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Metalation of 2-Methyl-2(2-thienyl)-1,3-dioxolane With *n*-Butyllithium A New Synthetic Route to Various 2,5-Disubstituted Thiophenes.

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The utility of the 1,3-dioxolane moiety as a blocking group for carbonyl compounds is undoubtedly enhanced by its marked stability to alkaline mediums (1); mediums in which carbonyl compounds often undergo facile conversion to other functional groups. The 1,3-dioxolanes have, however, been generally accepted to be reactive toward organometallic reagents. Mallory, Rovinski, and Sheer (2) have reported the production of β -hydroxy ethers by reaction of the 1,3-dioxolane moiety with methylmagnesium bromide. Berlin, Rathore, and Peterson (3) have utilized the 1,3-dioxolane function derived from substituted and non-substituted benzaldehydes as intermediates in the synthesis of a number of alkyl aryl ketones. Kochetkov, Nifantev, and Nesmeyanov (4) have been successful in selectively adding Grignard reagents to β -keto dioxolanes, while a more recent report by Ulbricht (5) describes the facile decomposition of 2-phenyl-1,3-dioxolane with *n*-butyllithium.

There appears to be no previous reports of 1,3-dioxolanes functioning successfully as carbonyl blocking agents during butyllithium metalations. Results are now available which demonstrate that this group can, at least in the case reported, be employed as a carbonyl blocking agent during such metalations (Scheme A). When I was treated with an equivalent amount of *n*-butyllithium, metalation occurred exclusively at the five carbon with no detectable degradation of the cyclic ether. This indicates that the acid base reaction at the *alpha* position of thiophene is faster, and produces a harder base (6), than is usually found in the nucleophilic organometallic system which attack dioxolanes with ring opening.

That metalation occurred at the 5-thienyl carbon was verified by elemental analysis of products and comparison of infrared spectrum, refractive indices, vapor phase chromatogram and mixture melting point of derivatives with an authentic specimen (7) of IV.

Verification that decomposition of the dioxolane moiety did not occur during metalation was accomplished in the following manner. Aliquot portions of the metalation mixture (1 mole dioxolane: 1 mole *n*-butyllithium) were withdrawn at 15 minute intervals for 8 hours, decomposed with mildly acidic water, and immediately extracted with ether. The ether

extracted organic material was analyzed by gas-liquid chromatography to show the presence of only a single component (I).

In a typical experiment, I in anhydrous ether, was treated at room temperature with a 10% excess of *n*-butyllithium in hexane. After an appropriate metalation period of one hour, the lithio salt (Ia) was condensed with an electrophilic reagent to produce the desired 2,5-disubstituted thienyl derivatives, which in most cases were initially isolated as the dioxolane derivative and subsequently decomposed to the corresponding ketone (Table I).

The addition of an equivalent amount of hydrochloric acid to the lithio salt derived from the combination of Ia and the appropriate electrophilic reagent, followed by extraction with ether, allows isolation of the acid sensitive dioxolane derivatives. An ethereal solution of the 1,3-dioxolanes produces near quantitative yields of ketones when refluxed with 6 *N* hydrochloric acid.

In summary, this work reports the first successful utilization of the 1,3-dioxolane moiety as a carbonyl blocking group during butyllithium metalations. This technique has proved to be a convenient synthetic route to a number of 2,5-disubstituted thiophene derivatives. Evidence is given supporting the indicated position of metalation on the thienyl nucleus and the synthesis of twelve previously unreported compounds, selected to show the versatility of the reaction sequence, is described.

EXPERIMENTAL

The melting points reported were determined on a Fisher-Johns melting point apparatus and are uncorrected. The infra-red spectra were determined with a Beckman IR-5 spectrophotometer. Gas chromatography was performed with an Aerograph Autoprep A-700 using a 20 foot by 3/8 inch column packed with 30% SE-30 on Chrom. W. A column temperature of 250°C and a helium flow rate of 42 ml./min. was employed. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee.

2-Methyl-2-(2-thienyl)-1,3-dioxolane (I).

A modified procedure of Sulzbacher, Bergmann, and Pariser (8) was employed.

