was purified chromatographically.[20] Simultaneous removal of the benzyl and cyclohexylidene groups was accomplished by hydrogenation of 6 (10% palladium on carbon, ambient temperature and pressure, 24 h) in 15:4:1 methanol–water–concentrated hydrochloric acid. After filtration, neutralization with Amberlite IR-45 (OH form), and removal of solvent, the residue was directly treated with 1:1 acetic anhydride–pyridine at room temperature. Standard processing (chromatographic purification) after 24 h afforded 47% of a single product, 2, mp 177–178 °C (needles, ethanol). Synthetic 2 was indistinguishable from 2 prepared from hikizimycin in terms of melting point (lit.[6] mp 180.5–181.5 °C; mixture melting point undepressed), specific rotation [synthetic 2, $[\alpha]^{22}_D$ +90° (c 0.58, $CHCl_3$); 2 from natural sources, $[\alpha]^{29}_D$ +85° (c 1.0, $CHCl_3$)[6]], thin-layer chromatographic data, and 400-MHz ^1H NMR data,[25] where spectra of 2 from synthesis and natural sources were superimposable.

Thus, the Wittig reaction produced exclusively the *Z* olefin and the cis hydroxylation (of the *E* olefin) produced only one of the two possible diastereoisomeric diols, presumably due to steric effects, whose configuration was demonstrated by conversion exclusively to methyl peracetyl-α-hikosaminide (2). The methodology demonstrated in this synthesis opens the way for the preparation of many highly complex long-chain carbohydrates.

Acknowledgment. We thank Dr. B. C. Das of the Institut de Chimie des Substances Naturelles, C.N.R.S., Gif-sur-Yvette, for a sample of methyl peracetyl-α-hikosaminide prepared from hikizimycin, and Dr. R. Nagarajan, Eli Lilly and Company, for a sample of hikosaminylcytosine, which we converted into 2. The 400-MHz ^1H NMR spectra were recorded by Dr. Michael Geckle of the University of Alabama in Birmingham, Comprehensive Cancer Center, supported by NCI Grant No. CA13148. We also appreciate some valuable discussions with Dr. S. R. Wu. K.D.B. received partial support from an Amoco Fellowship.

Registry No. 2, 50619-43-7; **3d**, 74844-33-0; **4a**, 29388-46-3; **4b**, 71756-39-3; **4c**, 74844-34-1; **4d**, 71756-41-7; **4e**, 74844-35-2; **4f**, 74844-36-3; **5a**, 74868-63-6; **5b**, 74868-64-7; **5c**, 74868-65-8; **5d**, 74868-66-9; **6**, 74854-29-8.

(25) Selected chemical shifts (δ) and coupling constants for 2 are as follows: H_1, 4.84 (d); H_4, 4.58 (dd); H_5, 3.83 (dd); H_7, 5.86 (dd); $J_{1,2}$ = 3.4 Hz; $J_{2,3}$ = 10.3 Hz; $J_{6,7}$ = 1.2 Hz; $J_{7,8}$ = 10.0 Hz.

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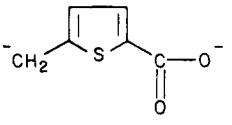
Dianions of Methylated Thiophene-2-carboxylic Acids: Their Formation and Reactivity

Summary: Methylated thiophene-2-carboxylic acids can be readily homologated by treatment with LDA (2 equiv) followed by the addition of carbon-containing electrophiles.

