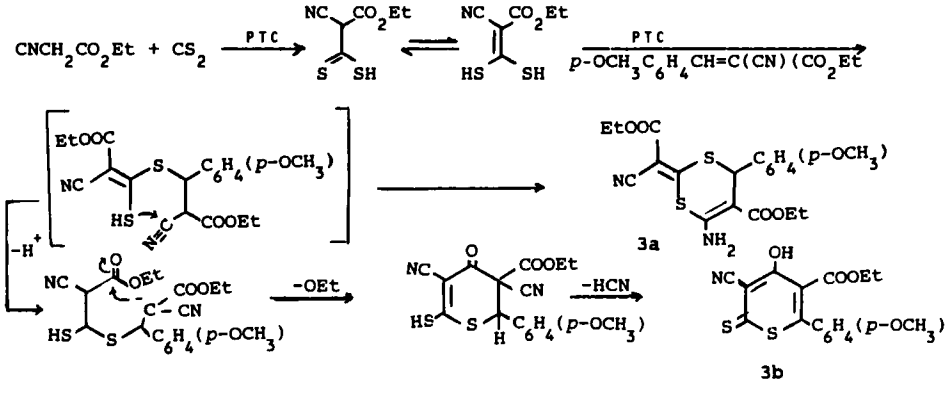
[a]) Uncorrected [b]) Saisfactory microanalyses obtained; C,+ 0.3%, N, + 0.45%, S,+ 0.2% [c]) Measured on Nicolet 710 FT-IR spectrophotometer [d]) Measured with a Varian EM 360 L using TMS as internal standard .

pathway was assumed to proceed *via* an initial formation of the cyanoketene S,S-dithioic acid, followed by two successive nucleophilic attacks of $—S^-$ ion at the ethylenic double bond and of $—:^-C(CN)_2$ carbon at the cyano group, respectively, with subsequent HCN elimination.

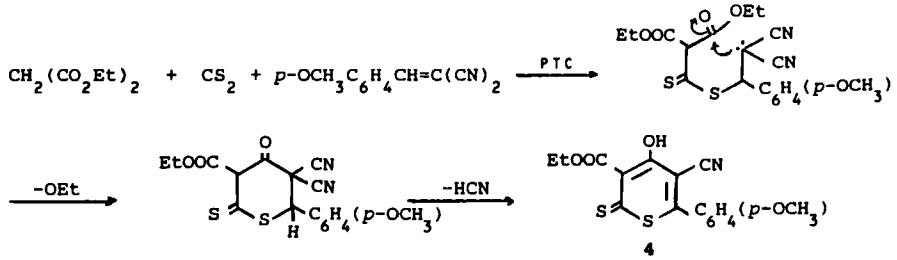
In all cases the desired products were precipitated during the course of the reaction and can be obtained either by dissolving the K_2CO_3 layer in water or simply by treatment of the aqueous K_2CO_3 layer with dilute HCl.

Analogous with malononitrile, the reaction of ethyl cyanoacetate, CS_2 with *p*-methoxybenzylidene ethyl cyanoacetate under the same experimental conditions gave two products. The major one was separated by dissolving the K_2CO_3 layer in water and proven to be 4-amino-5-ethoxycarbonyl-6-*p*-methoxyphenyl-2-ylidene ethyl cyanoacetate-6H-1,3-dithiolane **3a**, the minor product was obtained from the mother liquor and was proven to be 3-cyano-4-hydroxy-5-ethoxycarbonyl-6-*p*-methoxyphenylthiopyrane-2-thione **3b**.

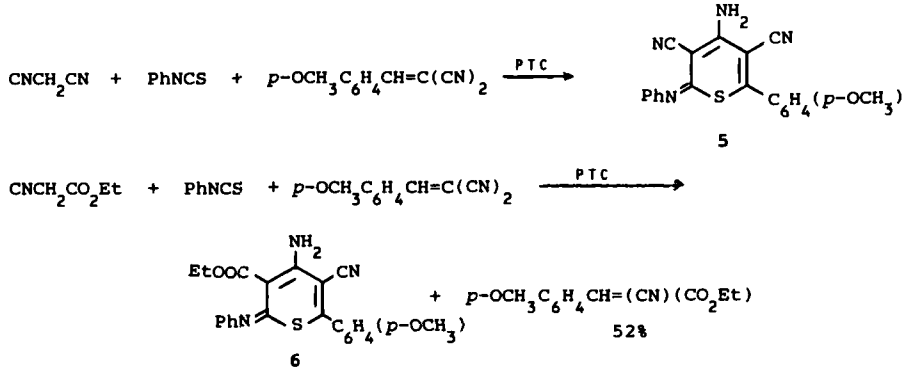
The reaction pathway is thus assumed to start with a nucleophilic attack of the $—S^-$ ion at the ethylenic double bond to give the intermediate adduct which was cyclized either by another nucleophilic attack of the second $—S^-$ ion at the cyano group to give the 1,3-dithiolane ring **3a** or by a nucleophilic attack of $:^-C(CN)(COOEt)$ carbon at the ethoxycarbonyl group with elimination of ethanol molecule followed by elimination of HCN molecule to give compound **3b**.



