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REGIOSPECIFIC MONOALKYLATION OF 3-BUTENENITRILE

G. R. Kieczykowski, R. H. Schlessinger, and R. B. Sulsky
Department of Chemistry, University of Rochester
Rochester, New York 14627

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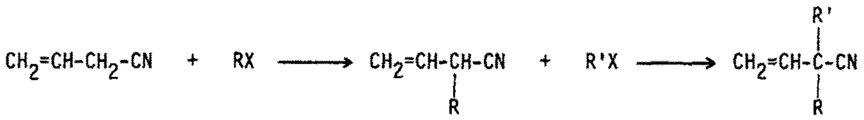
We have been interested in the construction of quaternary carbon atoms bearing both a vinyl substituent and a nitrile functionality. Compounds of this type are of potential utility as synthons in the synthesis of sesquiterpene systems. It occurred to us that a simple means of achieving this goal would be the alkylation of 3-butenenitrile (1). Two recent publications by Brenner and Bovete strongly suggest



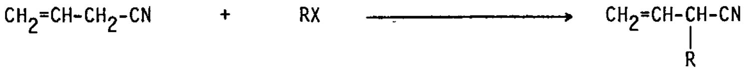
$$CH_2=CH-CH_2-CN \quad + \quad RX \longrightarrow CH_2=CH-\underset{R}{\underset{|}{C}}H-CN \quad + \quad R'X \longrightarrow CH_2=CH-\overset{R'}{\underset{R}{C}}-CN$$

1

that the lithium enolate derived from 1 undergoes only dialkylation under a variety of conditions (a result of rapid anion exchange).[1] These results were incompatible with our synthetic needs and prompted us to examine the possibility of realizing stepwise and regiospecific alkylation of 1. Herein, we report the results of this investigation.

Monoalkylation at the α-position of 1 can be realized in the following manner.

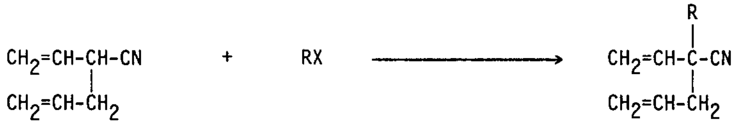
Nitrile 1 (1 equiv) was added neat at -78° to a solution of lithium diisopropylamide (1 equiv, 0.5 M in THF). The resulting faintly yellow solution was stirred for 25 min at -78° and then the alkylating agent (1.04 equiv) was added. Under these conditions, the products formed are represented by the structure 2 where R is the residue introduced by alkylation with the following halides: methyl iodide (yield 75%, reaction time 25 min), allyl bromide (98%, 30 min), propargyl bromide (90%, 30 min), 1-bromo-3-chloro-2-butene (97%, 40 min), benzyl bromide (95%, 4 hrs)[2], *iso*-propyl iodide (72%, 40 min)[3], *n*-butyl iodide (90%, 1 hr) , and ethyl bromoacetate (95%, 35 min).[4]



$$CH_2{=}CH{-}CH_2{-}CN \quad + \quad RX \longrightarrow CH_2{=}CH{-}\underset{\displaystyle R}{\underset{|}{C}}H{-}CN$$

1 2

A second alkylation reaction leading to nitriles with a quaternary α-carbon atom also has been carried out. The nitriles 3 and 4 have been used for these alkylations. In the case of 3, the same experimental conditions already described for the alkylation of 1 were employed.[5] Nitrile 3 gave rise to products represented by the formula 5 utilizing the following halides: methyl iodide (yield 86%, reaction time 40 min), allyl bromide (94%, 50 min), 1-bromo-3-chloro-2-butene (97%, 1 hr), benzyl bromide (97%, 45 min), *iso*-propyl iodide (95%, 3.5 hrs), *n*-butyl bromide (83%, 4.2 hrs), and ethyl bromoacetate (95%, 40 min).



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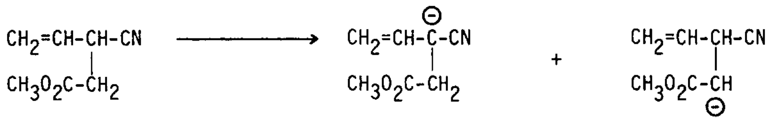
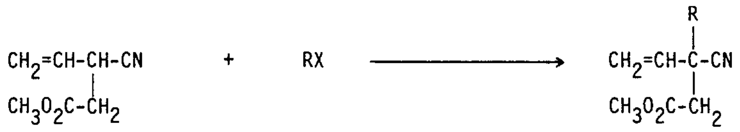
Treatment of the nitrile 4 with lithium diisopropylamide gave a mixture of anions 6 and 7.[6] When lithium hexamethyldisilazane was employed as the base however, only anion 6 was generated.



4 6 7

Thus, nitrile 4 (1 equiv, neat) on addition at -78° to a solution of lithium hexamethyldisilazane (1 equiv, 0.5 M in THF) gave the faintly yellow anion 6 after stirring for 40 min at -78°. Alkylation of 6 gave rise to products represented by the structure 8 using the following halides: methyl iodide (yield 86%, reaction time 40 min), allyl bromide (98%, 1 hr), 1-bromo-3-chloro-2-butene (92%, 1.3 hrs), benzyl bromide (97%, 30 min), *n*-butyl iodide (90%, 1 hr), and ethyl bromoacetate (97%, 1 hr).



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1. a) S. Brenner and M. Bovete, *Tetrahedrom Letts.*, 1377 (1974), b) S. Brenner and M. Bovete, *Tetrahedron*, 31, 153 (1975). Monoalkylation reactions of saturated nitrile systems have been reported by D. S. Watt, *Tetrahedron Letts.*, 707 (1974).
2. This reaction was carried out at 0.33 M.
3. This reaction was done in the presence of 1 equiv of hexamethylphosphoramide.
4. Satisfactory spectral and physical data were obtained for all new compounds. Reaction mixtures were quenched at -78° with saturated ammonium chloride.
5. In these experiments, the anion (red orange color) was allowed to form for 40 min at -78° before the alkylating agent was introduced.
6. The presence of this anion mixture was demonstrated by methylation experiments.