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SYNTHESIS WITH α-CYANOENAMINES. 2-DIETHYLAMINO-4-LITHIO-4-PHENYLTHIO-2-BUTENONITRILE AS A β-CARBOXYL VINYL ANION EQUIVALENT.

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Summary : The lithio derivative of 2-diethylamino-4-phenylthio-2-butenonitrile is a practical equivalent of the unknown β-carboxyl-vinyl anion, as shown by its facile alkylation with alkyl halides, aldehydes and α-enones, followed by hydrolysis,oxidation and elimination.

α-Cyanoenamines, which are readily available from tertiary amides by a one-pot procedure[1a], show many useful properties for organic synthesis[1,2]. Of particular interest was the observation that the lithio derivative of α-diethylamino-2-propenonitrile reacts with electrophiles exclusively at the γ carbon atom. This discovery, coupled with the facile hydrolysis of the modified α-cyanoenamines into carboxylic acids, provides a convenient method for three-carbon extensions at electrophilic carbon atoms.

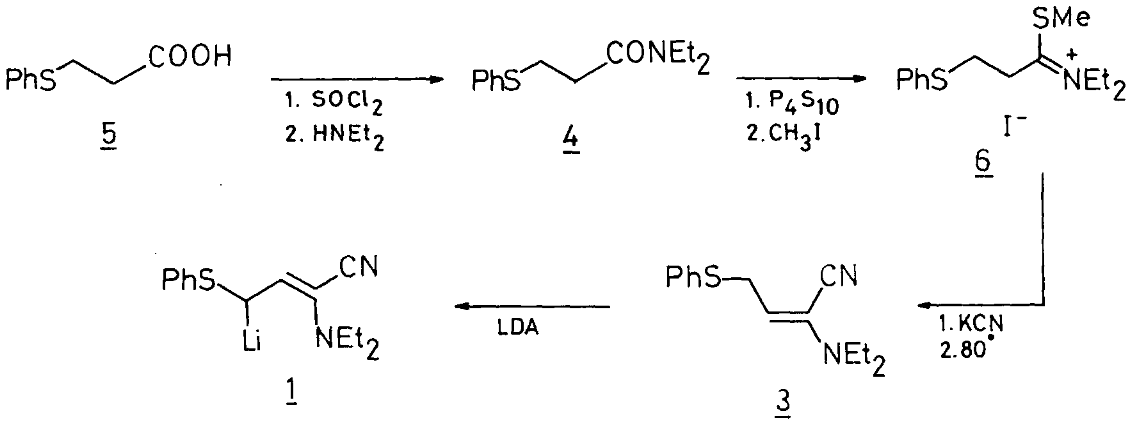
1

2

Scheme 1

We now wish to describe a new reagent 1 derived from α-cyanoenamines, which can function, inter alia, as the equivalent of a β-carboxyl vinyl anion unit 2. (Scheme 1)

The starting material for 1, 2-diethylamino-4-phenylthio-2-butenonitrile 3, was readily prepared by the sequence of reactions[3] shown in Scheme 2[4]. The amide 4 (oily, bp 140°C/10^{-2} Torr) which was prepared in 80-90% yield from the known[5] acid 5, was converted into the corresponding thioamide with P_4S_{10} (2.5 equiv.) in dimethoxyethane (50°C-60°C) in the presence of a catalytic amount of sodium bicarbonate. The methylation was directly effected on the crude thioamide with methyl iodide (3 equiv.) in acetonitrile at 40°C; the pure cristalline salt 6 was obtained in 60% yield. A solution of 6 in acetonitrile was treated with KCN (overnight, 20°C). Elimination of methanethiol occured on heating the filtered solution and distilling acetonitrile at atmospheric pressure. The pure α-cyanoenamine was obtained in 86% yield after flash chromatography[6] (silicagel, ether-pe-



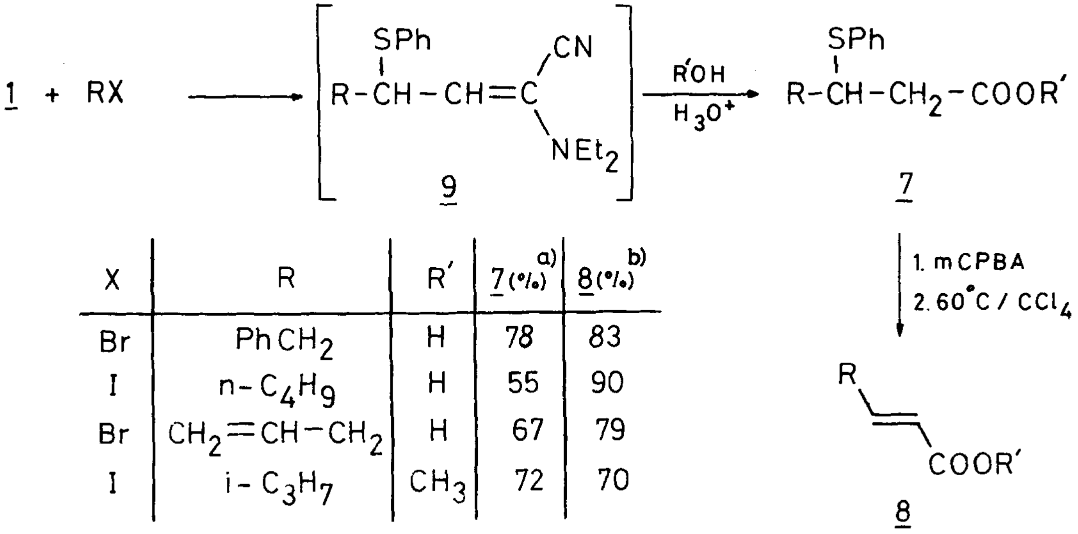
Scheme 2

troleum ether 5:95) : IR (neat) 2205 and 1600 cm^{-1}; NMR (CDCl$_3$, 60 MHz) : δ 7.1 (m, 5H), 4.87 (t,1H), 3.73 (d,2H), 3.03 (q,4H), 0.97 (t,6H). The E configuration was assigned on the basis of the chemical shift of the vinylic proton and by ^{13}C nmr[2c,7].