To a 3-necked flask fitted with a nitrogen inlet, a true bore stirrer, and a 12" Vigreux column to which was attached a Barrett trap and

reflux condenser was added a mixture of 2-acetylthiophene (25 g., 0.1984 mole), ethylene glycol (12.3 g., 0.1984 mole), and *p*-toluenesulfonic acid (1 g.) in 200 ml. of dry benzene. The resulting mixture was refluxed vigorously until the theoretical amount of water had been collected. The mixture was concentrated to 40 ml., the undissolved *p*-toluenesulfonic acid was removed by filtration, and 200 ml. of cyclohexane was added. Standing overnight at 5°C produced 24.2 g. (72%) of crystalline material melting at 33-34° after recrystallization from a benzene-cyclohexane mixture.

2-Methyl-2-(2-thienyl-5-lithio)-1,3-dioxolane (Ia).

An ethereal solution of I (5 g., 0.0294 mole) was treated dropwise at room temperature, under nitrogen atmosphere, with *n*-butyllithium in hexane (23.3 ml., 0.030 mole). The reaction mixture immediately began to discolor and after one hour was deep brown. The lithio salt (Ia) was then condensed in the prescribed manner with an appropriate electrophile.

2-Acetyl-5-thiophenecarboxylic Acid (II).

Ia (0.02 mole), in anhydrous ether, was treated for 3 hours at room temperature with an excess of gaseous anhydrous carbon dioxide. The resulting suspension was washed with 50 ml. of water and the aqueous phase was acidified to a pH of 3, heated at 70°C for 5 hours, cooled and repeatedly extracted with ether. The combined ethereal extracts were

dried over magnesium sulfate and concentrated to give 2.35 g. (70%) of II melting at 213° [lit. (9) m.p. 203-206°].

Treatment of II with 2,4-dinitrophenyl hydrazine produced the hydrazone derivative, X (90%), m.p. 283°.

Phenyl-2-thienyl-(5-acetyleneketal)carbinol (VII).

Ia (0.015 mole), in boiling anhydrous ether, was treated with an excess of freshly distilled benzaldehyde (2.12 g., 0.02 mole) followed by refluxing for 3 hours and standing at ambient temperature under nitrogen for 36 hours. The mixture was shaken with water and an equivalent amount of aqueous hydrochloric acid was added (1.5 ml. of 0.01 N) with cooling. Repeated ethereal extractions of the aqueous phase followed by drying of the combined extracts over magnesium sulfate, concentration and distillation of the residue *in vacuo* gave 2.5 g. (60%) of VII boiling at 160°/0.10 mm.

2-Methyl-2-(2-thienyl-5-trimethylsilyl)-1,3-dioxolane (VIII).

Ia (0.015 mole), in anhydrous ether (50 ml.), was added at room temperature under nitrogen atmosphere to an equivalent amount (1.62 g., 0.015 mole) of freshly distilled trimethylsilylchloride. The solution was gently refluxed for 2 hours and subsequently allowed to stand at ambient temperature for 8 hours. Filtration of the lithium chloride, followed by solvent evaporation and distillation *in vacuo* produced 3.5 g. (96%) of VIII boiling at 81°/0.10 mm.

