(1975); (b) J. F. J. Engbersen, Ph.D. Thesis, University of Groningen, 1976.
(13) W. Karzijn and J. B. F. N. Engberts, to be published.
(14) In the NMR spectrum of **1** ($CDCl_3$) the ketene methylene absorption is found at δ 3.13, consistent with polarization of the double bond due to resonance interaction with both oxygen atoms. Attempts to study hydrogen bonding interaction between the C-1 carbon and hydrogen bond donors like phenol in CCl_4 failed because of rapid reaction of the ketene acetal to yield the corresponding orthoester.
(15) R. R. Krug, W. G. Hunter, and R. A. Grieger, *J. Phys. Chem.*, **80**, 2335, 2341 (1976).
(16) Cation–cation interactions in aqueous solutions of *n*-Bu_4NBr have been associated with mutual cooperative stabilization of the hydration spheres in the overlap region. Evidence for this effect has been found in the increasing magnitude of the negative deviation of the apparent molal volume (Φ_v) of *n*-Bu_4NBr from the Debye–Hückel limiting law (i.e., $\delta\Phi_v/\delta c^{1/2}$ is negative) at concentrations above ~0.2 M: F. Franks and H. T. Smith, *Trans. Faraday Soc.*, **63**, 2586 (1967).
(17) W. Karzijn and J. B. F. N. Engberts, *Recl. Trav. Chim. Pays-Bas*, **96**, 95 (1977).
(18) H. L. Friedman and C. V. Krishnan, *Water: Compr. Treatise*, **3**, 52 (1973).
(19) J. E. Desnoyers, M. Arel, G. Perron, and C. Jolicoeur, *J. Phys. Chem.*, **73**, 3346 (1969).
(20) A. Kankaanperä and R. Aaltonen, *Suom. Kemistil. B*, **43**, 183 (1970).
(21) Vigorous stirring was found to be essential for rapid dissolution of the substrate and high reproducibility of the rate constants.

Alkylation of 1-Cyanocyclohexene[1]

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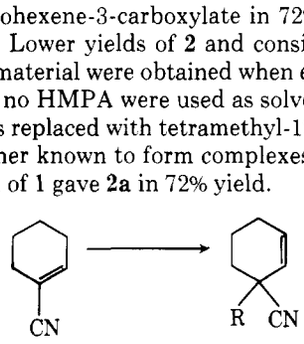
The alkylation of extended enolates derived from conjugated acids, esters, and ketones is an important part of synthetic methodology.[2] We report here some useful observations on the alkylation of a conjugated nitrile and some of its relatives.

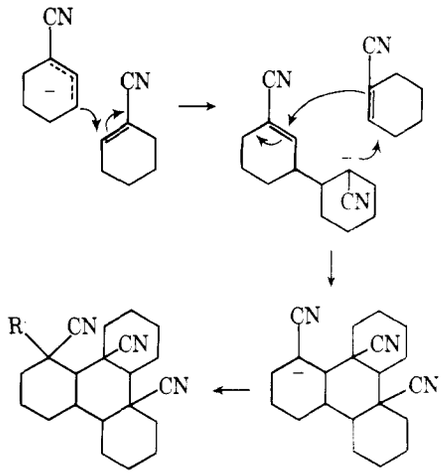
1-Cyanocyclohexene (**1**)[3] was converted into the corresponding anion by the action of LDA in THF containing HMPA, and the resulting anion was quenched with excess alkylating agent. Under these conditions products **2a–c** were obtained in yields of 78, 63, and 55%, respectively. Methyl cyclohexene-3-carboxylate[4] was converted into methyl 3-methylcyclohexene-3-carboxylate in 72% yield under these conditions. Lower yields of **2** and considerable amounts of polymeric material were obtained when ether, DME, or THF containing no HMPA were used as solvents; however, when HMPA was replaced with tetramethyl-12-crown-4 (in THF), a crown ether known to form complexes with lithium ions,[5] methylatin of **1** gave **2a** in 72% yield.



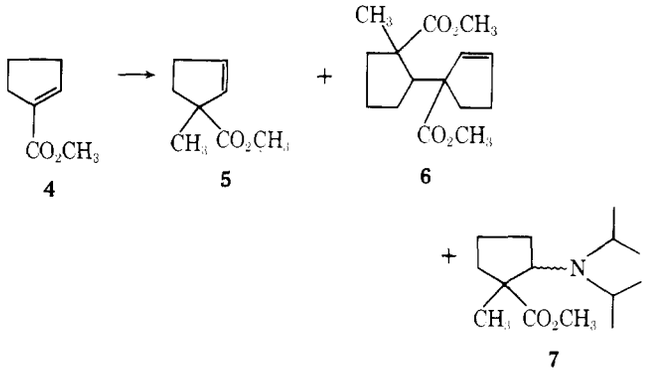
1 **2a**, R = CH_3
b, R = $CH(CH_3)_2$
c, R = $CH_2CH{=}C(CH_3)_2$

When DME containing TMEDA was used as solvent, methylation of **1** gave **2a** (45%) and a small amount of a mixture of trimers **3a,b**, the structures of which rest on spectral data (Experimental Section). Quenching of the anion (in DME–TMEDA) with water led to recovery of **1** (49%) and of pure trimer **3b.** These trimers are thought to arise as shown below.