Sir: The use of the thiophene nucleus as a template for the construction of a wide variety of compounds (e.g., hydrocarbons, fatty acids, and amino acids) has been well documented.[1] The general utility of this procedure could be improved markedly if a simple method was available for the preparation of a variety of substituted thiophene derivatives. Recently, we examined the dilithiation of methylated thiophene-2-carboxylic acids and the reactivities of the resultant dianions toward several electrophiles. Our initial findings from studies using acids 1–4[2] are summarized in Table I.[3]

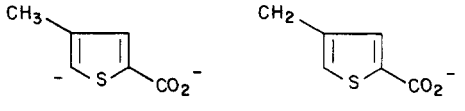
The reactions of 5-methylthiophene-2-carboxylic acid (entries 1–3) clearly support the intermediacy of dianion 6. The ease of generation of this dianion is attributable



6

to resonance stabilization. In contrast, when 2,5-dimethylthiophene was treated under more stringent conditions with *n*-BuLi–TMEDA, rather limited metalation was observed.[4] Direct homologation of acid 1 as shown here represents a route which is apparently superior to the classical Wynberg approach[5] for the synthesis of 2,5-disubstituted thiophenes.

In the case of 4-methylthiophene-2-carboxylic acid, the result recorded in entry 4 indicates that dianion 7 instead of 8 is the reactive intermediate. This result is not surprising, since in 7 the sulfur atom, owing to its polarizability,[6,7] presumably helps stabilize the adjacent negative charge, whereas in 8, significant inductive and resonance stabilization is lacking.



7 8

To our surprise, the reactions of 3-methylthiophene-2-carboxylic acid were more complex. The reaction of entry 5 gave the single ester 9,[8] whereas, that of entry 6 led to a mixture of products 11 and 12 (38:62). Azeotropic reflux of this mixture in toluene in the presence of a trace of PTSA gave a mixture of acid 13 and lactone 14. The identities of both 11 and 13 were confirmed by inde-

(1) For a comprehensive review, see Meyer, A. I. "Heterocycles in Organic Synthesis"; Wiley: New York, 1974.

(2) Acid 1 was purchased from Aldrich Chemical Co. Treatment of 3-methylthiophene in ether with *t*-BuLi at −70 °C followed by carbonation gave a mixture of 2 and 3 in a ratio of 88:12. Pure 2 was obtained after two recrystallizations from acetonitrile, mp 118–120 °C [lit. 116–117 °C (Goyte, V. N.; Tilak, D. B.; Gadekarand, K. N.; Sahasrabudhe, M. B. *Tetrahedron* **1967**, *23*, 2443)]. Acid 3 was prepared from 3-methylthiophene-2-carboxaldehyde (supplied by Aldrich) by Jones' oxidation. Compound 4, mp 169–170 °C [lit. 171–172 °C (Gatterman, L. *Justus Liebigs Ann. Chem.* **1888**, *244*, 29)] was synthesized from 3-methylthiophene by sequential treatment with *t*-BuLi and iodomethane in ether at −70 °C and then lithiation with *n*-BuLi in ether at room temperature followed by carbonation.

(3) A typical procedure, exemplified by the preparation of 5, is described in the supplementary material.

(4) Clarke, A. I.; McNamara, S.; Meth-Cohn, O. *Tetrahedron Lett.* **1974**, 2373.

(5) Wynberg, H.; Logothetis, A. *J. Am. Chem. Soc.* **1956**, *78*, 1958.

(6) Streitwieser, A., Jr.; Ewig, S. P. *J. Am. Chem. Soc.* **1975**, *97*, 190.

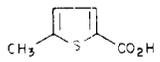
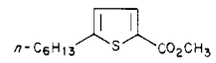
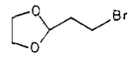
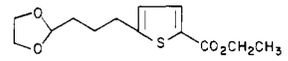
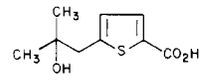
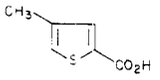
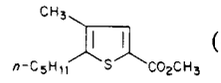
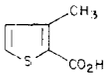
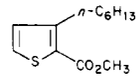
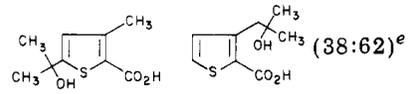
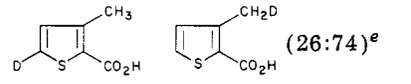
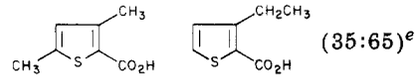
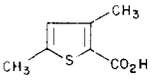
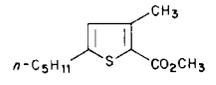
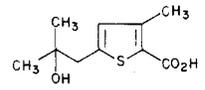
(7) Bernardi, F.; Csizmadia, J. G.; Mangini, A.; Schlegel, H. B.; Whangbo, M.-H.; Wolfe, S. *J. Am. Chem. Soc.* **1975**, *97*, 2209.

