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A HOMOLOGOUS ESTER CLAISEN REARRANGEMENT VIA THE COPE REARRANGEMENT OF O-TRIMETHYLSILYLCYANOHYDRINS

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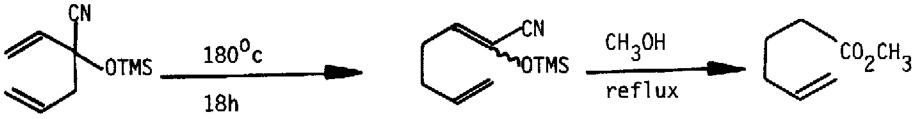
Summary: The Cope rearrangement of 1,5-dienyl trimethylsilylcyanohydrins to α-trimethylsilyoxy-α,β-unsaturated nitriles and their cleavage to methyl δ-hexenoates is discussed.

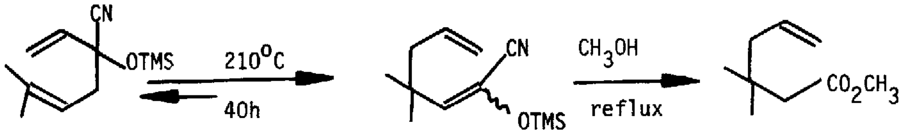
Existing Claisen rearrangement[1] methodology permits the generation of γ,δ-alkenoic acids[2] and esters[3]. Although it is possible to prepare δ,ε-alkenoates *via* homoester enolate allylation, the difficulty of alkylating at the more substituted carbon of an allylic electrophile cannot be realized by these methods[4]. We have been able to achieve this goal through the Cope rearrangement of O-trimethylsilylcyanohydrins which provide α-trimethylsilyloxy-α,β-unsaturated nitriles. Methanolysis of the rearrangement products directly provides the methyl esters.

The substrates <u>1a-6a</u> were prepared by alkylation of the lithium anion of the O-trimethylsilylcyanohydrin with the appropriate allylic bromide[5]. The O-trimethylsilylcyanohydrins were prepared from the aldehydes by the method of Evans[6,7].

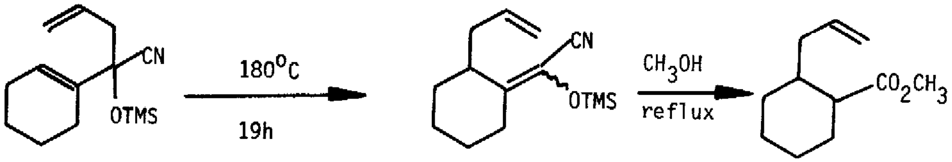
The rearrangements were conducted in NH_4OH washed evacuated ampoules at 180-210°C. In the case of the aromatic system <u>6a</u> the transformation could be conducted at an appreciably lower temperature[8]. The O-trimethylsilylcyanohydrins showed no nitrile infrared stretching frequency while their rearrangement products displayed absorption at 2220-2225 cm^{-1}. The rearrangement products are mixtures of double bond isomers and are formed under conditions of thermodynamic control since heating (<u>2a</u> and <u>4a</u>) does not change the equilibrium position. In <u>6b</u> the E-isomer predominated (2/1) as witnessed by the downfield shift (~0.3ppm) of the aromatic hydrogen proximate to the nitrile.



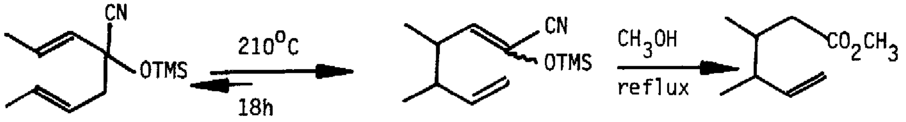
1a (79%)[a] 1b 1c (42%)[b]



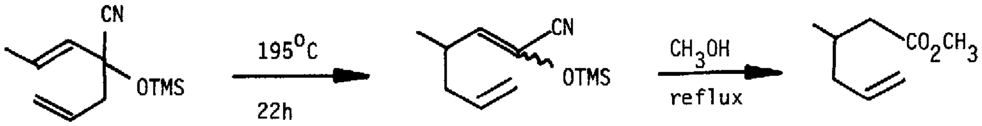
2a (48%)[a] 2b (94/6)[c] 2c (67%)[b]



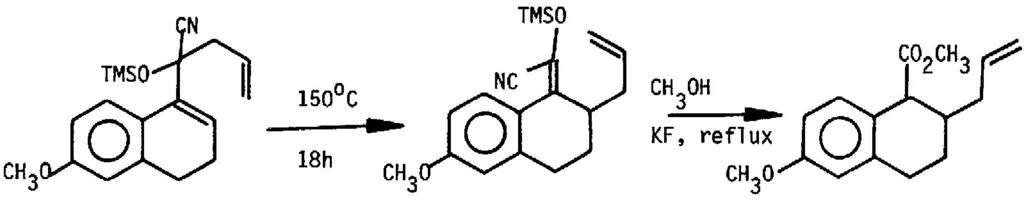
3a (93%)[a] 3b 3c (72%)[b]



4a 4b (82/18)[c] 4c (80%)[b]



5a 5b 5c (70%)[b]



6a (83%)[a] 6b 6c (73%)[b]

a) distilled yield, b) distilled yield from Xa, *c) equilibrium value*

Compounds 1a, 3a, 5a, and 6a, wherein the rearranging allyl residues are degenerate, showed no detectable (GC) amount of starting material. The conjugation of the double bond with the cyano and trimethylsilyloxy groups accounts for the favorable equilibrium. The conjugative effects, albeit cross-conjugated, are more significant than alkyl substituents in establishing the equilibrium position as is witnessed by the transformation 2a (6%) $\rightleftarrows$ 2b (94%)[9].

The rearrangement products are readily converted into their methyl esters in refluxing methanol and, in the case of 6b, more efficiently with KF/CH_3OH, ostensibly through the α-ketonitriles. Esters 3c and 6c are mixtures (partially separated, 50/50 OV-101, GC-MS) of diastereomers. Ester 4c reveals a single high field (270 MHz) doublet for the chain methyl groups. Although it would be expected that the *threo* isomer would be produced under conditions of kinetic control *via* a chair-like transition state[1], it has not been determined with certainty that the *erythro* isomer is not present.

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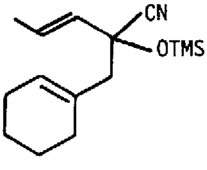
8. Yields of alkylated O-trimethylsilylcyanohydrins are of isolated materials. Pure 4a could only be obtained by preparative gas chromatography. The yields (isolated) of esters are based upon the cyanohydrins. All new compounds gave satisfactory combustion analyses and spectroscopic data.
9. Attempted rearrangement of i and ii gave mixtures of ester and ketone in addition to unidentified by-products. The ketones were present after the rearrangment step and arise from desilylation and loss of hydrogen cyanide. The presence of N,N-diethylaniline during the rearrangement to remove residual acid, or prior silylation of the ampoule did not appreciably alter the product distribution.



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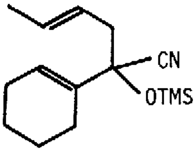

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