

S-CYANOMETHYL DITHIOCARBAMATE, SELECTIVE ALKYLATION
AND KETONE SYNTHESIS IN AQUEOUS MEDIUM

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Recently, several methods are available for ketone synthesis using organo-sulfur compounds via their sulfur-stabilized carbanions.¹⁾ In most cases, however, the experimental procedure requires very strictly anhydrous conditions due to the employment of strong bases such as *n*-BuLi for the generation of carbanions. On the other hand, stable carbanions derived from active methylene compounds are easily prepared in aq. alkali.²⁾ However, alkylation of such stable carbanions often requires more elevated reaction temperatures and frequently yields a mixture of mono- and di-alkylated products. Moreover, it is generally difficult to eliminate the protecting groups for the generation of ketones in the final stage after alkylation.

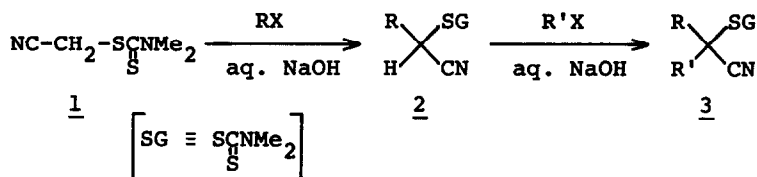
Considering the above problems in mind, we have investigated the possibility of new reagents for ketone synthesis which meet the following requirements:

- 1) Alkylation in aqueous medium
- 2) Selective alkylation (Mono- and di-alkylation)
- 3) Facile elimination of protecting groups by aq. alkali or *N*-bromosuccinimide (NBS) instead of metal salts such as Hg²⁺ or Cu²⁺ 1)

We wish to report here the utility of *N,N*-dimethyldithiocarbamoyl acetonitrile (1)³⁾ as a new reagent for ketone synthesis.

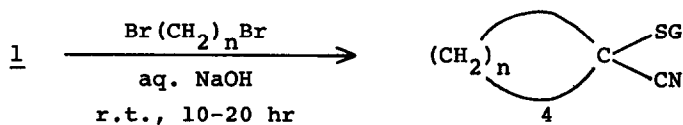
(a) Alkylation procedures;

Treatment of α -cyanodithioester (1) with alkyl halides (1.0 to 1.5 equivalents) in the presence of catalytic amount of $n\text{-Bu}_4\text{N}^+\text{I}^-$ in 50% aq. NaOH at room temperature for 3-6 hr gave monoalkylated products (2) in high yields. Dialkylated products (3) were obtained in high yields by stirring for 10-40 hr under the same conditions (Table 1).

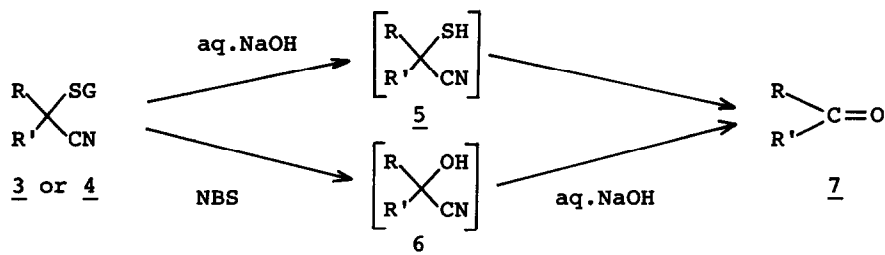


These results clearly demonstrate the reaction-time controlled selectivity in the alkylation of 1. It is presumably due to the combination of cyano and dithioester group that offers suitable stability and reactivity of the carbanion derived from 1, towards alkylation.

Similarly, dialkylated cyclic products (4) were obtained using $1,\omega$ -dibromoalkanes in high yields (Table 2).

(b) Elimination procedures;

Elimination of protecting groups (cyano and dithiocarbamoyl group) were easily performed by treatment of 3 with NaOH (15 equivalents) in refluxing 75% aq. ethanol for 20 hr to give the corresponding ketones (7) in good yields (Table 1)⁴. Isolation of an intermediate, α -mercaptionitrile (5) was successfully carried out by using lesser amounts of NaOH (4 to 8 equivalents)⁵.