(8) The GC analysis (1% OV-210 on Chromosorb Q, 100 °C) of the predistillation material indicated the presence of <2% of ester 10.[9]

(9) The authentic sample of this product was conveniently provided from the reaction of entry 9.

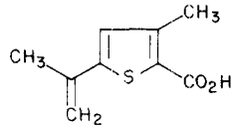
0022-3263/80/1945-4528$01.00/0

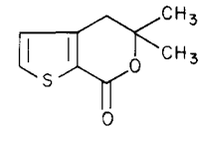
Table I. Reactions of Dilithiated Dianions[a] of Methylated Thiophene-2-carboxylic Acids with Electrophiles

entry	acid	electrophile	product (yield, %)[b]	bp or mp, °C
1	 1	n-$C_5H_{11}Br$	 (65)[c,d]	80-88 (0.05 mm)
2	1		 (69)[c,d] 5	142-147 (0.1 mm)
3	1	CH_3COCH_3	 (61)[f]	116-118
4	 2	n-$C_5H_{11}Br$	 (48)[c,d]	82-88 (0.05 mm)
5	 3	n-$C_5H_{11}Br$	 (66)[c,d] 9	80-90 (0.05 mm)
6	3	CH_3COCH_3	 (38:62)[e] 11 12	
7	3	D_2O	 (26:74)[e]	
8	3	CH_3I	 (35:65)[e]	
9	 4	n-C_4H_9Br	 (72)[c,d] 10	83-85 (0.05 mm)
10	4	CH_3COCH_3	 (60)[f]	119-120

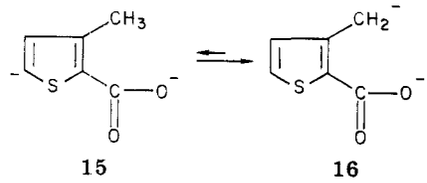
[a] LDA (2 equiv), THF, 0 °C, 1 h. [b] Isolated yield, not optimized. [c] The ester was obtained from the corresponding acid by esterification with CH_3I (or CH_2CH_3I)-K_2CO_3-DMF and was purified by distillation. [d] The distillation residue usually consists of a variable amount of the dialkylated product and polymers. [e] Estimated by NMR analysis. [f] The NMR analysis of the crude product indicated the presence of >80% of the desired adduct.

pendent syntheses.[10] The results recorded for entries 7 and 8 are similar to that of entry 6.


13


14

A possible explanation for the above observations follows. Treatment of **3** with LDA (2 equiv) affords an equilibrium mixture of **15** and **16** in which the latter

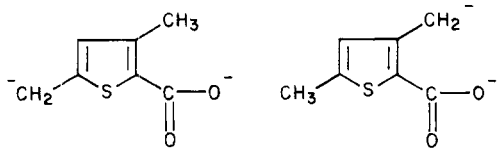

15 16

predominates, possibly due to resonance stabilization. The addition of a highly reactive electrophile (e.g., acetone, deuterium oxide, or methyl iodide) to the above mixture of dianions presumably gives a product mixture reflecting the equilibrium ratio of **15** and **16**. In the instance where a less reactive electrophile (e.g., n-pentyl bromide) was used, a higher proportion of the product derived from dianion **16** was observed. We reason that the electronic charge centered around the reactive site in **16** bears higher P character than does its counterpart in **15**; consequently, dianion **16** is more effective than **15** toward less reactive electrophiles. In view of these observations, direct homologation of acid **3** (entry 5) can be regarded as a method complementary to that recently reported by Vlattas,[11] for the preparation of 3-substituted thiophene-2-carboxylic acids.

