Tetrahedron Letters, Vol.26,No.14,pp 1691-1694,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain
©1985 Pergamon Press Ltd.

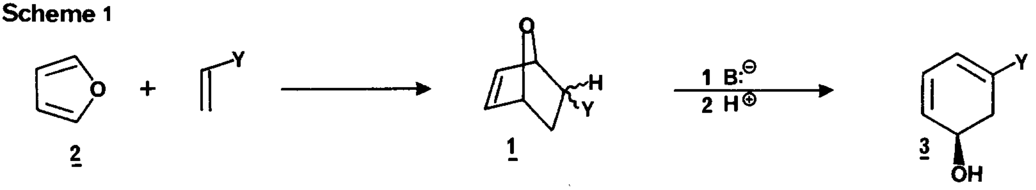
SYNTHESIS AND DIELS-ALDER REACTIONS OF 5,5-DICYANOCYCLOPENTADIENE: REGIOSELECTIVE SYNTHESIS OF 1,5-DISUBSTITUTED-1,3-CYCLOHEXADIENES

Gary I. Dmitrienko*, Marc E. Savard, Richard W. Friesen and Mibbo S. Thandi
Guelph-Waterloo Centre for Graduate Work in Chemistry, Waterloo Campus,
Department of Chemistry, University of Waterloo, Waterloo, Ontario, Canada N2L 3G1

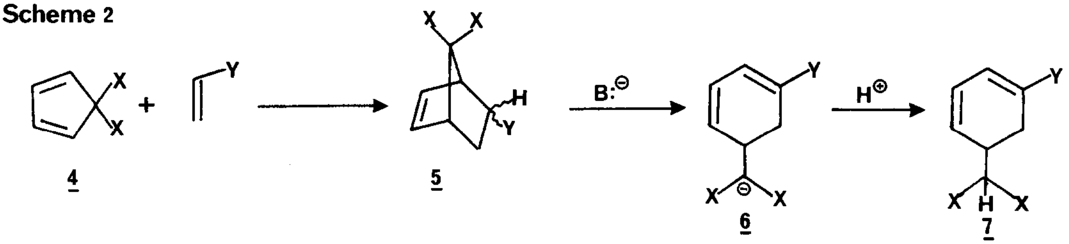
Abstract: 5,5-Dicyanocyclopentadiene, readily prepared in three steps from commercially available cis-1,4-dichloro-2-butene, undergoes Diels-Alder reactions with a number of dienophiles to give 5-substituted 7,7-dicyanobicyclo[2.2.1]hept-2-enes with high endo-selectivity. The adduct produced with methyl acrylate undergoes base-induced retro-Michael reactions to give 1-carbomethoxy-5-dicyanomethyl-1,3-cyclohexadiene.

The use of the Diels-Alder reaction for the regio- and stereochemically controlled synthesis of six-membered ring systems has served as the basis for the design of a large number of efficient syntheses of natural products[1]. Ortho and para-substituted cyclohexenes and cyclohexadienes can be constructed in a predictable fashion employing Diels-Alder reactions but meta-substituted cyclohexyl compounds are less readily available using this methodology. Recently, reports have appeared from several laboratories concerning a strategy which allows for the construction of certain meta-substituted cyclohexyl systems **3** via base induced ring opening reactions (retro-Michael reactions) of 7-oxabicyclo[2.2.1]heptenes **1** derived from furans **2** via Diels-Alder cycloaddition reactions.[2] The success of such approaches in the synthesis of important carbocyclic natural products[3] prompts us to report, in preliminary form, our related studies aimed at the efficient synthesis of meta-substituted cyclohexadienyl systems **7** via base-induced retro-Michael reactions of bicyclo[2.2.1]hept-2-enes **5** derivable from Diels-Alder reactions of a suitable cyclopentadiene **4**.