As far as we know in ketone syntheses using organosulfur compounds, this is a first example of the effective elimination of protecting groups by aq. alkali.

In addition, on treatment of 3 or 4 with NBS or NCS for 1 hr at room temperature in 40% aq. acetonitrile followed by aq. NaOH for 30 min, the corresponding ketones were obtained in good yields (Table 1 and 2). Isolation of the expected cyanohydrin intermediates (6) was not attempted.

Table 1. Alkylation and Hydrolysis⁶⁾


RX	<u>2</u> Yield (%)	<u>3</u>		Yield (%)	<u>7</u> Yield (%)		
		R	R'X		NBS	NCS	NaOH
CH ₃ I	82	CH ₃	Amyl-Br	94	88		
EtI	91	CH ₃	Hexyl-Br	96	73		
 Cl	86	Et	Amyl-Br	87	70	55	50
Amyl-Br	90	Et	Hexyl-Br	88	71	70	60
PhCH ₂ Br	88	CH ₃	PhCH ₂ Br	91			

Table 2. Dialkylated cyclic compounds (4)⁶⁾

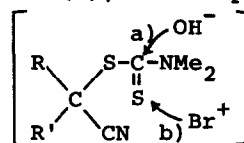
n	<u>2</u> ^{a)}	<u>3</u>	<u>4</u> ^{b)}	<u>5</u>	<u>6</u> ^{c)}
Yield (%)	none	98	87	~100	none
Mp (°C)	—	102-5	71-2	123-5	—

a) The structure of this product was not confirmed.

b) Cyclopentanone was obtained in 65% yield by NBS method.

c) 1,8-Bis(N,N-dimethyldithiocarbamoyl)-1,8-dicyanoctane and 1-(N,N-dimethyldithiocarbamoyl)-1-cyano-7-bromoheptane were obtained in 18% and 56% yields, respectively.

In contrast to the simple sulfides (RSCH₂R'), these characteristics of 1 are clearly caused by the introduction of the dithioester group [-S-C(=S)-] which is subjected to both (a), facile nucleophilic attack (OH⁻), and (b), electrophilic attack (Br⁺), in the first stage of the hydrolysis.



The present method has potential synthetic utilities in the following respects;

- 1) The starting material, α -cyanodithioester (1) is readily accessible.
- 2) The high selectivity for mono- and di-alkylation are particularly advantageous for the syntheses of unsymmetrical ketones by introduction of different alkyl groups stepwise.
- 3) Facile elimination of protecting groups by aq. alkali or NBS⁷⁾ is performed. Further studies of the applications of α -cyanodithioester are in progress.

References and Footnotes

- 1) D. Seebach, *Synthesis*, 1, 17 (1969); T. Mukaiyama, K. Narasaka, and M. Furusato, *J. Amer. Chem. Soc.*, 94, 8641 (1972) and references cited therein.
- 2) E.V. Dehmlow, *Angew. Chem. internat. Edit.*, 13, 170 (1974)
- 3) Compound 1 was quantitatively obtained from chloroacetonitrile and sodium N,N-dimethyldithiocarbamate at room temperature in methanol. Mp 73-74°C (EtOH), NMR (CDCl₃) δ 4.23(s, CH₂), 3.26, 3.58(2s, NCH₃)ppm.
- 4) Undesirable side reactions, such as, aldol condensation, were not observed.
- 5) R=Ethyl, R'=Amyl, IR; ν_{SH} 2580, $\nu_{C\equiv N}$ 2250 cm⁻¹
- 6) The yields given are for isolated products and the purification is carried out by means of recrystallization or column chromatography. All compounds obtained here exhibited satisfactory spectral and physical properties. Ketones were identified by comparison of the physical properties with the authentic samples.
- 7) Phenylthioacetonitrile (PhSCH₂CN) has been alkylated in aq. alkali medium, [M. Makosza, E. Bialecka, and M. Ludwikow, *Tetrahedron Letters*, 1972, 2391]. However, the elimination of cyano and phenylthio group is limited only to the case of aryl substituted compounds [Ar(R)C(CN)SPh], [S.J. Selikson, and D.S. Watt, *Tetrahedron Letters*, 1974, 3029].