pinacol transformation appears to involve formation of the aldol product B, intramolecular silyl migration[9] to give C, and finally rearrangement[10] of the antiperiplanar carbon–carbon bond to give dione **2**. The alternative pinacol-like rearrangement of intermediate B to give the bicyclo[2.2.1]heptane derivative D is apparently precluded due to steric/strain considerations.

The conversion of tricyclic dione **2**, prepared from bicyclic[2.2.2]octenone **3** in 40% overall yield, into quadrone **1** and examination of the scope of this tandem aldol–pinacol transformation are in progress.

Acknowledgment. We thank Professor Steven D. Burke for generously providing a sample of tricyclic dione.

Registry No. 2, 81740-63-8; **3**, 67316-12-5; **4**, 81740-64-9; **5**, 81740-65-0; **6**, 81740-66-1; **7**, 81740-67-2; **8**, 81740-68-3; 3-iodo-2-chloropropene, 39557-31-8.

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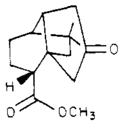
(8) Subsequent confirmation of this structural assignment was made by comparison (IR, ^{1}H NMR, ^{13}C NMR) of dione **2** with a sample prepared independently and generously provided by Professor S. Burke and by conversion of **2** into the epi ester ii prepared previously.[4a]



ii

(9) Jones, S. S.; Reese, C. B. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2762–2764.

(10) For a silyl oxide leaving group analogy, see Monti, S. A.; Larsen, S. D. *J. Am. Chem. Soc.* **1977**, *99*, 8015–8020.

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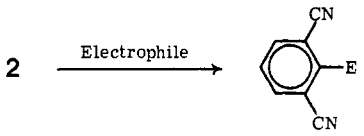
Directed Ortho Lithiation of Isophthalonitrile. New Methodology for the Synthesis of 1,2,3-Trisubstituted Benzenes

Summary: The lithiation of 1,3-dicyanobenzene with lithium diisopropylamide occurs in high yield, regiospecifically at the 2-position, to give aryllithium species stable at temperatures below −90 °C.

Sir: Directed ortho lithiations of benzenes with heteroatom-containing substituents have been extensively studied.[1,2] Cyano groups have been employed as activating groups to effect direct lithiation of thiophene,[3] selenophene,[3b] and dihydropyridines,[4] using a nonnucleophilic lithium dialkylamide as lithiating agent. Parham and Jones generated quenching products from 2-lithiobenzonitrile prepared from the halogen–metal exchange of 2-bromobenzonitrile and *n*-butyllithium at −78 °C.[5] The only reported benzonitrile to undergo directed ortho lithiation is 3-chlorobenzonitrile[2] in which a chelating effect of the chlorine can be invoked to explain the regiospecificity. The 2-lithio derivative was trapped in 30% yield with dimethyl disulfide. We report conditions for the efficient ortho lithiation of 1,3-dicyanobenzene (**1**), an example of ortho lithiation of a substituted benzene directed by a functional group lacking lone pairs of electrons which can plausibly be invoked in a stabilizing chelation of the lithium ion.

Table I. Reaction of 2 and 4 with Electrophiles



3 - 8

electrophile	product[a]	mp, °C	% yield[b]
I_2	**3**, E = I	208-209	79
$(CBrCl_2)_2$	**4**, E = Br	189-190 (lit. 190-190.5)[c]	81
C_2Cl_6	**5**, E = Cl[d]	154-156	77
PhSSPh	**6**, E = SPh	109-110	68
$(CH_3)_3SiCl$	**7**, E = $(CH_3)_3Si$	86-88	83
CH_3I	**8**, E = CH_3	132-134 (lit. 135-136)[e]	83[f]
PhCHO	**9**,[g]	162-163	71

[a] Satisfactory analytical data (±0.4% for C, H, N and, when appropriate, halogen or S) were reported for all new compounds listed in the table. Compounds **3**, **5**, **6**, and **7** gave AB_2 patterns and compound **9** gave an ABC pattern in the aromatic region of the ^{1}H NMR spectrum ($CDCl_3$, 220 MHz). [b] Isolated material, after purification. [c] Fendler, E. J.; Fendler, J. H.; Griffin, C. E.; Larsen, J. W. *J. Org. Chem.* **1970**, *35*, 287. [d] Turner, N. J.; Battershell, R. D. *Contrib. Boyce Thompson Inst.* **1970**, *24*, 203. No physical data were reported. [e] Lindsay, W. S.; Stokes, P.; Humber, L. G.; Boekelheide, V. *J. Am. Chem. Soc.* **1961**, *83*, 943. [f] This yield was obtained when a 10-fold excess of methyl iodide was added to **2**. [g] Isolated after the crude reaction mixture was warmed with dilute hydrochloric acid.

