Studies of the Reaction of 3-Bromo-2,5-dimethylthiophene 1,1-Dioxide with Some Organocopper Reagents

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The coupling reactions of some organocopper reagents with 3-bromo-2,5-dimethylthiophene 1,1-dioxide leading to 3-alkyl and 3-aryl substituted 2,5-dimethylthiophene 1,1-dioxides have been found to proceed in high yields (50-100%). The less stable organocopper reagents reacted faster and at lower temperatures than the more stable ones. It is more convenient to use alkylcopper than lithium dialkylcuprate reagents, which give higher yields without side reactions.

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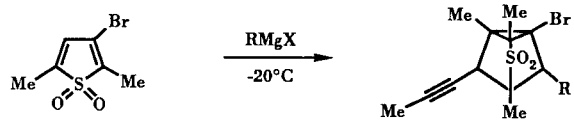
Introduction.

Thiophene 1,1-dioxides have recently attracted attention as useful precursors in organic synthesis [1]. In a previous study of the reaction of 3-bromo-2,5-dimethylthiophene 1,1-dioxide (**1**) with organolithium derivatives, two competing reactions were observed. One reaction path, starting with halogen-metal exchange, follwed by ring-opening, leads to lithium enyne sulphinates, which can be trapped with electrophiles such as benzyl bromide. The other path consists of a 1,6-Michael-type addition of the lithium reagent to the 5-carbon of the thiophene 1,1-dioxide, followed by ring-opening and elimination of sulphur dioxide and lithium bromide to give enynes [2,3,4] (Scheme 1).

The reaction of **1** with some Grignard reagents at -20° resulted in a series of Michael-type additions, leading to the cage compound [5] (Scheme 2).

We were therefore interested in exploring how other organometallic reagents behave and have therefore undertaken a study of the reaction of **1** with some organocopper reagents. The copper reagents used were methyl-, ethyl-, *n*-butyl, *t*-butyl- and 2-thienylcopper and the corresponding lithium dialkylcuprates and lithium di(2-thienyl)cuprate.

Scheme 2

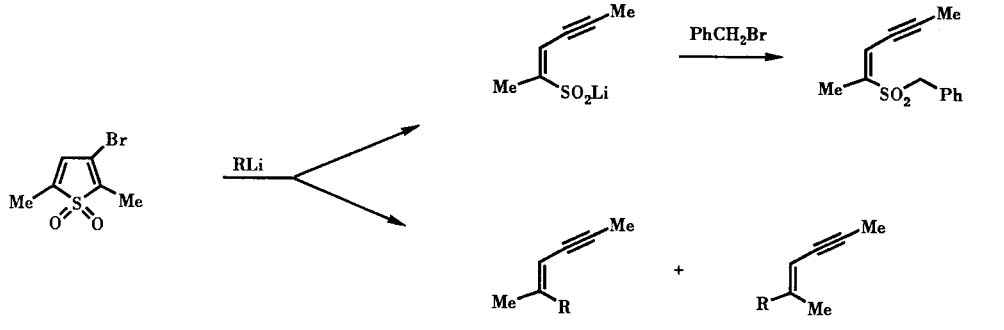


Copper reagents, such as alkyl- and arylcopper or organocuprates, undergo conjugate addition [6] to α,β-unsaturated systems containing electron-withdrawing groups, especially carbonyl groups or substitution reactions with halides [7]. They have many synthetic uses (for recent reviews *cf* [8,9]).

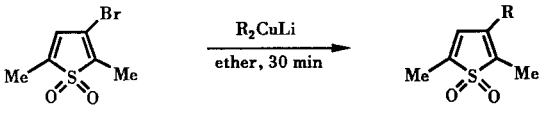
Results.

