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REACTION OF α-CYANOACRYLATES WITH FUNCTIONALLY SUBSTITUTED THIOLS, ETHANEDITHIOL, AND HYDROGEN SULFIDE

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Functionally substituted thiols, i.e., thioglycolic acid and cysteamine and cysteine hydrochlorides, facilely undergo addition at the double bond of α-cyanoacrylates, forming the corresponding adducts in quantitative yields: $R'SCH_2CH(CN)COOR$ [R' = CH_2COOH; $CH_2CH_2NH_2 \cdot HCl$; $CH_2CH(COOH)NH_2 \cdot HCl$]. Under similar conditions, the reaction with ethanedithiol gives the diadduct $[CH_2SCH_2CH(CN)COOR]_2$; the monoadduct $HSCH_2CH_2SCH_2CH(CN)COOR$ is formed in a significantly lower yield. Hydrogen sulfide does not undergo addition to α-cyanoacrylate in the absence of a catalyst; $S[CH_2CH(CN)COOR]_2$ is formed quantitatively in the presence of Et_3N. In the presence of triethylamine, this sulfide undergoes intramolecular cyclization (the Ziegler–Thorpe reaction) with formation of 4-amino-5-cyano-3,5-bis(ethoxycarbonyl)thiacyclohex-3-ene.

Previously, we showed that, unlike other nucleophiles (water, alcohols, and amines) various sulfhydryl compounds (thiols and thiocarboxylic and thiophosphoric acids) do not cause polymerization of α-cyanoacrylates (I), but facilely undergo addition to them, forming the corresponding adducts (II) in high yields [1].

$$\underset{\text{(I)}}{CH_2=C(CN)COOR} + R'SH \rightarrow \underset{\text{(II)}}{R'SCH_2CH(CN)COOR}$$

Therefore, it seems important to explore the possibility of extending this reaction to thiols containing various functional groups, in particular, of acid and basic nature and also to dithiols and hydrogen sulfide.

We have determined that thioglycolic acid reacts with ethyl cyanoacrylate (Ia, R = like other thiols, forming an adduct (IIa, R = Et; R' = CH_2COOH) in virtually quantitative yield.

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On the other hand, thiols containing an amino group cause only polymerization of cyanoacrylates. However, if one uses not free amino thiols but their salts (e.g., cysteamine or cysteine hydrochlorides), the reactions occur smoothly, giving only the corresponding adducts (IIb, R = Et; R' = $HCl \cdot H_2NCH_2CH_2$) and [IIc, R = Et; R' = $HCl \cdot H_2NCH(COOH)CH_2$]. A convenient solvent for reactions with amino thiol salts is acetic acid which, as we showed previously [1], does not cause polymerization of cyanoacrylates. The structure of the thus-obtained compounds (IIa-c) was shown unambiguously by NMR spectra (Table 1).

The reaction of ethanedithiol with ethyl α-cyanocrylate (Ia) occurred exothermically. At reagent ratio 1:2, the corresponding bis adduct (IIIa) was formed in virtually quantitative yield:

$$HSCH_2CH_2SH + 2CH_2 = C(CN)COOR \rightarrow [CH_2SCH_2CH(CN)COOR]_2$$
(Ia–c) (IIIa–c)

R = Et(a); $CH_2CH{=}CH_2$ (b); H (c).

The structure of this compound was also confirmed by PMR data (see Table 1). In principle, taking into account the significant separation of the two asymmetric centers, we could expect the formation of two diastereomers (III) in approximately equal amounts. However, the PMR spectra of (IIIa), recorded in various solvents ($CHCl_3$, acetone, and C_6H_6) and also with addition of the shift reagent [$Eu(Fod)_3$], exhibited no splitting of peaks. Only the ^{13}C NMR spectrum contained peaks of individual diasteromers in a 1:1 ratio.