Although it is possible that chelation involving the π electrons of the cyano triple bond plays a role in this reaction, the π-electron density of the cyano function (in the Hückel approximation) is approximately 4 times greater at the more remote nitrogen than at the proximal carbon.[6]

The preparation of **2** by lithium–hydrogen exchange using lithium diisopropylamide (LDA) is complete within 3 min at −96 °C. The 220-MHz ^{1}H NMR spectrum of the crude product obtained by quenching the lithiation reaction mixture with CH_3OD reveals that 100% of **2** is formed.[8] When benzonitrile was subjected to the same reaction conditions, no 2-deuteriobenzonitrile was detected by ^{1}H NMR.[9]

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(1) See, for example: (a) Meyer, N.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 521. (b) Beak, P.; Brown, R. A. *J. Org. Chem.* **1979**, *44*, 4463. (c) Meyers, A. I.; Lutomski, K. *Ibid.* **1979**, *44*, 4465. (d) Watanabe, M.; Snieckus, V. *J. Am. Chem. Soc.* **1980**, *102*, 1457. (e) Figuly, G. D.; Martin, J. C. *J. Org. Chem.* **1980**, *45*, 3728.

(2) For a recent comprehensive review, see: Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1.

(3) (a) Gronowitz, S.; Eriksson, B. *Arkiv. Kemi* **1963**, *21*, 335 [*Chem. Abstr.* **1963**, *59*, 13918f]. (b) Dubus, P.; Decroix, B.; Morel, J.; Pastour, P. *Bull. Soc. Chim. Fr.* **1976**, 628.

(4) Schmidt, R. R.; Berger, G. *Chem. Ber.* **1976**, *109*, 2936.

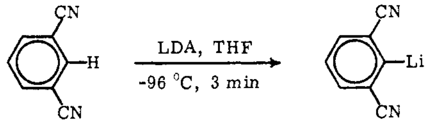
(5) Parham, W. E.; Jones, L. D. *J. Org. Chem.* **1976**, *41*, 1187.

(6) Such π-electron-based chelation could more plausibly be invoked for the recently reported reaction of phenylacetylene with *n*-butyllithium and potassium *tert*-butoxide, which was postulated to give ring potassiation (Hommes, H.; Verkruijsse, H. D.; Brandsma, L. *Tetrahedron Lett.* **1981**, 2495), or the reaction of diphenylacetylene with 2 mol of *n*-butyllithium, which gives addition to the triple bond followed by ortho lithiation of the phenyl ring adjacent to the added butyl group.[7] In both cases the π-electron density in the intermediate monolithio derivative, which is subject to ring metalation, is expected to be greater at the carbon nearer the ring which is lithiated.

(7) Mulvaney, J. E.; Gardlund, Z. G.; Gardlund, S. L. *J. Am. Chem. Soc.* **1963**, *85*, 3897.

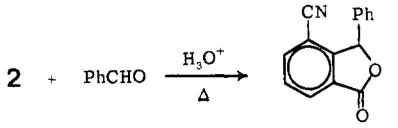
(8) ^{1}H NMR for 1 ($CDCl_3$, 220 MHz): δ 7.96 (s, 1), 7.90 (d, 2), 7.65 (t, 1).

0022-3263/82/1947-2681$01.25/0



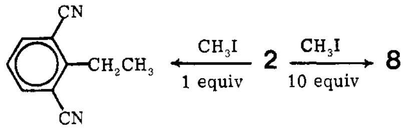
1 2

Reactions of 2 with electrophiles were carried out by a standard procedure[10] to give the expected products (Table I). Phthalide 9 was formed by heating the crude product from the reaction of 2 and benzaldehyde with dilute aqueous hydrochloric acid.

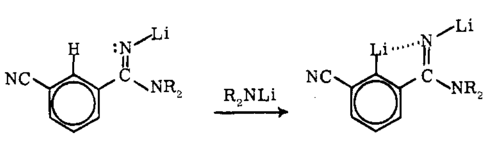


9

When 2 was treated with excess (10 equiv) methyl iodide, dicyanotoluene 8 was isolated (83%). However, when only 1 equiv of methyl iodide was added, the major product (0.33 mol/mol of 2) was 2,6-dicyano-1-ethylbenzene. We ascribe this to abstraction by 2 of the acidic benzylic proton of the initially formed 8, followed by alkylation of the benzylic anion by methyl iodide to form the ethyl compound.



