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THIOL ESTERS IN ORGANIC SYNTHESIS. XI. A FACILE APPROACH TO β-HYDROXYPROPIONITRILES AND ACRYLONITRILES. CYANOTHIOLACETATE AS MASKED β-HYDROXYPROPIONITRILE CARBANION[1,2]

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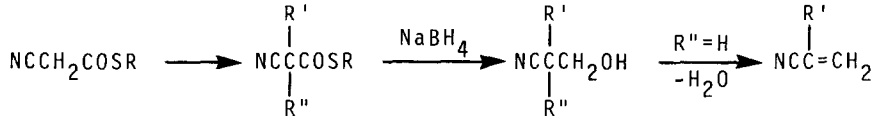
Summary: The preparation of β-hydroxypropionitriles and acrylonitriles is facilitated by the use of cyanothiolacetate as a formal equivalent of β-hydroxypropionitrile carbanion.

The ease of reduction of thiol ester group with sodium borohydride[3,4] suggests a number of interesting possibilities for its use as a latent hydroxymethyl unit in synthesis, especially when such a unit with or without protection can not be directly involved in a desired transformation. In this communication, we wish to report a general approach to the synthesis of β-hydroxypropionitriles and acrylonitriles (Scheme 1), which is greatly facilitated due to the ability of the thiol ester group present in the starting material to serve both as an activating group for the carbon-carbon bond formation and a convenient source of hydroxymethyl moiety.

Scheme 1



Cyanothiolacetates which are available directly from cyanoacetic acid[5] undergo dialkylation readily with a variety of alkyl halides (Table 1). Treatment of benzyl cyanothiolacetate (1) with 2.2 equiv. each of benzyl bromide and sodium hydride in 1,2-dimethoxyethane at room temperature for 20 hr gave dibenzyl derivative 2 in 89% yield. Similar alkylation of t-butyl cyanothiolacetate (3) with n-butyl iodide and allyl bromide gave products 4 and 5 respectively. Ring formation can be induced using a suitable alkyl dihalide as shown by the reaction of 3 with 1,5-diiodopentane (1.2 equiv.) which gave rise to a 77% yield of compound 6. On exposure to sodium borohydride (4 mol. equiv.) at room temperature using anhydrous isopropanol (for 2) or ethanol (for 4-6) as a solvent,

Table 1. Direct Alkylation of Cyanothiolacetates

Cyanothiolacetate	Reagents (equiv.)	Time[a] hr	Product NCCR'R"COSR	Yield %
$NCCH_2COSCH_2Ph$ 1	$PhCH_2Br$(2.2);NaH(2.2)	20	2 R=R'=R"=CH_2Ph	89
$NCCH_2COSC(CH_3)_3$ 3	n-BuI(2.5);NaH(2.5)	18	4 R=t-Bu;R'=R"=n-Bu	67
	CH_2=$CHCH_2Br$(2.5);NaH(2.5)	3	5 R=t-Bu;R'=R"=CH_2CH=CH_2	70
	$I(CH_2)_5I$(1.2);NaH(2.2)	17	6 R=t-Bu;R',R"=$(CH_2)_5$	77
	i-PrBr(1);t-BuOLi(1)	15[b]	11 R=t-Bu;R'=H;R"=i-Pr	80[e]
	n-BuCl(1);t-BuOLi(1)	36[b,c]	12 R=t-Bu;R'=H;R"=n-Bu	92[e]
	$CH_3(CH_2)_7Br$(1);t-BuOLi(1)	40[b,d]	13 R=t-Bu;R'=H;R"=n-octyl	61[e]
19	$PhCH_2Br$(1);NaH(1)	9	29 R=t-Bu;R'=i-Bu;R"=CH_2Ph	85
20	EtI(1);NaH(1)	22	30 R=t-Bu;R'=CH_2CH=CHPh;R"=Et	70

[a]Unless otherwise specified, all reactions were performed in DME at ambient temperature. [b]Performed in THF in the presence of 1 equiv. of HMPA. [c]Run at refluxing temperature. [d]Run at -5°C. [e]Based on consumed starting material.

Table 2. Selective Reduction of Cyanothiolacetates to β-Hydroxypropionitriles

Substrate	Time[a] hr	Product NCCRR'CH_2OH	Yield %	Substrate	Time[a] hr	Product NCCRR'CH_2OH	Yield %
2	24[b]	7 R=R'=CH_2Ph	96	17	0.5[c]	25 R=H;R'=cyclohexyl	98
4	19	8 R=R'=n-Bu	90	22	0.25[c]	26 R=H;R'=i-Bu	84
5	11	9 R=R'=CH_2CH=CH_2	80	23	1[c]	27 R=H;R'=CH_2CH=CHPh	78
6	18	10 R,R'=$(CH_2)_5$	94	24	1[c]	28 R=H;R'=s-octyl	95
11	15	14 R=H;R'=i-Pr	91	29	13	31 R=i-Bu;R'=CH_2Ph	90
12	20	15 R=H;R'=n-Bu	98	30	19	32 R=CH_2CH=CHPh;R'=Et	90
13	1	16 R=H;R'=n-octyl	99				

[a]Unless otherwise specified, all reactions were performed in ethanol at ambient temperature using 4 mol. equiv. of sodium borohydride. [b]Performed in isopropanol. [c]Run at 0°C.