Scheme A

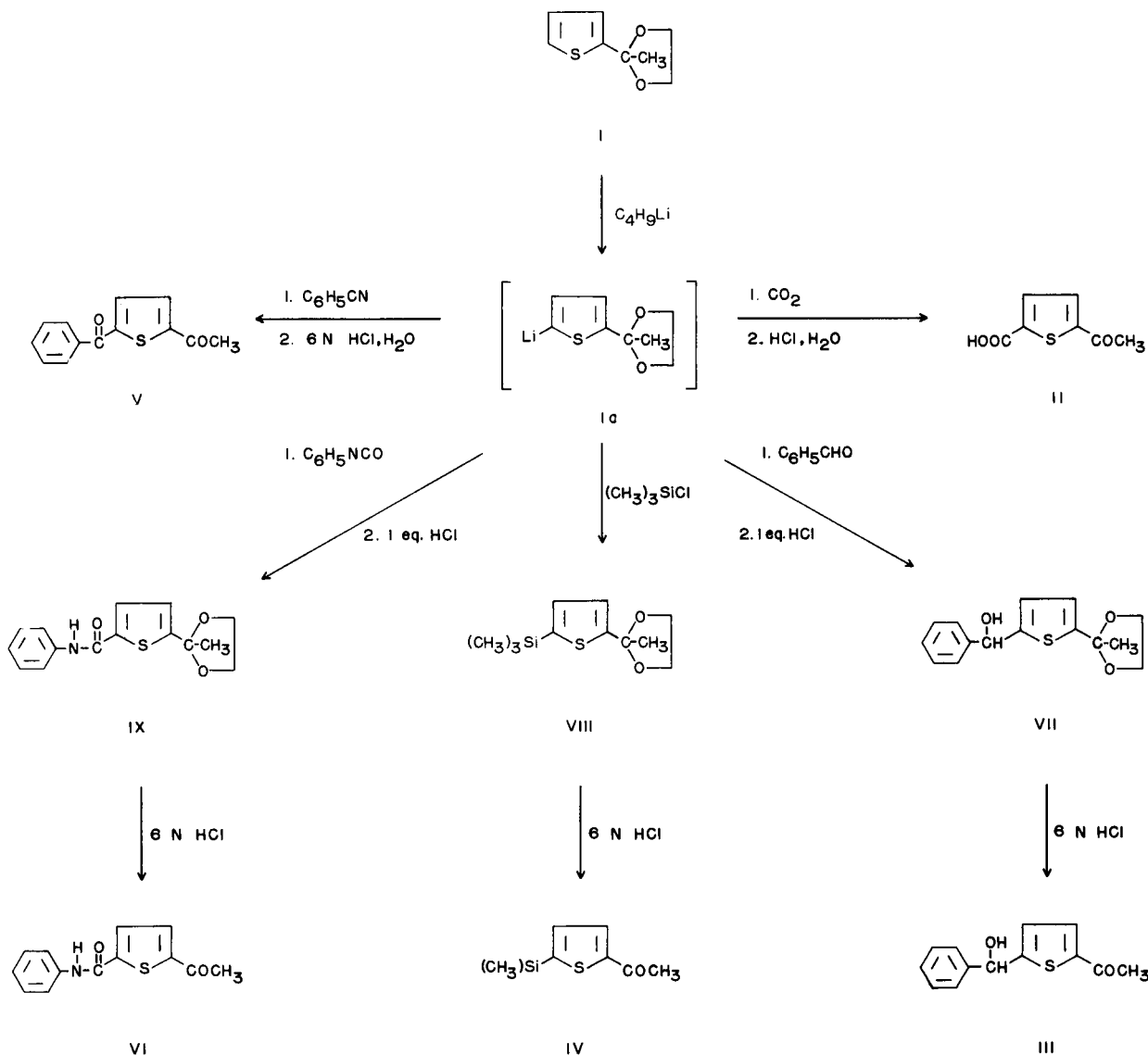
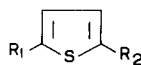
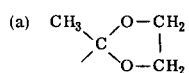


TABLE I
2, 5-Disubstituted Thiophene Derivatives



Compound	R ₁	R ₂	Yield %	M. P. °C	B. P. °C	Formula	Calcd %		Found %	
							C	H	C	H
I	H-	a	72	33-34	102-4/20mm.	C ₈ H ₁₀ O ₂ S	56.45	5.92	56.42	5.92
II	-COOH	b	70	213 (d)		C ₇ H ₈ O ₃ S	49.85	3.53	49.10	3.59
III	C ₆ H ₅ CHOH-	b	85	123.0-124.5		C ₁₃ H ₁₂ O ₂ S	67.21	5.21	67.23	4.92
IV	(CH ₃) ₃ Si-	b	93		127-8/25mm.	C ₉ H ₁₄ OSSi	54.50	7.12	54.15	6.95
V	C ₆ H ₅ CO-	b	66	123		C ₁₃ H ₁₀ O ₂ S	67.80	4.38	67.62	4.31
VI	C ₆ H ₅ NHCO-	b	90	206-207		C ₁₈ H ₁₁ NO ₂ S	63.65	4.52	63.43	4.59
VII	C ₆ H ₅ CHOH-	a	60		160/.10mm.	C ₁₅ H ₁₆ O ₃ S	65.19	5.84	65.89	5.44
VIII	(CH ₃) ₃ Si-	a	96		81/.1mm.	C ₁₁ H ₁₆ O ₂ SSi	54.50	7.42	54.90	7.62
IX	C ₆ H ₅ NHCO-	a	65	127.5-128.0		C ₁₅ H ₁₅ NO ₃ S	62.26	5.23	62.19	5.18
X	-COOH	c	90	283.0		C ₁₃ H ₁₀ N ₄ O ₆ S	44.57	2.88	44.80	3.00
XI	C ₆ H ₅ CHOH	c	85	216-217.5		C ₁₉ H ₁₆ N ₄ O ₆ S	55.33	3.91	54.93	3.79
XII	(CH ₃) ₃ Si-	c	75	(e)		C ₁₅ H ₁₈ N ₄ O ₄ SSi	47.60	4.79	47.26	4.83
XIII	C ₆ H ₅ CO-	c	70	214-216 (f)		C ₁₉ H ₁₄ N ₄ O ₆ S	55.60	3.43	55.07	3.54
XIV	C ₆ H ₅ NHCO-	c	80	250.5-252.0		C ₁₉ H ₁₅ N ₅ O ₆ S	53.64	3.55	53.46	3.70