It should be noted that because of the extreme ease of addition of the SH group at the double bond of (I) it was not possible to obtain the corresponding monoadduct of (IV) in good yield. Even in the presence of a large excess of ethanedithiol the main reaction product was the bis adduct (III).

$$HSCH_2CH_2SH + (Ia) \rightarrow (IIIa) + HSCH_2CH_2SCH_2CH(CN)COOEt$$
(IV)

Allyl α-cyanoacrylate (Ib) also reacted similarly to (Ia). In this case, the formation of the bis adduct (IIIb) showed that under the selected conditions the addition occurred only at the acrylate double bond and did not affect the allyl double bond (the latter, as is known [2], adds thiols only in the presence of specially added acid or basic catalysts or by a free-radical mechanism in the presence of peroxides or UV irradiation).

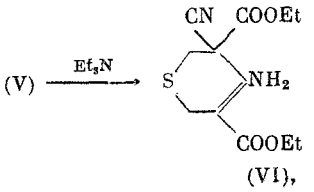
In the absence of a catalyst, the addition of ethanedithiol to free α-cyanoacrylic acid,* giving (IIIc), occurred just as facilely as did the addition to α-cyanoacrylates.

It should be emphasized that, unlike in the case of thiols, H_2S does not undergo addition to cyanoacrylates in the absence of the main catalyst (a similar difference in the reactions of thiols and H_2S with acrylates was known previously [4]). However, in the presence of catalytic amounts of triethanolamine the reaction occurred very fast, giving sulfide (V) in high yield:

$$H_2S + 2CH_2 = C(CN)COOEt \xrightarrow{Et_3N} S[CH_2CH(CN)COOEt]_2$$
(V)

the structure of which was also confirmed unambiguously by PMR data.

In the presence of catalytic amounts of Et_3N, sulfide (V) was converted quantitatively to substituted thiacyclohexene (VI):



(VI).

*For preparation of free α-cyanoacrylic acid, we modified and simplified somewhat the method described in the patent [3], which made it possible to significantly increase the yield and purity of the obtained product (the detailed synthesis method will be published later).

TABLE 1. Yields and Characteristics of Compounds (II)-(VI) (t, triplet; q, quartet; s, singlet; m, multiplet)

