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SYNTHESIS AND REACTIVITY OF A STABLE PRECURSOR OF 2-CYANO-1,3-BUTADIENE [a)]

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Abstract - A new, productive synthesis of 3-cyano-2,5-dihydrothiophene-1,1-dioxide (3) is described. This substituted sulfolene serves as a stable precursor of 2-cyano-1,3-butadiene and can be used in the Diels-Alder reactions without isolation of the unstable diene.
The Diels-Alder reactions of 2-cyano-1,3-butadiene appear to proceed in high yield only with electron-deficient dienophiles, but ^{13}C NMR shows that in some cases the products are a mixture of regioisomeric cycloadducts.

The Diels-Alder reaction is undoubtedly one of the cornerstones of organic chemistry. In this contest, a remarkable number of 1,3-dienes have been prepared with suitably positioned electron-donor or -acceptor substituents, rendering the diene thermally reactive and allowing efficient regiocontrol in 4+2 cycloaddition.[1]

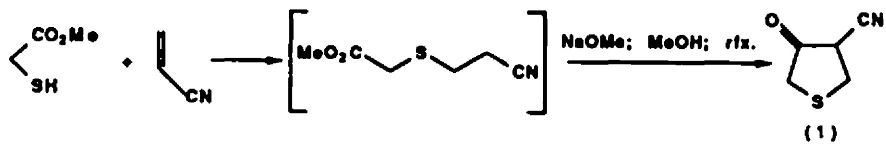
One general method of 1,3-diene synthesis which has been shown to be stereospecific is the cheletropic extrusion of sulphur dioxide from 2,5-dihydrothiophene-1,1-dioxides (3-sulfolenes), which occurs in a completely stereospecific disrotatory manner.[2]

Recent studies[3,4] from two different research groups on the successful alkylation and acylation of 2,5-dihydrothiophene-1,1-dioxides as well as on the possibility to add their α carbanions to carbonyl compounds including α,β-unsaturated ketones with high regioselectivity, have greatly expanded the applicability of this methodology.

Further, Takajama et al.[5] have reported that the thermolytic desulfonylation of 3-sulfolenes can be easily performed operating at lower temperature and with many different reaction conditions with respect to those generally employed in the vapour phase thermolysis.

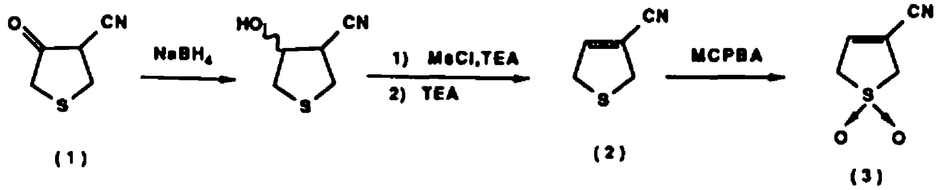
Continuing our researches on 4-cyano-3-oxo-tetrahydrothiophene (1), in this paper we wish to describe a new simple method to synthesize sulfone (3), a stable crystalline compound which can be considered the synthetic equivalent of 2-cyano-1,3-butadiene and its reactivity with some representative dienophiles.

The required 4-cyano-3-oxo-tetrahydrothiophene (1) was prepared in 50% overall yield through Dieckmann cyclization of the Michael adduct between acrylonitrile and methyl thioglycolate in the presence of sodium methoxide in refluxing methanol according to a procedure described in the patent literature.[6]



Sodium borohydride reduction of (1) followed by treatment of crude reduction mixture with methansulfonyl chloride in the presence of an excess of triethylamine afforded the 3-cyano-2,5-dihidrothiophene (2) in 72% overall yield.

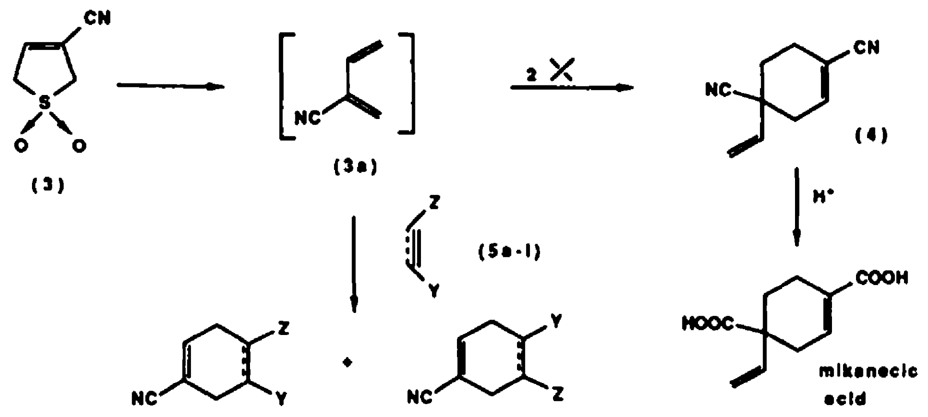
The 2,5-dihydrothiophene (2) was oxidized to the nicely crystalline sulfone (3) using m-chloroperbenzoic acid according to the McIntosh's procedure in 92% yield.