All organocopper reagents were prepared *in situ* from the corresponding organolithium reagents in an inert atmosphere. The reactions were carried out under nitrogen in ether or tetrahydrofuran as the solvent. The ratio of the substrate and reagent usually was 1:3. The reactions were performed at temperatures of -78°, -20°, 0° and room temperature depending on the stability of the reagent used (Schemes 3 and 4). Organic cuprates were most often

Scheme 1

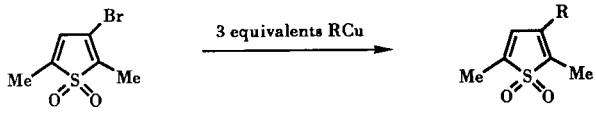


Scheme 3



R = Me, Et, *n*-Bu, *t*-Bu and Th

Scheme 4



R = Me, Et, *n*-Bu, *t*-Bu and Th

used since they give higher yields of both substitution and 1,4-addition products than the organic copper reagents [10]. They also appear to be more basic than organocopper species [11] and give side reactions. They are also more apt to give halogen-metal exchange leading to symmetrical coupling products [12]. However, it was previously observed in this laboratory that symmetrical coupling products were formed in the reaction between 1-methyl-2-pyrrolyl and 2-iodothiophene [13].

We found that **1** reacted with organocuprates (Scheme 3) and organocopper reagents (Scheme 4) with substitution and not *via* conjugate addition. Somewhat unexpectedly, we found that the organocopper reagents gave higher yields than organocuprates (Tables 1 and 2). Except for 2-thienylcopper almost quantitative yields were obtained with the organocopper reagents. We found that alkylcopper compounds (and cuprates) other than methyl could displace bromine at -78° in a few hours (or less in the case of cuprates), whereas methyl copper required temperatures of 0° and 2-thienylcopper reacted first at room temperature.

Table 1

Reaction Conditions and Yields for the Reactions of 3-Bromo-2,5-dimethylthiophene 1,1-Dioxide with Lithiumdialkyl Cuprate

Reaction [c] product	R	Moles of the reagent used	Reaction temperature (°C)	Yield (%)
2	Me	3.0	-20	78
3	Et	2.5	-78	83
4	*n*-Bu	2.0	-78	53
5	*t*-Bu	3.0	-78	11
6	Th [a]	1.0	rt [b]	17

[a] Th = thienyl. [b] rt = room temperature. [c] Yields determined by gc. Isolated yields were 10-20% lower due to the mechanical losses during isolation.

Table 2

Reaction Conditions and Yields for the Reactions of 3-Bromo-2,5-dimethylthiophene 1,1-Dioxide with Alkylcopper Compounds

Reaction [a] product	R	Reaction temperature (°C)	Reaction time (h) in ether	in THF	Yield (%) in ether	in THF
2	Me	0	1	1/2	100	95
3	Et	-78	4	1	100	84
4	*n*-Bu	-78	4	1	100	91
5	*t*-Bu	-78	1	1/2	47	89
6	Th	rt	1	1/2	44	
	49Π					

[a] Yields determined by gc. Isolated yield is about 20% less in diethyl ether and only a few % less in THF.

The reaction of the most reactive species, lithium di-*t*-butyl cuprate, with **1** was very fast and went to completion in a few minutes, but gave a complex mixture of reaction products. *t*-Butylcopper also reacted very fast with **1**, but about half of **1** always remained in the reaction mixture. In order to increase the yield we varied the reaction conditions. Thus the temperature of the reaction was varied from -78° to room temperature, but this did not significantly affect the amount of the substitution product. Longer reaction times also had no significant effect on the yield. The concentration of the reactants was varied, and it was found that when the ratio between **1** and *t*-butyl copper was 1:6, the yield was about 80%. Finally, we changed the solvent from diethyl ether to tetrahydrofuran and obtained even higher yields (89%). We also tried all other reactions in tetrahydrofuran as the solvent (Table 2). Our results show that the reaction of **1** with alkylcopper reagents proceeds faster in tetrahydrofuran than in ether. The solubility of the reactants and reaction products is much better in tetrahydrofuran than in ether. The fact that the 3-alkyl-2,5-dimethylthiophene 1,1-dioxides **2-6** have low solubility in ether causes problems in the work-up. In agreement with this, isolated yields are always 10-20% less than gc yields due to mechanical losses.