Compound	Yield, %	Mp, °C[a]	Empirical formula	Found/Calculated, %[b]				Parameters of PMR spectra (δ, ppm; J Hz)[c]
				C	H	N	S	
(IIa)	95	20	$C_8H_{11}NO_4S$	43,80 / 44,23	4,93 / 5,10	Not determined		CH_3 (1,28t); CH_2CH_3 (4,26 q); SCH_2COOH (AB: 3,43; 3,50; J_{AB} = 15,5); CH_2CH (ABX: 3,21; 3,30; 4,29; J_{AB} = 14,0; J_{AX} = 8,5; J_{BX} = 5,5); COOH (9,70s)
(IIb)	97	71–72	$C_8H_{15}ClN_2O_2S$	40,29 / 40,24	6,39 / 6,33	11,61 / 11,74	13,46 / 13,43	CH_3 (1,31t); CH_2CH_3 (4,31q); NCH_2CH_2S (3,16m; 3,38m); CH_2CH (ABX: 3,20; 3,25; 4,12; J_{AB} = 13,5; $J_{AX} + J_{BX}$ = 13,0)
(IIc)	95	152–154	$C_9H_{15}ClN_2O_4S$	37,56 / 38,23	5,49 / 5,35	9,66 / 9,91	11,41 / 11,34	CH_3 (1,15t); CH_2CH_3 (4,16 q); SCH_2CH and $NCHCH_2S$ (2,9—3,2m; 4,0—4,1m)
(IIIa)	90	99–101	$C_{14}H_{20}N_2O_4S_2$	48,75 / 48,82	5,42 / 5,85	8,26 / 8,13	18,74 / 18,62	SCH_2CH_2S (2,94s); CH_2CH (ABX: 3,13; 3,16; 3,80; J_{AB} = 13,0: $J_{AX} + J_{BX}$ = = 13,0); CH_3 (1,35t); CH_2CH_3 (4,32 q)
(IIIb)	65	99–100	$C_{16}H_{20}N_2O_4S_2$	52,45 / 52,17	5,59 / 5,47	7,35 / 7,60	17,37 / 17,41	SCH_2CH_2S (2,93s); CH_2CH (ABX: 3,13; 3,15, 3,82; J_{AB} = 14,0; $J_{AX} + J_{BX}$ = = 13,0); $CH_2CH{=}CH_2$ (A_2MTX: 4,74; 5,95; 5,34; 5,41; J_{AM} = 5,5; J_{AT} = = J_{AX} = 1,4; J_{MG} = 10,0; J_{MX} = 17,0; J_{TX} = 1,4)
(IIIc)	95	125–126	$C_{10}H_{12}N_2O_4S_2$	42,13 / 41,65	4,22 / 4,20	9,50 / 9,72	22,13 / 22,24	SCH_2CH_2S (3,00s); CH_2CH (ABX: 3,21; 3,24; 4,26; J_{AB} = 13,0; $J_{AX} + J_{BX}$ = = 13,0); COOH (8,6s)
(IV)	32[d]	25–26	$C_8H_{13}NO_2S_2$	44,12 / 43,81	6,05 / 5,97	6,10 / 6,38	28,10 / 29,24	SCH_2CH_2S (2,70m; 2,87m); CH_2CH (ABX: 3,06; 3,08; 3,77; J_{AB} = 13,0; J_{AX} + + J_{BX} = 13,0); CH_3 (1,30t); CH_2CH_3 (4,25q)
(V)	80	63–64	$C_{12}H_{16}N_2O_4S$	50,74 / 50,69	5,57 / 5,67	9,73 / 9,85	11,07 / 11,28	CH_2CH (ABX: 3,19; 3,23; 3,80; J_{AB} = = 14,0; $J_{AX} + J_{BX}$ = 13,0); CH_3 (1,33t); CH_2CH_3 (4,29 q)
(VI)[e]	95	–	$C_{12}H_{16}N_2O_4S$	50,79 / 50,69	5,36 / 5,67	9,72 / 9,85	11,26 / 11,28	CH_2SCH_2 (ABCD: 2,58; 2,89; 2,72; 3,17; J_{AB} = 12,8; J_{CD} = 16,0; J_{AD} = 1,7; J_{AC}, J_{BD} < 0,5); CH_3 (0,83t); CH_3 (0,95t); CH_2CH_3 (3,78; 3,81; $^2J_{HH}$ = 10,5); CH_2CH_3 (3,93; 3,98; $^2J_{HH}$ = 10,5)

Notes. a) Compound (VI) was recovered as oil; (IIIc) was recrystallized from water; and (IIIa), IV), and (V) were recrystallized from benzene. b) Found/Calculated: Cl, %: 14.81/14.85 (IIb), 12.64/12.54 (IIc). c) Spectra of compounds (IIa) and (IIIc) were recorded in acetone-d_6; (VI) in C_6D_6; (IIb, c) in H_2O; and the others in $CDCl_3$. Carbon-13 (DEPT) NMR spectrum of (IIc): 13.3 (CH_3), 31.0 (SCH_2CHCN), 32.6 ($CH_2CHCOOH$), 39.4 ($CHCN$), 53.1 ($CHCOOH$), 64.5 (CH_2CH_3); (IIIa): 14.1 (CH_3); 31.65 and 31.77 (CH_2CH), 39.26 and 39.43 (CH), 39.9 (CH_2S), 63.52 and 63.63 (OCH_2). d) Compound (IIIa) was formed simultaneously (see Experimental). e) IR spectrum (CCl_4, ν, cm^{-1}): 3440, 3310 (NH_2), 2268 C≡N), 1750 (C=O), 1600 (C=C); 1600 (δ_{NH_2}). Mass spectrum, m/z: (relative intensity, %): 284(70), M^+; 238(65), 158(100).