Scheme 1

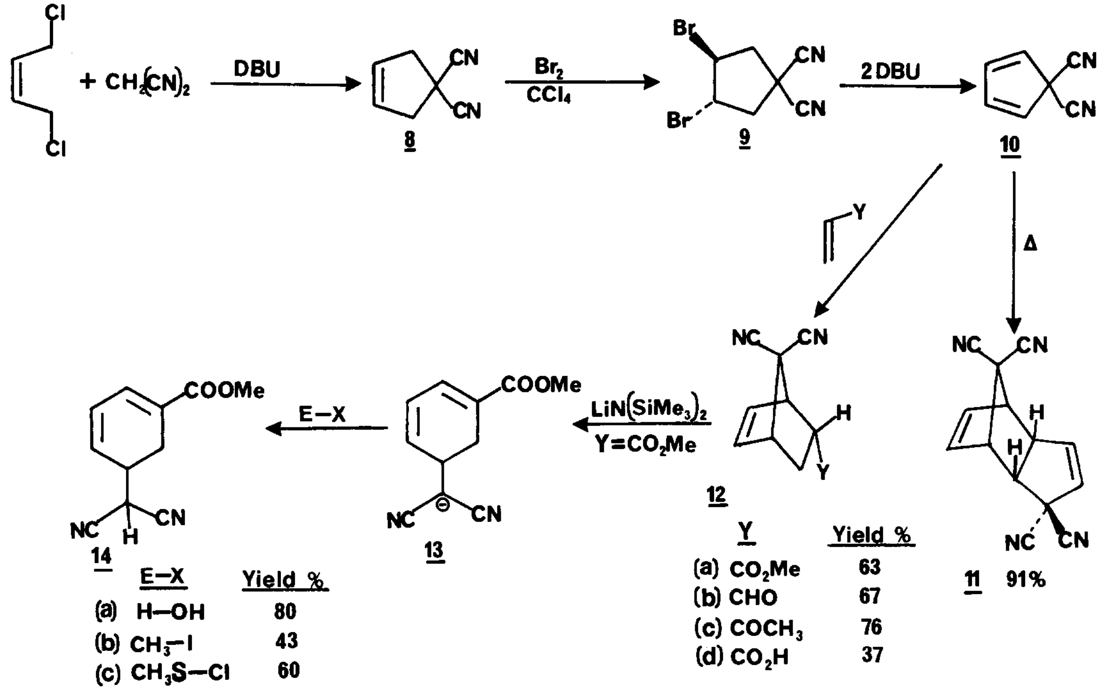


Scheme 2



In order that such an approach be successful, it was necessary that the substituents, X, be capable of stabilizing the negative charge of the anion **6**. It was decided that cyano substituents might be appropriate in this regard and, as a result, our first efforts in this area were aimed at an efficient synthesis of the previously unknown 5,5-dicyanocyclopentadiene **4** (X = CN).[4] 4,4-dicyanocyclopentene **8**, prepared as described by Oediger[5] and coworkers was reacted with molecular bromine to yield the crystalline dibromide **9** in 95% yield. Reaction of **9** with two equivalents of DBU in refluxing THF in the absence of any added dienophile gave a dimer of 5,5-dicyanocyclopentadiene **10** (91% yield) identified as the endo-Diels-Alder adduct **11** by detailed ^{1}H NMR analysis ($J_{1,2}$ = 4.2 Hz). The diene **10** could also be generated at low temperature (0°) in methylene chloride and, after removal of solvent *in vacuo* in the cold, characterized by its mass spectrum (m/e 116) and its ^{1}H NMR spectrum (AA'BB' system).[6] The adducts **12 a-c** were obtained by reacting the diene generated in this way with an excess (25 equivalents) of the appropriate dienophile at room temperature in an inert atmosphere for 24 h. The acid **12d** was obtained by hydrolysis of the crude adduct obtained by reaction of the diene **10** with acryloyl chloride. In each case only the endo adduct was observed.