In all cases, the products were analyzed by gas chromatography (gc), isolated and characterized. The reaction products were purified by column flash chromatography using ethyl acetate-hexane as the eluent. Solids were recrystallized from ether. Satisfactory spectral data (^{1}H nmr, mass spectra, ir), high resolution mass spectra and elemental analysis were obtained for all compounds.

On the basis of the results obtained we can conclude that the best conditions for coupling reactions between 3-bromo-2,5-dimethylthiophene 1,1-dioxide and organocopper reagents are low temperature, tetrahydrofuran as the solvent and alkyl copper as reagent. The mild conditions used and the short reaction times, as well as the high yields obtained, makes this reaction useful for the synthe-

sis of alkylated and especially arylated thiophene 1,1-dioxides.

EXPERIMENTAL

Infrared spectra were recorded on a Perkin Elmer 298 spectrophotometer. The ^1H nmr spectra (deuteriochloroform as solvent) were recorded on a Varian XL 300 spectrometer. Quantitative gas chromatographic analyses were performed on a Varian 3300 gas chromatograph equipped with a 2 m column of 3% OV 17 on Gaschrom Q, 100-120 mesh and a flame ionization detector. Mass spectra were obtained on a Finnigan 4021 (Data system Incos 2100) gas chromatograph-mass spectrometer operating at 70 eV. High resolution mass spectra were recorded on a JEOL JMS-SX 102 spectrometer. Elemental microanalyses were performed at Dornis and Kolbe, Mikroanalytisches Laboratorium, Mulheim a.d. Ruhr, Germany. Column chromatography was carried out using Merck silica gel 60 (230-400 mesh ASTM) and ethyl acetate-hexane as eluent. TLC analyses were performed on silica gel 60 F_{254} using Merck Alufolien. Melting points are uncorrected. All preparation and handling of organometallic compounds were carried out under nitrogen. Anhydrous reagents and solvents were used. Diethyl ether and tetrahydrofuran were freshly distilled from sodium dispersion. Copper(I) iodide and copper(I) bromide were commercial products (Merck) and were used without further purification. The glassware was dried at 120°, assembled while hot and flushed with dry nitrogen prior to introducing the reagents.

n-Butyllithium, *t*-butyllithium and methyllithium were commercial products (Merck). Ethyllithium was prepared using the procedure of Gilman [14]. 2-Thienyllithium and 2-thienylcopper were prepared according to Nilsson [15].

3-Bromo-2,5-dimethylthiophene 1,1-dioxide was prepared by oxidation of the corresponding thiophene with *m*-chloroperbenzoic acid using the procedure of Melles [16] and the work-up procedure of van Tilborg [17,18].

Methylcopper.

To a suspension of cuprous iodide at 0° (571 mg, 3.0 mmoles) in 5 ml of anhydrous ether methyllithium (1.88 ml, 3.0 mmoles) was added dropwise during 10 minutes. The suspension immediately turned bright yellow (methylcopper).

Lithium Dimethylcuprate.

To a suspension of cuprous iodide at 0° (571 mg, 3.0 mmoles) in 5 ml of anhydrous ether methyllithium (3.76 ml, 6.0 mmoles) was added dropwise during 15 minutes. The suspension immediately turned bright yellow (methylcopper) and then as more methyllithium was added, turned into a light tan solution.

Ethylcopper.

To a suspension of cuprous iodide (2.46 g, 12.96 mmoles) in 20 ml of anhydrous ether stirred at -50° ethyllithium (13.76 ml, 12.96 mmoles) was added. A black suspension immediately formed. It was stirred for 30 minutes.

Lithium Diethylcuprate.

To a suspension of cuprous iodide (1.015 g, 5.35 mmoles) in 10 ml of anhydrous ether stirred at -50°, ethyllithium (10 ml, 10.7 mmoles) was added. A black suspension immediately formed and after the addition of two equivalents of ethyllithium, a black solution resulted. It was stirred for 30 minutes.

n-Butylcopper.

To a suspension of cuprous iodide (1.14 g, 6.0 mmoles) in 10 ml of anhydrous ether stirred at -40° *n*-butyllithium (2.85 ml, 6.0 mmoles) was added dropwise. The suspension became bright yellow.