Attempts to alkylate 1-cyanocylopentene[6] under the above conditions (THF–HMPA–LDA) were fruitless; thus, methylation of ester **4**[7] gave **5** (27%), **6**[8] (9%), and **7** (8%). On the other hand, the use of tritylllithium as the base for the methylation of **4**, or its acid as the dianion, gave **5** in 45–55% yield.



3a, R = CH_3
b, R = H



4 **5** **6** **7**

Experimental Section[8]

Typical Procedure for Alkylations. To a solution of 41.0 mmol of lithium diisopropylamide in 50 mL of THF (N_2) containing 47.0 mmol of HMPA at −78 °C was added 40.0 mmol of **1** in 10 mL of THF. After 10 min, excess methyl iodide was added (syringe). The resulting solution was stirred at −78 °C for 10 min, allowed to warm to 25 °C, and quenched with ice water. The product was extracted into hexane, washed with saturated NH_4Cl and 10% aqueous HCl, dried, and concentrated. The crude product was passed through a short column of alumina to remove HMPA and distilled to yield 3.78 g (78%) of **2a:** bp 88–91 °C (20 torr); IR (CCl_4) 2225 cm^{-1}; NMR (CCl_4) δ 6.02–5.38 (m, 2), 2.22–1.58 (m, 6), 1.40 (s, 3); mass spectrum (70 eV) *m/e* (rel intensity) 121 (26), 54 (100).

Anal. Calcd for $C_8H_{11}N$: C, 79.29; H, 9.15; N, 11.56. Found: C, 79.30; H, 9.29; N, 11.54.

Reaction of 1 in DME Containing TMEDA. The anion of **1** (47 mmol) in 50 mL of DME containing 50 mmol of TMEDA was generated as above. When the anion was quenched with water and worked up as above **1** (49%) and 50 mg of a solid were recovered. Recrystallization of the solid from toluene gave pure **3b:** mp 298–299 °C; IR (KBr) 2220 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 321 (100), 295 (48), 268 (30), 254 (29), 214 (42), 108 (43).

Anal. Calcd for $C_{21}H_{27}N_3$: C, 78.46; H, 8.47; N, 13.07. Found: C, 78.35; H, 8.43; N, 13.22.

When the anion above was quenched with methyl iodide, **2a** (45%), and 550 mg of **3a** containing 10% of **3b** (two spots on TLC, Alumina/benzene), mp 218–220 °C was obtained: IR (CCl_4) 2225 cm^{-1}; NMR (CCl_4) δ 1.65 (s, 3, CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 335 (100), 321 (10), 309 (46), 282 (40), 254 (11), 229 (83), 202 (43), 109 (44).

3-Isopropyl-3-cyanocyclohexene (2b) has bp (Kugelrohr) 100–120 °C (18 torr): IR (CCl_4) 2225 cm^{-1}; NMR (CCl_4) δ 6.10–5.40 (m, 2), 2.20–1.50 (m, 7), 1.10 (d, 3, CH_3, J = 6.5 Hz), 1.02 (d, 3, CH_3, J = 6.5 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 150 (1), 149 (4), 108 (11), 107 (100), 106 (15), 92 (6), 80 (22), 79 (11), 77 (7).

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Anal. Calcd for $C_{10}H_{15}N$: C, 80.48; H, 10.13; N, 9.38. Found: C, 80.48; H, 10.06; N, 9.26.

3-Prenyl-3-cyanocyclohexene (2c) has bp (Kugelrohr) 100–150 °C (5 torr): IR (CCl_4) 2225 cm^{-1}; NMR (CCl_4) δ 6.05–5.30 (m, 2), 5.40–5.05 (t, 1, J = 8 Hz with fine splitting from methyl groups), 2.40–2.10 (br d, 2, $RCH_2CH{=}C(CH_3)_2$, J = 8 Hz), 2.20–1.50 (m, 12, broad singlets centered at 1.80 and 1.67 for two methyl groups); mass spectrum (70 eV) m/e (rel intensity) 175 (9), 108 (7), 107 (75), 106 (9), 80 (11), 79 (9), 69 (100), 41 (45).

Anal. Calcd for $C_{12}H_{17}N$: C, 82.23; H, 9.78; N, 7.99. Found: C, 82.09; H, 9.70; N, 7.95.