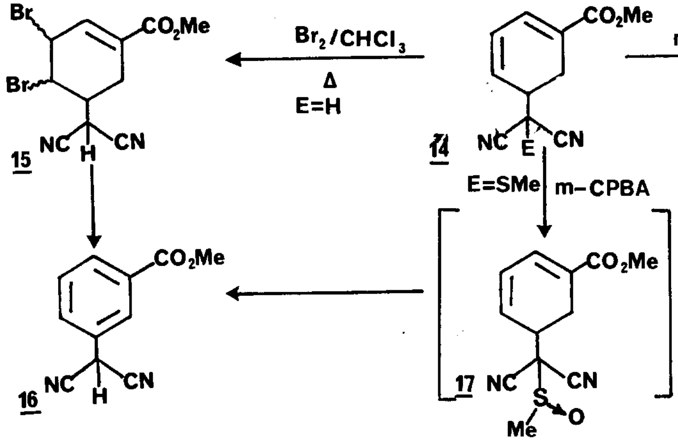
Scheme 3



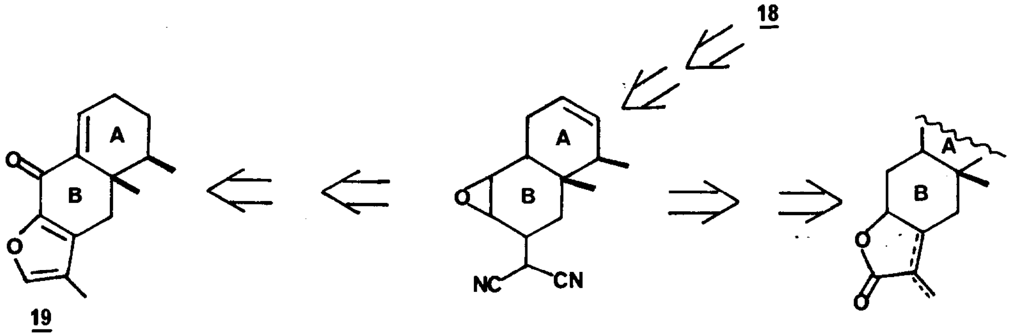
Ring opening of the ester **12a** was best effected by reaction with lithium hexamethyldisilazide in THF at -78°. Addition of 10% aqueous HCl followed by warming to room temperature yielded after workup and column chromatography the cyclohexadiene **14a**. Reaction of the anion with methyl iodide gave the diene **14b** and reaction with methane sulfenyl chloride gave **14c**.

Given the high degree of regio and stereoselectivity possible in chemical transformations of the dienes such as **3**, [2,3] it seems highly likely that selective synthetically useful transforma-

Scheme 4



Scheme 5



tions of the dienes **14** should also be available. Preliminary experiments indicate that the diene-**14a** can be functionalized regioselectively. Bromination gives a mixture of stereoisomeric dibromides **15** which could be dehydrobrominated to give **16**, a relatively rare example of a meta-substituted arylmalononitrile.[7] It was also possible to generate **16** by treatment of the sulfide **14c** with meta-chloroperbenzoic acid presumably via the sulfoxide **17**. Epoxidation of **14a** proceeds regio and stereoselectively to give the epoxide **18**. The utility of this synthetic approach to meta-substituted cyclohexyl systems in the total synthesis of carbocyclic natural products is currently being explored.

Among the potential synthetic applications of cyclohexadienes such as **14** or cyclohexenes such as **18** is the possibility that they might serve as precursors to the B ring of eremophilane type sesquiterpenes **19** [8] with the A/B ring fusion being established through a Diels-Alder reaction of the 1,2-C = C bond with a suitable diene. In addition, **18** is appropriately substituted for construction of a ring B fused γ-lactone or furan found in a considerable number of sesquiterpenes of this class (see retro-synthetic analysis in Scheme **5**).

Acknowledgements: The authors would like to acknowledge support of this work by the Natural Sciences and Engineering Research Council of Canada.