the structure of which was determined unambiguously with PMR, IR, and mass spectra. Similar cyclization (the Thorpe reaction [5]) is well known for dinitriles of the type $RX(CH_2CH_2CN)_2$ (X = N, P, As) but we have probably described the synthesis of derivatives of the thiacyclohexene series for the first time. It is of interest to note that very strong bases (alkali metal alcoholates or amides) are usually required for such cyclization but, as a rule, not in catalytic amounts but in equimolar amounts [5]. Such a difference was probably due to the significantly greater CH acidity of the cyanopropionic acid derivatives, in which the methine proton was activated not only by a nitrile group, but by an ester group.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded on a Bruker WP-200-SY spectrometer for solutions in $CDCl_3$, C_6D_6, or acetone-d_6. The IR spectra were recorded on a UR-20 spectrometer, and the mass spectra were recorded on a DS-60 instrument. The yields and characteristics of compounds (II)-(VI) described below are in Table 1.

Ethyl 3-(Carboxymethylthio)-2-cyanopropionate (IIa). To a solution of 2 g (22 mmoles) of thioglycolic acid in 20 ml of acetone with stirring for 1.5 h was added a solution of 2.66 g (21 mmoles) of ethyl cyanoacrylate in 20 ml of acetone, the whole was stirred for 2 h more, the solvent was driven off under vacuum, and the residue was stirred with cold hexane and filtered.

Ethyl 3-(2-Aminoethylthio)-2-cyanopropionate Hydrochloride (IIb). A solution of 0.6 g (4.75 mmoles) of ethyl cyanoacrylate in 20 ml of glacial acetic acid was added with stirring for 1.5 h to a solution of 0.56 g (5 mmoles) of cysteamine hydrochloride in 20 ml of glacial acetic acid. The whole was stirred for 2 h more, evaporated to half the volume, and poured into 60 ml of absolute ether. The precipitated crystals were filtered, washed with absolute ether, and dried.

Ethyl 3-(β-Amino-β-carboxyethylthio)-2-cyanopropionate Hydrochloride (IIc). This compound was obtained, similarly to the compound described above, from cysteine hydrochloride and ethyl cyanoacrylate.

3,3'-(Ethylenedithio)bis(2-cyanopropionic) Acid (IIIc) and Its Esters (IIIa) and (IIIb). To a solution of 0.95 g (10 mmoles) of ethanedithiol in 15 ml of a solvent [acetone in the case of (IIIa) and benzene in the case of (IIIb) and (IIIc)] was added with stirring 20 mmoles of α-cyanoacrylic acid or its ester in 15 ml of the solvent, the whole was stirred for 3 h more, the solvent was evaporated under vacuum, and the residue was recrystallized.

Ethyl 3-(2-Mercaptoethylthio)-2-cyanopropionate (IV). To a solution of 4.5 g (48 mmoles) of ethanedithiol in 15 ml of absolute benzene was added with stirring for 1.5 h 3 g (24 mmoles) of ethyl α-cyanoacrylate in 15 ml of absolute benzene. The whole was stirred for 2 h more, and the solvent and the unreacted dithiol were driven off under vacuum. The pasty residue was stirred with absolute ether, and the precipitated crystals of the bis adduct (IIIa) (3 g) were filtered. The filtrate was evaporated, and the residue was dried under vacuum at 50-60°C for removal of residues of the starting dithiol.

Diethyl 3,3'-Thiobis(2-cyanopropionate) (V). At 20°C, 50 ml of absolute benzene was saturated with hydrogen sulfide, and 5 g (40 mmoles) of ethyl α-cyanoacrylate and then two drops of Et_3N were added to this solution. The whole was stirred for 3 h more, the solvent was driven off under vacuum, and the residue was recrystallized from a small amount of benzene.

4-Amino-5-cyano-3,5-bis(ethoxycarbonyl)thiacyclohex-3-ene (VI). To a solution of 1.4 g (5 mmoles) of (V) in 50 ml of benzene was added one drop of Et_3N. After 2 h, the solvent was driven off, the residue was purified by passage through a column with silica gel (λ 100/160 μ), and the eluent was $CHCl_3$.

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