Addition of an amide anion to the carbon of a nitrile function of 1 could give a species (10) whose imide nitrogen might be capable of stabilizing the lithiation product (11), and the transition state leading to it, by a chelation of lithium.[2] Since 2 equiv of the lithium amide is required to form 10, our observation that 1.05 equiv of lithium amide leads to 100% incorporation of deuterium into recovered 1 when the intermediate aryllithium species is quenched with CH_3OD rules out 11 as the structure of the aryllithium species which is deuterated. It is almost certainly 2. A base even more sterically hindered than LDA, lithium 2,2,3,6-tetramethylpiperidide, gives results similar to those seen for LDA, making nucleophilic attack at carbon seem unlikely.[11]



10 11

Earlier reported methods for the synthesis of 2-substituted 1,3-dicyanobenzenes include that of Mao and Boekelheide,[12] which involves the lithiation of the bis(*N,N*-dimethylhydrazone) of isophthalaldehyde. The conversion of 2-substituted isophthalic acids to the dinitriles has also been employed.[13] Another isophthalic acid equivalent, 1,3-bis(4,4-dimethyl-2-oxazolinyl)benzene, has also been successfully lithiated in the 2-position in high yield.[14] The lithiation of the relatively inexpensive dicyanobenzene provides a route to this class of compounds in fewer steps and generally with higher overall yields than the other methods.

Further work currently in progress focuses on the mechanistic implications and the synthetic potential of this reaction.

Acknowledgment. This research was supported in part by a grant from the National Cancer Institute (CA 13963). We are grateful for helpful discussions with Professors Peter Beak and Albert Meyers. Mass spectra were obtained from facilities provided under grants from the National Institutes of Health (CA 11388 and GM 16864). The University of Illinois Midwest NSF Regional NMR Facility (CHE 79-16100) provided NMR spectra.

Registry No. 1, 626-17-5; 2, 81725-15-7; 3, 81725-16-8; 4, 22433-90-5; 5, 28442-78-6; 6, 81725-17-9; 7, 81740-10-5; 8, 2317-22-8; 9, 81725-18-0; benzaldehyde, 100-52-7; 2,6-dicyano-1-ethylbenzene, 41052-95-3.

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(9) We have recently obtained evidence for efficient ortho lithiation of 1,2-dicyanobenzene and 1,4-dicyanobenzene under the same conditions described here for 1,3-dicyanobenzene. The second cyano substitutent in the 1,2- and 1,4 isomers clearly increases the kinetic acidity of these species relative to benzonitrile.

(10) In a typical experiment, lithium diisopropylamide (LDA) [25 mL of a 0.33 M tetrahydrofuran (THF) solution, 8.2 mmol] was added dropwise over 0.5 h to a stirred solution of 1 (1.0 g, 7.8 mmol) in THF (70 mL) at −96 °C under N_2. After 0.5 h, the appropriate electrophile (usually 1.05 equiv) was added and the reaction mixture was allowed to warm slowly to room temperature. Solvent was removed under reduced pressure. The crude product was extracted from a suspension in aqueous sodium chloride with dichloromethane to remove all salts. The desired product was purified by chromatography or recrystallization from dichloromethane–pentane. Later studies indicate that if the LDA solution is cooled in a −107 °C bath and the dicyanobenzene in the minimum amount of THF is added slowly to this solution, the temperature of the solution remains below −90 °C; a highly colored, insoluble material is avoided and yields are somewhat improved.

(11) We rule out a mechanism in which 10 and 11 are transient intermediates, with rate-determining lithiation of 10 to form 11 followed by rapid elimination of LDA to form 2, by the observed first-order dependence of the rate of lithiation on LDA concentration:

$$1 \xrightarrow{R_2NLi} 10 \xrightarrow[\text{rate determining}]{R_2NLi} 11 \longrightarrow 2 + R_2NLi$$

Pseudo-first-order rate constants for reactions carried out with a large excess of LDA are linearly related to LDA concentration over the range 0.0026–0.0104 M. A second-order rate constant (first order in both 1 and LDA) was calculated, $k_2 = 0.41$ M^{-1} s^{-1} at −98 °C. The reaction of Scheme II, which would show a second-order dependence on LDA concentration, is therefore ruled out.

(12) Mao, Y. L.; Boekelheide, V. *J. Org. Chem.* **1980**, *45*, 2746 used the directed ortho lithiation of the bis(*N,N*-dimethylhydrazone) of isophthaldehyde to prepare 2-substituted 1,3-dicyanobenzenes. While 2 could conceivably have served as an intermediate in these reactions via rapid elimination of dimethylamide anion, the reactions appear to have been carried out at room temperature and we find that 2 is unstable even at temperatures as low as −78 °C. It is therefore unlikely that 2 is in fact an intermediate in the reactions of Mao and Boekelheide.

(13) Wallenfels, K.; Witzler, F.; Friedrich, K. *Tetrahedron* **1967**, *23*, 1353.

(14) Harris, T. D.; Neuschwander, B.; Boekelheide, V. *J. Org. Chem.* **1978**, *43*, 727.

Synthesis of the Hexahydronaphthalene Moiety of (±)-Compactin (ML-236B)

Summary: An efficient synthesis of the hexahydronaphthalene moiety of compactin using an intramolecular Diels–Alder reaction with a vinylallene as the diene is described.

Sir: Compactin (1)[1] and ML-236B[2] are identical fungal