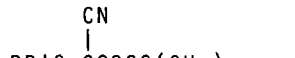
cyanothiolesters 2 and 4-6 were smoothly reduced to give the corresponding β-hydroxypropionitrile derivatives 7-10 (Table 2). In all cases, the reduction was found to be completely selective and the product was isolated in high yield.

Two procedures were examined for the monoalkylation of cyanothiolacetates. Direct alkylation requires carefully controlled conditions in order to suppress the highly competitive dialkylation process. The best results were obtained when 3 was used as the starting material with tetrahydrofuran as a solvent in the presence of 1 equiv. each of hexamethylphosphoramide, lithium t-butoxide, and an alkyl bromide or chloride and when the reaction was stopped on appearance of dialkylation product (ca. 60% completion). Under these conditions, the reaction of 3 and isopropyl bromide at room temperature for 15 hr gave 52% yield of the desired product 11 along with 4% yield of the dialkylation product and 35% recovery of the starting material. Similar results were obtained for the alkylation of 3 with n-butyl chloride and n-octyl bromide giving 12 and 13 respectively (Table 1). Sodium borohydride reduction of 11, 12 and 13 in ethanol resulted in the formation of the corresponding hydroxy nitriles 14-16 in nearly quantitative yields (Table 2).

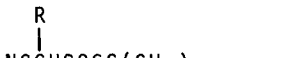
The second and the preferred method for monoalkylation involves a Knoevenagle-type condensation[6] of cyanothiolacetate 3 and a carbonyl compound followed by the selective reduction of the resulting carbon-carbon double bond. Thus, treatment of 3 with cyclohexanone and 1,4-diazabicyclo[2.2.2]octane (1.5 equiv. each) in tetrahydrofuran at room temperature for 20 hr afforded unsaturated cyanothiolacetate 17 (87% yield) which underwent 1,4-reduction on exposure to 1 mol. equiv. of sodium borohydride in ethanol at 0°C for 45 min to give the saturated compound 18 in 97% yield. This procedure affecting the overall monoalkylation is apparently general. Three additional compounds 19-21 were readily prepared in comparable yields from 3 and appropriate carbonyl compounds *via* the intermediacy of 22-24 respectively. For the preparation of β-hydroxypropionitriles, the condensation products could be conveniently reduced to the alcohol level using an excess of sodium borohydride in ethanol (Table 2). For example, when unsaturated thiolester 17 was treated with 4 mol. equiv. of the reagent at 0°C for 30 min, hydroxy nitrile 25 was formed in 98% yield. The reduction of 22-24 was shown to be equally facile leading directly to the formation of hydroxy nitriles 26-28.

To demonstrate the applicability of the method to the synthesis of β-hydroxypropionitriles possessing two nonidentical substituents at the α-carbon, we have also investigated the alkylation of cyanothiolacetates 19 and 20 with benzyl bromide and ethyl iodide. As expected the alkylation reactions proceeded readily at room temperature in 1,2-dimethoxyethane using sodium hydride as base (Table 1). Sodium borohydride reduction of the products 29 and 30 gave hydroxy nitriles 31 and 32 respectively (Table 2).

Two methods were successfully explored for the dehydration of monosubstituted β-hydroxypropionitriles. Indirectly, mesylation of n-octyl derivative 16 (methanesulfonyl chloride and triethylamine in chloroform; 6 hr at room temperature) followed by elimination (1,8-diazabicyclo[5.4.0]undec-7-ene in benzene; 4 hr at 80°C) gave a 94% yield of acrylonitrile 33. The same transformation could also be directly effected in 85% yield using dicyclohexylcarbodiimide (1.5 equiv.) and cuprous chloride (trace)[7] in refluxing ether for 24 hr. By the latter procedure, the following dehydration reactions were also carried out: 25→34 (80% yield), 27→35 (69% yield) and 28→36 (100% yield).



17	R,R'=$(CH_2)_5$
22	R=H; R'=i-Pr
23	R=H; R'=CH=CHPh
24	R=Me; R'=n-hexyl



18	R=cyclohexyl
19	R=i-Bu
20	R=CH_2CH=CHPh
21	R=s-octyl

33	R=n-octyl
34	R=cyclohexyl
35	R=CH_2CH=CHPh
36	R=s-octyl

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References and Notes

1. This paper is dedicated to Professor Gilbert Stork on the occasion of his 60th birthday.
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