When 3-cyano-2,5-dihydrothiophene-1,1-dioxide (3) was heated in refluxing toluene, a moderately rapid evolution of sulphur dioxide occurred and in the absence of added dienophile a high yield of 1,4-dicyano-4-vinylcyclohexene (4) was formed. No traces of isomeric materials could be detected by thin layer chromatography or by proton or carbon NMR.

The dimer (4) showed the same melting point of the compound reported by Marvel et al.[7] as the main product isolated from dimerization of 2-cyano-1,3-butadiene, in turn obtained by cracking the acetate of vinyl ketone cyanohydrin.

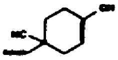
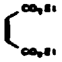
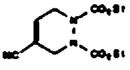
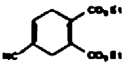
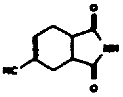
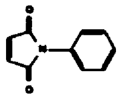
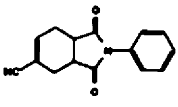
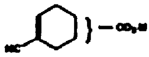
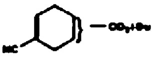
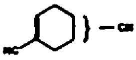
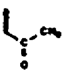
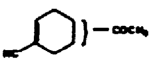
Acid hydrolysis of (4) produced a quantitative yield of mikanecic acid, a terpenoid dicarboxylic acid first isolated from the alkaline hydrolysis of the alkaloids Mikanoidine and Sarracine, which has been the object of several synthetic studies.[8]



When a dienophile (5a-l) was incorporated in the reaction mixture, TLC analysis revealed the formation of following compounds: a) only the dimer (4); b) the expected product; c) a mixture of dimer (4) and the expected product. In general, the obtained data showed that diene (3a) reacted well with electron-deficient dienophiles. (Table)

The regioselectivity of the Diels-Alder reactions of (3) seems to be variable. The cycloaddition reaction with dienophiles (5g-l) produced a mixture of 1,3 and 1,4 cycloadducts in approximately 3:1 ratio as indicated by ^{13}C NMR spectra. For instance (10) showed the following signals: δ 174.82, 174.46, 143.44, 144.87, 119.37, 112.27, 111.09, 52.27, 37.53, 38.07, 28.03, 28.52, 26.0, 25.24, 24.22 and 23.58, which are clearly due to the presence of two regioisomers. The same complexity was observed in the example (11), (12) and (13). The use of Lewis acid catalysts is being investigated as a possibility to improve the regioselectivity of this transformation.

TABLE Diels-Alder Reaction of 3-cyano-2,5-dihydrothiophene-1,1-dioxide (3)

dienophile	product (no.) m.p.	proton magnetic resonance	yield%
none	 (4) m.p.=[illegible] a	6.6(m,1); 3.3-4.0(m,3) 2.0-1.7(m,4)	60%
(5a) 	(4)		
(5b) 	(4)		
(5c) 	 (6) a	6.71(m,1); 4.60(m,2), 4.10-4.30(m,4) 3.08(m,2), 1.2-1.4(m,6)	96%
(5d) 	 (7) a a	6.6(m,1); 4.2(q,4) 3.2(d,4); 1.3(t,6)	60%
(5e) 	 (8) m.p.=186-189° a	11.1(b.s,1); 6.6 (m,1); 3.3-2.3(m,6)	98%
(5f) 	 (9) m.p.=132-137° a	7.6-7.2(m,5); 6.6 (m,1); 3.3-2.3(m,6)	90%
(5g) 	 (10) + (4) a a	6.6(m,1); 3.7(s,3) 2.7-1.7(m,7)	60%
(5h) 	 (11) a a	6.6(m,1); 2.6-1.6(m,7) 1.4(s,9)	63%
(5i) 	 (12) + (4) a a	6.6(m,1); 2.9(m,1) 2.7-2.2(m,4), 2.2-1.9(m,3)	60%
(5l) 	 (13) a a	6.7(m,1); 2.6-1.6(m,7) 2.2(s,3)	90%

eluting solvent mixture { aa = ether/light petroleum; a = ethyl acetate/light petroleum }

In summary, the results showed that the sulfone (3) could be considered a stable masked form of 2-cyano-1,3-butadiene and the reactivity of the latter answered the expectations of a synthetically valuable 1,3-diene.