Lithium Di-*n*-butylcuprate.

To a suspension of cuprous iodide (761 mg, 4.0 mmoles) in 5 ml of anhydrous ether stirred at -40°, *n*-butyllithium (3.80 ml, 8.0 mmoles) was added dropwise. The initial bright yellow color lasted until about half of the butyllithium had been added. This changed to a dark blue solution, and finally the solution turned a dark red-brown color.

t-Butylcopper.

To a suspension of cuprous iodide (285 mg, 1.5 mmoles) in 5 ml of anhydrous ether stirred at -40°, *t*-butyllithium (1.86 ml, 1.5 mmoles) was added dropwise over 10 minutes. The suspension turned black.

Lithium Di-*t*-butylcuprate.

To a suspension of cuprous iodide (285 mg, 1.5 mmoles) in 5 ml of anhydrous ether stirred at -40°, *t*-butyllithium (3.72 ml, 3.0 mmoles) was added dropwise during 15 minutes. The initial suspension turned black, but at the end a dark red-brown color could be detected.

2,3,5-Trimethylthiophene 1,1-Dioxide (**2**).

A solution of 223 mg (1.00 mmole) 3-bromo-2,5-dimethylthiophene 1,1-dioxide dissolved in 5 ml of anhydrous ether was slowly added with vigorous stirring (by syringe) to a cooled suspension of 3.0 mmoles of methylcopper (at 0°) or lithium dimethylcuprate (at -20°). After completion of the reaction cold water was added to the reaction mixture at the same temperature and stirred for at least 10 minutes. Insoluble copper salts were filtered off. The layers were separated and the aqueous phase was extracted three times with ether. The combined ethereal phase was washed twice with water, dried over magnesium sulphate and concentrated. The residue was separated by chromatography on silica gel with a mixture of ethyl acetate-hexane (30:70) and recrystallisation from ether afforded **2** as white crystals, mp 58-60°; ^1H nmr (deuteriochloroform): 1.92 (d, 3H, 3-CH_3, J = 1.2 Hz), 2.02 (d, 3H, 5-CH_3, J = 1.2 Hz), 2.12 (s, 3H, 2-CH_3), 6.16 (d, 1H, 4-CH, J = 1.9 Hz); ms: m/e 158; exact mass Calcd. for $C_7H_{10}O_2S$: 158.0402; Found: 158.0396.

Anal. Calcd. for $C_7H_{10}O_2S$: C, 53.16; H, 6.33. Found: C, 53.18; H, 6.63.

3-Ethyl-2,5-dimethylthiophene 1,1-Dioxide (**3**).

A solution of 964 mg (4.32 mmoles) or 482 mg (2.16 mmoles) of 3-bromo-2,5-dimethylthiophene 1,1-dioxide dissolved in 20 ml of anhydrous ether was slowly added with vigorous stirring to a cooled (-78°) suspension of previously prepared ethylcopper (12.96 mmoles) or lithium diethylcuprate (5.35 mmoles). Upon completion of the reaction and after the usual work-up, the organic product was isolated as a yellow oil, which solidified after three weeks in the refrigerator. Recrystallization from ether afforded **3** as white crystals, mp 54-56°; ^1H nmr (deuteriochloroform): 1.05 (t, 3H, 3-CH_3, J = 7.6 Hz), 2.01 (s, 3H, 2-CH_3), 2.11 (d, 3H, 5-CH_3, J = 0.8 Hz), 2.24 (q, 2H, 3-CH_2, J = 7.6 Hz), 6.22 (d, 1H, 4-CH, J = 1.6 Hz); ms: m/e 172; exact mass Calcd. for

$C_8H_{12}O_2S$: 172.0558; Found: 172.0556.

Anal. Calcd. for $C_8H_{12}O_2S$: C, 55.78; H, 7.08. Found: C, 55.62; H, 6.98.

3-*n*-Butyl-2,5-dimethylthiophene 1,1-Dioxide (**4**).