Methyl 3-methylcyclohexene-3-carboxylate has bp 90–92 °C (32 torr): IR (CCl_4) 1733 cm^{-1}; NMR (CCl_4) δ 5.65–5.50 (m, 2), 3.60 (s, 3, OCH_3), 2.30–1.30 (m, 6), 1.20 (s, 3, CH_3); mass spectrum (70 eV) m/e (rel intensity) 154 (9.6), 121 (10), 94 (11), 93 (100), 92 (14).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.25; H, 9.25.

Methyl 3-Methylcyclopentene-3-carboxylate (5). To a solution prepared from 4.40 g (18 mmol) of triphenylmethane and 200 mg (25 mmol) of lithium hydryde in 45 mL of dry THF was added a solution of 2.00 g (16.8 mmol) of cyclopentene carboxylic acid in 10 mL of THF. The mixture was heated at reflux until evolution of H_2 ceased (20 min) then cooled in an ice–salt bath while 10 mL of 1.8 M n-butyllithium in hexane (18 mmol) was added (syringe). The resulting deep red mixture was heated at 35 °C for 1 h, cooled to 0 °C, quenched with 3 mL of methyl iodide, and stirred at 30 °C for 3 h. After the usual extraction the acidic product was taken up in ether and treated with an ethereal solution of diazomethane to give (after solvent removal) 1.64 g of oil from which 1.12 g (48%) of **5** was separated by preparative TLC (silica gel): IR (CCl_4) 1735 cm^{-1}; NMR (CCl_4) δ 5.80–5.50 (m, 2), 3.63 (s, 3, OCH_3), 2.52–2.20 (m, 3), 1.92–1.45 (m, 1), 1.27 (s, 3, CH_3); mass spectrum (70 eV) m/e (rel intensity) 140 (4.9), 81 (100).

Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.42; H, 8.86.

Dimeric product 6[8] (TLC isolation) has: IR (CCl_4) 1735, 1725 cm^{-1}; NMR (CCl_4) δ 5.75–5.20 (m, 2), 3.58 (s, 3, OCH_3), 3.53 (s, 3, OCH_3), 2.60–1.35 (m, 11), 1.20 (s, 3, CH_3); mass spectrum (70 eV) m/e 266 (1), 234 (6), 208 (8), 207 (52), 206 (23), 193 (8), 175 (17), 147 (17), 146 (100), 145 (13), 133 (15), 126 (52), 125 (17).

Methyl 1-methyl-2(*N,N*-diisopropyl)aminocyclopentane carboxylate (7) (TLC isolation) has: IR (CCl_4) 1725, 1714 cm^{-1}; NMR (CCl_4) δ 3.56 (s, 3, OCH_3), 3.20–2.60 (m, 3), 2.30–1.30 (m, 6), 1.18 (s, 3, CH_3), 0.96 (d, 12, J = 6.5 Hz); mass spectrum (70 eV) m/e (rel intensity) 242 (3.2), 241 (21), 226 (26), 198 (17), 141 (13), 140 (100), 98 (67).

Anal. Calcd for $C_{14}H_{27}O_2N$: C, 69.66; H, 11.28; N, 5.80. Found: C, 69.86; H, 11.11; N, 5.92.

Registry No.—**1**, 1855-63-6; 1 anion, 68317-67-9; **2a**, 68317-68-0; **2b**, 68317-69-1; **2c**, 68317-70-4; **3a**, 68317-71-5; **3b**, 68317-72-6; **5**, 68317-73-7; **6**, 68317-74-8; **7**, 68317-75-9; methyl 3-methylcyclohexene-3-carboxylate, 68317-76-0; cyclopentenecarboxylic acid, 1560-11-8; 1-methyl-2-cyclopentene carboxylic acid, 68317-77-1.