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EXPERIMENTAL

Melting points and boiling points are uncorrected. Reaction courses and product mixture were routinely monitored by thin-layer chromatography (TLC) on silica gel precoated Merck plates. Infrared (IR) spectra were measured on a Perkin Elmer 297 spectrometer. Nuclear magnetic resonance (^1H NMR) spectra were obtained with a Brucker 200 spectrometer for solution in $CDCl_3$ and peak positions are given in parts per million downfield from tetramethylsilane as an internal standard. All drying operations were carried out with anhydrous magnesium sulphate.

3-cyano-2,5-dihydrothiophene (2). To an ice-cooled and stirred solution of 4-cyano-3-oxo-tetrahydrothiophene (1) (1.4 g, 0.01 mol) in EtOH 95% (50 ml), sodium borohydride (0.38 g, 0.01 mol) was added. The resulting suspension was stirred at room temperature for 2h. The reaction mixture was cooled at 0°C and carefully acidified with acetic acid to pH=6 and evaporated in vacuo. The residue was partitioned between water and ethyl acetate, the organic layer was washed with water (2x20 ml) and then, with brine (2x20 ml) and evaporated in vacuo. The crude alcohol was dissolved in methylene chloride (20 ml) and to the ice-cooled and stirred resulting solution triethyl amine (5.6 ml, 0.04 mol) followed by mesyl chloride (1.6 ml, 0.02 mol) were added dropwise. The reaction mixture was stirred at room temperature for 0.5h, diluted with methylene chloride (30 ml), the organic layer was washed with hydrochloric acid 5% (10 ml). The dried organic extracts were evaporated in vacuo and the oily residue distilled at b.p.: 80°C at 0.1 mm Hg to give (2) in 72% yield. IR (neat): 2200, 1640 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.0 (br s, 4H); 6.8 (s, 1H).

3-cyano-2,5-dihydrothiophene-1,1-dioxide (3). To an ice-cooled and stirred solution of 3-cyano-2,5-dihydrothiophene (2) (1.1 g, 0.01 mol) in methylene chloride (50 ml), m-chloroperbenzoic acid (3.5 g, 0.02 mol) was added in four portions and the solution stirred for 3h at 0°C and overnight at room temperature. The filtered solution was washed with saturated aqueous sodium carbonate (50 ml), dried, and concentrated to give a crude solid which was flash chromatographed eluting with ethyl acetate/petroleum ether 6:4 to give pure (3) (1.3 g, 92% yield) as a nicely crystalline solid melting to 151°C. IR (KBr): 2250, 1630, 1330, 1130 cm^{-1}; ^1H NMR ($DMSO-d_6$) δ 4.1 (m, 4H); 7.2 (m, 1H).

General procedure for the Diels-Alder reactions of (3). To a solution of 3-cyano-2,5-dihydrothiophene-1,1-dioxide (3) (0.14 g, 0.001 mol) in toluene (20 ml) was added the appropriate dienophile (0.01 mol) and the solution heated at reflux overnight. In the case of dienophiles (5c,e,f) only 0.001 mol were used.

The solvent and excess of dienophile were evaporated at reduced pressure and the residue flash chromatographed eluting with the solvent mixture indicated in the table.

Mikanecic Acid. A sample of 0.095 g (0.6 m.moli) of (4) was dissolved in 2 cc. of acetic acid and 5 cc. of concentrated hydrochloric acid. The resulting solution was heated under reflux for eight hours, then solvents were evaporated and the solid residue was dissolved in a saturated sodium hydrogen carbonate solution. The aqueous phase was first extracted with ethyl ether, then acidified with 5% hydrochloric acid solution and extracted with ethyl acetate. The organic extract was dried over anhydrous sodium sulfate and evaporated under reduced pressure to afford mikanecic acid as a solid which was recrystallized from ethyl ether/petroleum ether; yield: 0.118 g (65%); m.p.: 239-240°C. ^1H NMR ($DMSO-d_6$): δ 1.5-2.65[8] (m, 6H); 5.1 (m, 2H); 5.9 (m, 1H); 6.85 (m, 1H); 12.4 (s.b., 2H) as reported in the literature.

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