(b) -COCH₃. (c) -C(CH₃)=NNH-C₆H₃-2,4-di-NO₂. (d) lit. M.P. recorded as 203-206°. (e) Sublimes at

220-230° with decomposition when heated to 240°. (f) mono-2,4-dinitrophenylhydrazone derivative assumed to be less hindered acetyl derivative.

Phenyl-(2-acetylthienyl)-5-thiophenecarboxylic Acid Amide (IX).

Freshly distilled phenylisocyanate (1.43 g., 0.012 mole) in anhydrous ether (50 ml.) was treated with an ethereal slurry (100 ml.) of Ia (0.10 mole). The resulting mixture was refluxed for 6 hours, at which time saturated ammonium chloride solution (100 ml.) was added. The ethereal layer was separated and combined with ethereal washings (2 x 100 ml.) of the aqueous phase. The combined extracts were dried over anhydrous magnesium sulfate and concentrated to produce a viscous oil which, when dissolved in warm ethanol and cooled, gave 1.9 g. (65%) of IX melting at 127.5-128.0°.

2-Acetyl-5-benzoylthiophene (V).

A refluxing ethereal slurry (100 ml.) of Ia (0.011 mole) was treated with freshly distilled benzonitrile (1.24 g., 0.012 mole). The reaction mixture was allowed to reflux overnight at which time 100 ml. of 6 N hydrochloric acid solution was added. The ether was allowed to boil away and the resulting aqueous solution refluxed for an additional 5 hours. The acidic reaction medium was extracted several times with ether and the extracts were combined and concentrated to give a tan solid. Recrystallization from a mixture of cyclohexane and ethyl alcohol with Norite A gave 1.67 g. (66%) of a white solid, V, melting sharply at 123°.

General Procedure for Decomposition of 1,3-Dioxolanes to Ketones.

The production of phenyl-(2-acetyl)-5-thiophenecarboxamide (VI) from IX will serve as an example of this procedure. An ethereal solution (30 ml.) of IX (0.9 g.) was added to 15 ml. of 6 N hydrochloric acid and the resulting mixture refluxed for 3 hours. The mixture was cooled and the separated ether layer was combined with two 25 ml. portions of ether used to extract the aqueous phase. The combined extracts were dried over magnesium sulfate and evaporated to produce 0.73 g. (90%) of VI melting at 206-207° after recrystallization from alcohol. The following ketones were prepared according to this procedure:

1. Phenyl-2-thienyl-(5-acetyl)carbinol (III) was produced in 85% yield, m.p. 123-124.5° after recrystallization from ethanol.

The 2,4-dinitrophenyl hydrazone derivative (XI) was produced in the usual manner in 85% yield with a m.p. of 216-217.5°.

2. 2-Acetyl-5-trimethylsilylthiophene (IV) with a b.p. of 127-128°/25 mm. was prepared in 93% yield.

The 2,4-dinitrophenyl hydrazone derivative (XII) was prepared in the usual manner to give 75% of product which sublimes at 220-230° with decomposition at 240°.

The 2,4-dinitrophenyl hydrazone derivatives XIII and XIV were prepared in the usual manner.

1. XIII was prepared in 70% yield and melted at 214-216°. This mono-2,4-dinitrophenyl hydrazone derivative is assumed to be the less hindered acetyl derivative.

2. XIV was prepared in 80% yield, m.p. 250.5-252.0°.

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