The usual procedure was followed using 446 mg (2.0 mmoles) of 3-bromo-2,5-dimethylthiophene 1,1-dioxide in 10 ml of anhydrous ether and 6.0 mmoles of *n*-butylcopper or 4.0 mmoles of lithium di-*n*-butylcuprate. The reactions were run at -78° for 4 hours and one half hour, respectively, and worked-up to yield **4** as a yellow oil; ^{1}H nmr (deuteriochloroform): 0.92 (t, 3H, 3-CH_3, J = 7.1 Hz), 1.27 and 1.43 (m, 4H, 3-CH_2), 2.01 (s, 3H, 2-CH_3), 2.11 (d, 3H, 5-CH_3, J = 0.8 Hz), 2.22 (t, 2H, 3-CH_2, J = 7.6 Hz), 6.22 (d, 1H, 4-CH, J = 1.6 Hz); ms: m/e 200; exact mass Calcd. for $C_{10}H_{16}O_2S$: 200.0871; Found: 200.0865.

Anal. Calcd. for $C_{10}H_{16}O_2S$: C, 59.99; H, 8.02. Found: C, 60.68; H, 8.24.

3-*t*-Butyl-2,5-dimethylthiophene 1,1-Dioxide (**5**).

An ethereal solution (10 ml) of 3-bromo-2,5-dimethylthiophene 1,1-dioxide (112 mg, 0.5 mmole) was added slowly with vigorous stirring to a stirred solution of 1.5 mmoles *t*-butylcopper or lithium di-*t*-butylcuprate in ether at -78°. After half an hour in the case of cuprate and one hour in the case of *t*-butylcopper the reaction was worked-up and after chromatography on silica gel (ethyl acetate-hexane 35:65), **5** was obtained as white crystals, mp 126-128°; ^{1}H nmr (deuteriochloroform): 1.23 (s, 9H, 3-C$(CH_3)_3$), 2.12 (s, 3H, 5-CH_3), 2.19 (s, 3H, 2-CH_3), 6.41 (s, 1H, 4-CH); ms: m/e 200; exact mass Calcd. for $C_{10}H_{16}O_2S$: 200.0871; Found: 200.0872.

Anal. Calcd. for $C_{10}H_{16}O_2S$: C, 59.99; H, 8.02; S, 16.01. Found: C, 59.93; H, 7.96; S, 15.93.

2,5-Dimethyl-3-(2-thienyl)thiophene 1,1-Dioxide (**6**).

n-Butyllithium (7.18 ml, 15.0 mmoles) was added to the stirred solution of 2.52 g (30 mmoles) of thiophene in 25 ml of anhydrous ether. After stirring for 30 minutes, this solution was added to a suspension of 2.15 g (15 mmoles) of cuprous bromide (for 2-thienylcopper) or 1.07 g (7.5 mmoles) (for lithium di-2-thienylcuprate) in 40 ml of anhydrous ether. It was stirred for one hour and after that 1.12 g (5.0 mmoles) 3-bromo-2,5-dimethylthiophene 1,1-dioxide (in the reaction with thienylcopper) and 1.67 g (7.5 mmoles, in the reaction with lithium di-(2-thienyl)cuprate, dissolved in 25 ml of dry ether, was added. The reaction was run one hour (in the case of thienylcopper) or half an hour (in the case of the cuprate). After the usual work-up and chromatography using ethyl acetate-hexane (35:65) white crystals were obtained, mp 86-88°; ^{1}H nmr (deuteriochloroform): 2.22 (d, 3H, 5-CH_3, J = 0.8 Hz), 2.34 (s, 3H, 2-CH_3), 6.73 (d, 1H, 4-CH, J = 1.7 Hz), 7.18 (dd, 1H, 4'-CH, J = 5.1 and 3.7 Hz), 7.35 (d, 1H, 3'-CH, J = 3.2 Hz), 7.55 (dd, 1H, 5'-CH, J = 5.1 and 1.2 Hz); ms: m/e 226; exact mass Calcd. for $C_{10}H_{10}O_2S_2$: 226.0128; Found: 226.0122.

Anal. Calcd. for $C_{10}H_{10}O_2S_2$: C, 53.08; H, 4.46; S, 28.33. Found: C, 53.31; H, 4.68; S, 28.05.

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