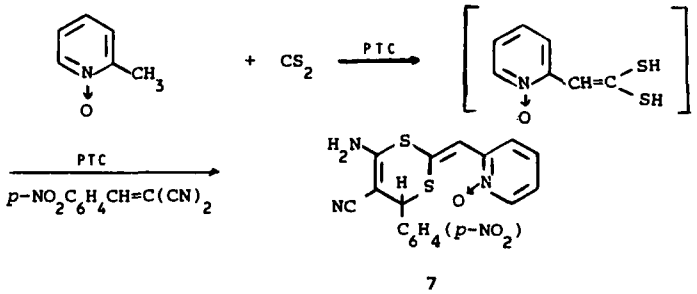
The reaction of diethylmalonate with CS_2 and *p*-methoxybenzylidene-malononitrile under PTC conditions yields 5-cyano-3-ethoxycarbonyl-4-hydroxy-6-*p*-methoxyphenylthiopyrane-2-thione **4** *via* a nucleophilic attack of $—S^-$ ion at the ethylenic double bond followed by another nucleophilic attack of $:^-C(CN)_2$ carbon at the ethoxycarbonyl group.



The reaction of malononitrile or ethyl cyanoacetate with phenyl isothiocyanate and *p*-methoxybenzylidenemalononitrile under PTC conditions was also carried out gave 4-amino-3,5-dicyano-6-*p*-methoxyphenyl-2-phenyliminothiopyrane **5** in 71% yield or 4-amino-5-cyano-3-ethoxycarbonyl-6-*p*-methoxyphenyl-2-phenylimino-thiopyrane **6** in 39% yield were obtained, respectively. The reaction was assumed to proceed *via* an initial formation of the ketene N,S-derivative followed by a nucleophilic attack of the $-S^-$ ion at the ethylenic double bond and cyclization with loss of HCN molecule. The reaction was found to give along with compound **6**, the *p*-methoxybenzylidene ethyl cyanoacetate in 52% yield, however, the mechanism responsible for its formation is under study.



This study was also extended to use some active substrates, thus picoline-*N*-oxide was successfully reacted with CS_2 and *p*-nitrobenzylidenemalononitrile using the same experimental (PTC) conditions where 4-amino-5-cyano-6-*p*-nitrophenyl-6H-2-(2-pyridylidene-*N*-oxide)-1,3-dithiolane **7** was obtained in 43% yield. The reaction pathway was assumed to proceed *via* the formation of the dithioic acid derivative followed by two successive nucleophilic attacks of the two —SH groups at the ethylenic double bond and the cyano group, respectively.



EXPERIMENTAL

All melting points were determined on a Kopfler melting point apparatus and were uncorrected. IR spectra were obtained (KBr disc) on Nicolet 710 FT-IR spectrophotometer. ^{1}H-NMR spectra were obtained on a Varian EM 360 L at 60 MHz using TMS as an internal standard. The elemental analyses were carried out on an elemental analyzer model 240 C.

General Procedure. An equimolar mixture (0.01 mole) of the active methylene reagent or picoline-*N*-oxide, CS_2 or phenyl isothiocyanate in 50 ml benzene was treated with 7 gm of anhydrous K_2CO_3 and a catalytic amount of TBAB. The reaction mixture was stirred for about 30 min. and 0.01 mole of the appropriate arylidenemalononitrile or arylidene ethyl cyanoacetate was gradually added over about 30 min. The mixture was then stirred for different periods of time and at different temperatures, cf. Table I. At the end of the reaction, TLC, the reaction mixture was filtered off. The benzene layer was washed with water and dried over Mg_2SO_4 and was then evaporated and *p*-methoxybenzylidene ethyl cyanoacetate was obtained. The K_2CO_3 layer was dissolved in water where the desired products were precipitated, filtered off and recrystallized from the proper solvent. In some cases, however, some of the reported products were obtained from the mother liquor after treatment with dilute HCl to give the desired product cf. Table I.

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