References:

1. Desimoni, G.; Tacconi, G.; Barco, A.; Pollini, G. "Natural Products Synthesis Through Pericyclic Reactions"; American Chemical Society: Washington, **1983;** p. 119-164 and references cited therein.
2. Brion, F., Tetrahedron Lett. (1982), 5299; Keay, B.A.; Rajapaksa, D.; Rodrigo, R., Can. J. Chem., (1984), 62, 1093; Keay, B.A.; Rodrigo, R. Can. J. Chem. (1983), 61, 637.
3. Keay, B.A.; Rodrigo, R. Can. J. Chem. (1983), 61, 637; Campbell, M.M.; Kaye, A.D.; Sainsbury, M., Tetrahedron Lett. (1983), 4745; Rajapaksa, D.; Keay, B.A.; Rodrigo, R., Can. J. Chem. (1984), 62, 826.
4. Reaction of sodium cyanocyclopentadienide with cyanogen chloride has been reported to yield a mixture of (1,2-), (2,3-), (1,3-) and (1,4-) dicyanocyclopentadienes but none of **4** (X = CN). See Webster, G.W.; J. Am. Chem. Soc. (1966), 88, 3046. It is possible that **4** (X = CN) was produced in this reaction but dimerized to **10** which escaped detection because of very low solubility in the ether solvent employed. For an alternative explanation for the failure to observe **4** (X = CN) in this reaction see: Wudl, F.; Nalewajik, D.; Rotella, F.J. and Gebert, E., J. Am. Chem. Soc., (1981), 103, 5885.
5. Oediger, H.; Moller, F., Liebigs Ann. Chem. (1976), 348.
6. The dibromide **9** was prepared as a colourless analytically pure crystalline solid (m.p. 102-104°) in 95% yield by dropwise addition of a solution of molecular bromine (2.1 mL; 41.0 mmol) in dry methylene chloride (20 mL) to a solution of **8** [5] (4.82 g; 40.9 mmol) in methylene chloride (50 mL), stirring at room temperature for 30 minutes, washing with aqueous sodium bisulfite and water and removal of solvent in vacuo from the dried (Na_2SO_4) organic phase. Anal. Calc. for: $C_7H_4Br_2H_2$: C, 30.25; H, 2.17; Br, 57.52; N, 10.08. Found: C, 30.49; H, 2.10; Br, 57.53; N, 10.30. ^{13}C-NMR δ 116.93 (CN); 51.62 (C-Br); 46.86 (CH_2); 30.79 (C-CN). ^{1}H-NMR δ 4.68 (ddd, 2H, CHBr, J = 4.7, 1.6, 1.4 Hz); 3.64 (dd, 2H, CH_2, J = 15.4, 4.7 Hz); 3.11 (ddd, 2H, CH_2 J = 15.4, 1.4, 1.6 Hz).
   5,5-Dicyanocyclopentadiene **10** was prepared by adddition of DBU (2.15 mL; 14.4 mmol) to a solution of **9** (2.00 g; 7.2 mmol) in dry methylene chloride (100 mL), stirring for one hour, washing with 6% aqueous HCl and brine, and concentration of the dried (Na_2SO_4) organic phase in vacuo at ice bath temperature (failure to control the temperature in the evaporation yielded samples of **10** contaminated with the dimer **11**). mass spectrum m/z = 116 (Molecule ion for $C_7H_4N_2$). At 400 MHz, the ^{1}H NMR spectrum of **10** consisted of a symmetrical six line pattern with spacings of 1.22, 1.22, 1.47, 1.22 and 1.22 Hz centred at δ = 6.91 ppm with a mirror image six-line pattern centred at δ 6.52 ppm. The Diels-Alder adducts, **12**, were prepared in analytically pure form by dissolving **10** in the appropriate dienophile (25 equivalents), stirring at room temperature in a nitrogen atmosphere, removing the excess dienophile in vacuo and chromatography on silica gel with elution by 40% v/v ethyl acetate-hexane.
7. Davis, W.A.; Cava, M.P., J. Org. Chem., (1983), 48, 2774.
8. Pinder, A.R., Fortschr. Chem. Org. Naturst. (1977), 34, 81-186.

(Received in USA 1 November 1984)