A typical procedure for the formation of 1 and its reaction with electrophilic reagents is as follows : a solution of 3 (∿ 3.1 mmoles) in 3.5 ml of THF is added to a solution of lithium diisopropylamide (prepared from 3.8 mmoles of diisopropylamine and 2.2 ml of a 1.6 M solution of *n*-BuLi in hexane) in 3.5 ml of THF at a rate which keeps the temperature between -60°C and -50°C. A solution of the electrophilic reagent (1.1 equiv. with respect to 3) in THF is added dropwise at -50°C. The temperature is raised to 0°C over a period of 2 hrs. After work-up (ether + 0.5 M NH$_4$Cl), the crude alkylated α-cyanoenamine is analysed by NMR. In most cases it was directly converted to the 3-phenylthio-substituted acid (3N HCl), or ester (3N HCl in CH$_3$OH). Oxidation and thermolysis according to the known procedure[8] gave the α,β unsaturated acids or esters.

The results with alkyl halides are shown in Scheme 3. The sequence proceeds well with various alkylating agents and gives good yields of acids or esters 7. These were readily converted into the α,β unsaturated acids or esters 8. A careful analysis of the crude alkylated α-cyanoenamines 9 shows *no evidence for α-alkylation*. Thus, alkylation of 1 exclusively occurs at the γ position. This behaviour contrasts with that of the anion of the corresponding ether (2-trimethylsilyloxy-4-methylthio-2-butenonitrile) which undergoes exclusively α-alkylation[9].

This behaviour of 1 toward electrophilic reagents is fairly general as shown in Scheme 4. The reaction with acetaldehyde also occurs at the γ-position (66%). It was found more convenient to acetylate the adduct before its methanolysis to 10. Compound 1 also added exclusively 1,4 across the conjugated systems of cyclopentenone and cyclohexenone; yields of 11 and 12 were 67% and 85%, respectively.

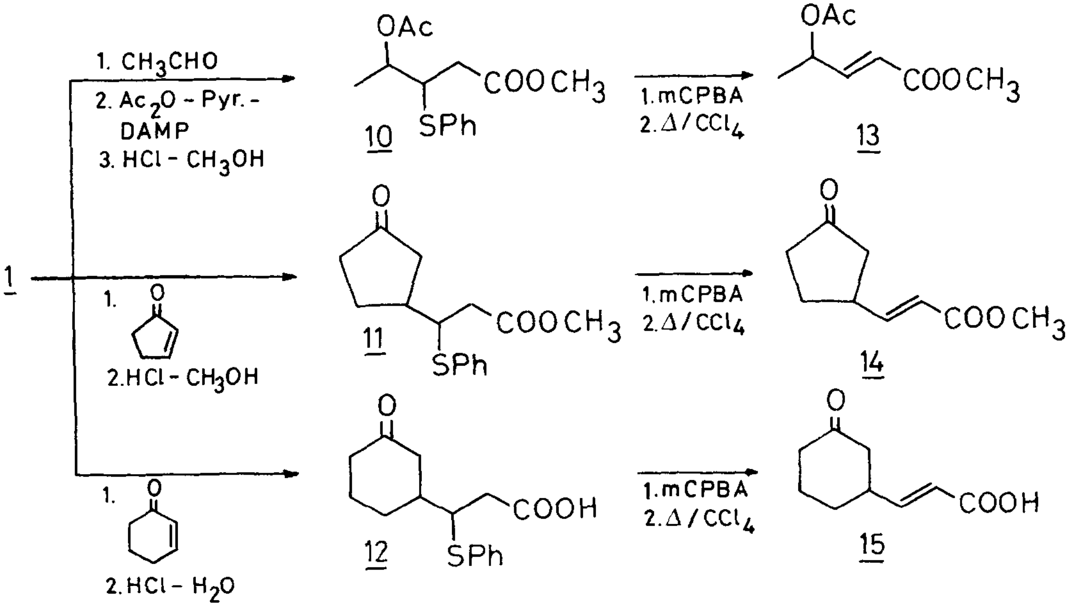


X	R	R′	$\underline{7}$ (%)[a)]	$\underline{8}$ (%)[b)]
Br	$PhCH_2$	H	78	83
I	$n-C_4H_9$	H	55	90
Br	$CH_2=CH-CH_2$	H	67	79
I	$i-C_3H_7$	CH_3	72	70

a) from 3
b) from 7

Scheme 3

The easy conversion of 10, 11, 12 into the conjugated esters 13 (80%), 14 (84%) and acids 15 (74%) completes the sequence and further illustrates the behaviour of 1 as a β-carboxyl-vinyl anion equivalent.[10]



Scheme 4

The ready availability of 1, its highly regioselective reactions and facile conversion into a β-acryl unit makes it a practical reagent for three-carbon chain extension. We are continuing to explore the synthetic potential of this useful synthon.

Acknowledgments

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