References and Notes

(1) We thank the National Science Foundation for financial support.
(2) (a) J. A. Marshall and G. M. Cohen, *J. Org. Chem.*, **36**, 877 (1971); (b) W. S. Johnson, M. B. Gravestock, R. J. Parry, R. F. Meyers, T. A. Bryson, and H. W. Miles, *J. Am. Chem. Soc.*, **93**, 4330 (1971); (c) J. L. Hermann, G. R. Kieczykowski, and R. H. Schlessinger, *Tetrahedron Lett.*, 2433 (1973); (d) M. W. Rathke and D. Sullivan, *ibid.*, 4249 (1972); (e) R. A. Lee and W. Reusch, *ibid.*, 969 (1969); (f) P. E. Pfeffer, L. S. Silbert, and E. Kinsel, *ibid.*, 1163 (1973); (g) P. E. Pfeffer and L. S. Silbert, *J. Org. Chem.*, **36**, 3290 (1971); (h) G. A. Koppel, *Tetrahedron Lett.*, 1507 (1972); (i) J. F. Bagli and H. Immer, *Can. J. Chem.*, **46**, 3115 (1968); (j) T. C. McMorris, R. Seshadri, and T. Arunachalam, *J. Org. Chem.*, **39**, 669 (1974); G. R. Kieczykowski, R. H. Schlessinger, and R. B. Sulsky, *Tetrahedron Lett.*, 4647 (1975).
(3) T. Holm, *Acta Chem. Scand.*, 1577 (1964).
(4) R. B. Wagner, *J. Am. Chem. Soc.*, **71**, 3214, 3216 (1949).
(5) We thank Dr. Richard Bartsch for suggesting this experiment. For a review of crown ether chemistry see C. H. Pederson and H. F. Frensdorff, *Angew. Chem., Int. Ed. Engl.*, **11**, 16 (1972).
(6) O. H. Wheeler and I. Lemar, *J. Am. Chem. Soc.*, **78**, 63 (1956).
(7) L. Piaux, *Ann. Chim. (Paris)*, **4**, 147, 215 (1935).
(8) An insufficient quantity of **6** was isolated for complete characterization by combustion analysis.
(9) NMR spectra were recorded with a Perkin-Elmer R-32 (90 MHz) spectrometer using Me_4Si as an internal standard. Mass spectra were recorded using a Hitachi RMU-6 mass spectrometer. Elemental analyses were determined by Bernhardt Microanalytisches Laboratorium, Elbach über Engelskirchen, West Germany.

Improved Synthesis of 3,4-Dihydroxyphenylpyruvic Acid[1]

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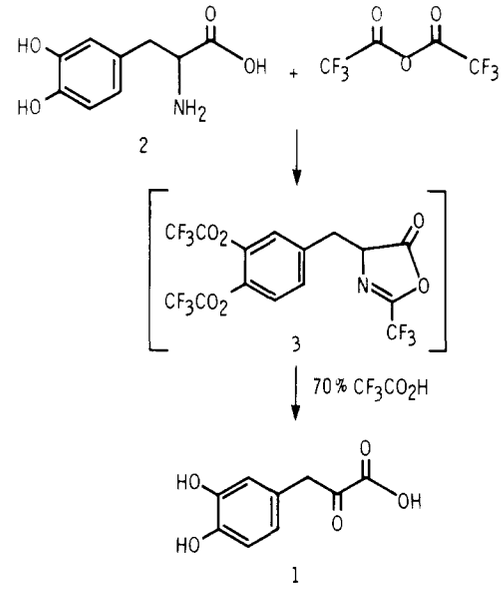
Several lines of research[2,3] in our laboratory prompted an investigation of a more facile synthesis of 3,4-dihydroxyphenylpyruvic acid (**1**). Since a previously reported synthetic procedure[4,5] proved to be unsatisfactory in our hands, we attempted to exploit Weygand's observation[6] that the hydrolysis of trifluoromethyloxazolones produced pyruvic acids. Another attractive feature of this approach is the fact that oxazolones are readily available from α-amino acids which in turn can be obtained commercially with various isotopic labels. Isotopically labeled phenylpyruvic acids are not commercially available.

We have found that hydrolysis of the putative trifluoromethyloxazolone intermediate (**3**) in 70% aqueous trifluoroacetic acid at room temperature produced **1** in 87% yield. The product (**1**) precipitated as it was formed and was isolated by filtration. This procedure avoids conditions known to be detrimental to the stability of **1**, i.e., exposure to base and oxygen, especially when it is in solution. Undistilled **3** contains incompletely reacted amino acid which eventually contaminates the product with the *N*-trifluoroacetyl derivative of **2** if the distillation step is omitted. An overall yield of 69% of **1**



from **2** was realized. The crystalline solid (**1**) is quite stable when stored at 4 °C but slowly decomposes at room temperature.

Experimental Section

Melting points were determined on a Fisher-Johns block. Mass spectra were obtained with an LKB 9000 mass spectrometer while NMR were recorded on a Varian Associates A-60 NMR spectrometer using tetramethylsilane as an internal standard.

3,4-Dihydroxyphenylpyruvic Acid (1). A slurry of L-3,4-dihydroxyphenylalanine (**2**) (5 g, 2.5 mmol) in trifluoroacetic anhydride (26.3 g, 12.5 mmol) was stirred until completely dissolved. After the solution was refluxed for 24 h (bath temperature 85 °C), trifluoroacetic acid was removed by distillation and the residue vacuum distilled on a short path apparatus (140 °C (3 mm)) to give a light yellow oil. The distillate was taken up in 70% aqueous trifluoroacetic acid and allowed to stand at room temperature for 24 h. The resulting slurry was cooled to 4 °C and filtered, washing twice with 10 mL of cold H_2O. The filtrate (2.8 g of **1**) could be recrystallized from water

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