The last two reactions in Table I (entries 9 and 10) were designed to determine the relative regioselectivities of the 3- and 5-methyl groups of **4**. The results from both entries support the predominance of **17** rather than **18**. While similar resonance stabilization forms can be written for **17** and **18**, the preference for reaction at the 5-methyl group (**17**) may be explained by the principle of separation of charges.

(10) Compound **11** was prepared from 3-methylthiophene in two steps: (a) t-BuLi, Et_2O, -70 °C, then CH_3COCH_3 and (b) n-BuLi (2 equiv), Et_2O, room temperature, then CO_2. Azeotropic reflux of **11** in toluene in the presence of PTSA gave compound **13**.

(11) Della Vecchia, L.; Vlattas, I. *J. Org. Chem.* 1977, *42*, 2649.



17 18

In conclusion, we have shown that methylated thiophene-2-carboxylic acids can be easily dilithiated with LDA (2 equiv). Treatment of the resulting dianions with carbon-containing electrophiles provides a variety of homologues of the starting acids. It should be noted that acids 1–4, used in this study, are either commercially available or are readily accessible.[2] Therefore, direct homologation of the appropriate methylated carboxylic acid offers a convenient and efficient method for the synthesis of various substituted thiophene-2-carboxylic acids which, in turn, can be transformed into a variety of substituted thiophenes by virtue of the inherent versatility of the carboxy group. It is therefore anticipated that our procedure will lead to an even broader use of the thiophene nucleus as a template in organic synthesis.

Acknowledgment. We are indebted to Drs. R. F. Hirschmann and E. J. Cragoe for their encouragement and to Drs. J. B. Bicking, M. G. Bock, and R. L. Smith for many helpful discussions throughout the course of this investigation. We also thank Dr. W. C. Randall and his staff for elemental analyses and Mr. A. Augenblick for GC analyses.

Registry No. 1, 1918-79-2; 2, 14282-78-1; 3, 23806-24-8; 4, 65613-27-6; 5, 74965-72-3; 9, 74965-73-4; 10, 74965-74-5; 11, 74965-75-6; 12, 74965-76-7; 13, 74965-77-8; 14, 74965-78-9; methyl 5-hexylthiophene-2-carboxylate, 74965-79-0; 5-(2-hydroxy-2-methylpropyl)thiophene-2-carboxylic acid, 74965-80-3; methyl 4-methyl-5-pentylthiophene-2-carboxylate, 74965-81-4; 3-methyl-5-deuteriothiophene-2-carboxylic acid, 74965-82-5; 3-deuteriomethylthiophene-2-carboxylic acid, 74965-83-6; 3-ethylthiophene-2-carboxylic acid, 74965-84-7; 3-methyl-5-(2-hydroxy-2-methylpropyl)thiophene-2-carboxylic acid, 74965-85-8; pentyl bromide, 110-53-2; 2-(2-bromoethyl)-1,3-dioxolane, 18742-02-4; acetone, 67-64-1; water-d_2, 7789-20-0; methyl iodide, 74-88-4; butyl bromide, 109-65-9.

Supplementary Material Available: Experimental details for the preparation of 5 and NMR data of the products (3 pages). Ordering information is given on any current masthead page.

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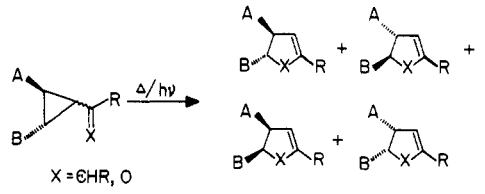
Aluminum Oxide Assisted Stereoselective Rearrangement of a Cyclopropyl Ketone to 4,5-Dihydrofuran

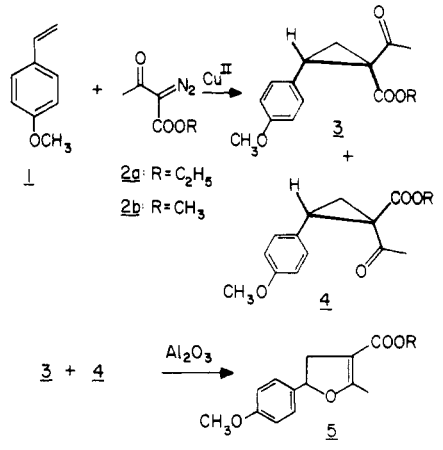
Summary: Contrary to the general observation that thermally and photochemically induced cyclopropyl ketone to dihydrofuran arrangements take place with partial loss of the stereochemical identity of the starting cyclopropane, a characteristic shared by the closely related vinylcyclopropanes and vinyloxiranes, a case of totally stereospecific, alumina-assisted cyclopropyl ketone to dihydrofuran rearrangement at room temperature was observed.

Sir: The thermal and photochemical isomerization of cyclopropyl ketones and imines to dihydrofurans and dihydropyrroles has been known since Cloke[1] first described the irreversible rearrangement of phenylcyclopropanimine to 2-phenyl-4,5-dihydropyrrole at 170 °C. Ever since the extension of this discovery to cyclopropyl aldehydes and ketones was reported by Wilson,[2] only a limited number of reports have appeared in the literature,[3-6] in contrast to the extensive kinetic, stereochemical, and theoretical studies of the closely related vinylcyclopropane to cyclopentene[7] and vinyloxirane to dihydrofuran[8] rearrangements. These three processes share in common the fact that the stereochemical identity of the starting cyclopropane derivative is not reflected in the five-membered-ring product (see Scheme I),[6,9] presumably due either to the intervention of diradical species[10] free to rotate, to what has been termed by Doering as continuous diradical transition states,[11] or to the combination of four concerted [1,3] sigmatropic shifts,[7] although the issue remains at present under intense debate.

Scheme I



Scheme II



In addition, the stereomutation of cyclopropanes[12] and cyclopropyl ketones[6] that would tend to randomize even further the stereochemistry of rearranged products has been shown to take place under the same thermal and photochemical conditions. In the present communication

(1) Cloke, J. B. *J. Am. Chem. Soc.* **1929**, *51*, 1174.
(2) Wilson, C. L. *J. Am. Chem. Soc.* **1947**, *69*, 3002. Armitage, D. M. A.; Wilson, C. L. *Ibid.* **1959**, *81*, 2437.
(3) Dauben, W. G.; Shaffer, G. W. *J. Org. Chem.* **1969**, *34*, 2301.
(4) Zimmerman, H. E.; Boettcher, R. J.; Braig, W. *J. Am. Chem. Soc.* **1973**, *95*, 2155.
(5) Doering, W. v. E.; Birladenau, L. *Tetrahedron* **1973**, *29*, 499.
(6) McGreer, D. E.; McKinley, J. W. *Can. J. Chem.* **1973**, *51*, 1487.
(7) Andrews, G. D.; Baldwin, J. E. *J. Am. Chem. Soc.* **1976**, *98*, 6705, 6706.
(8) Vogel, E.; Gunther, D. *Angew. Chem., Int. Ed. Engl.* **1967**, *5*, 385. Pomelet, J. C.; Manisse, N.; Chuche, J. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1970**, *270*, 1894. Paladini, J. C.; Chuche, J. *Tetrahedron Lett.* **1971**, 4383.
(9) Wilcott, M. R., III; Cargle, V. H. *J. Am. Chem. Soc.* **1967**, *89*, 723.
(10) Mazzocchi, P. H.; Tamburin, H. J. *J. Am. Chem. Soc.* **1975**, *97*, 554.
(11) Doering, W. v. E.; Sachdev, K. *J. Am. Chem. Soc.* **1975**, *97*, 5512.
(12) Berson, J. A.; Pedersen, L. D.; Carpenter, B. K. *J. Am. Chem. Soc.* **1976**, *98*, 122. Baldwin, J. E.; Carter, C. G. *Ibid.* **1979**, *101*, 1325 and references cited therein.

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