CHEMISTRY LETTERS, pp. 703-706, 1992.

# Reaction of Tri-2-thienylmethyllithium with Alkyl Halides. Substitution on Carbanion Center *vs.* Thiophene Ring[†]

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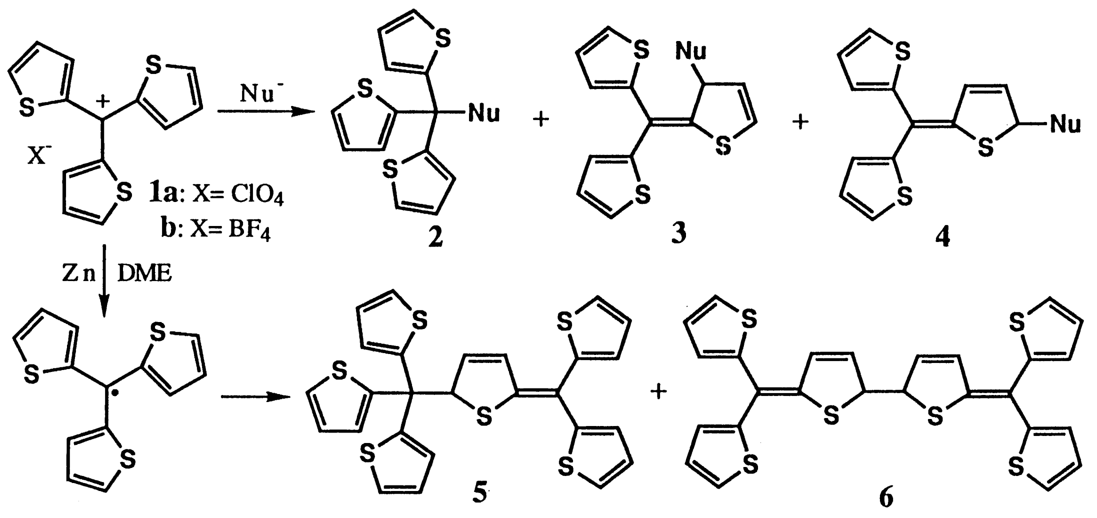
Tri-2-thienylmethyllithium, produced by treatment of tri-2-thienylmethane with butyllithium in the presence of *N,N,N',N'*-tetramethylethylenediamine at -78 °C in tetrahydrofuran, reacts with primary alkyl halides to give the alkylated products on the carbanion center nearly quantitatively, while the reaction with secondary and tertiary alkyl halides affords not only the substitution products at the carbanion center but also those at the 3-position of the thiophene ring.

We have recently reported that the reaction of tri-2-thienylmethylcarbenium perchlorate (**1a**) with carbon nucleophiles occurs not only on the carbenium ion center but also on the 3- and 5-positions of the thiophene ring to give **2**, **3**, and **4** in high combined yields,1) while triphenylcarbenium ion is known to react with nucleophiles only on the carbenium ion center. We have also reported that the tri-2-thienylmethyl radical, generated by reduction of the tetrafluoroborate salt **1a** with metals, affords two dimers **5** and **6**, the ratio of which depends on reaction conditions.2) In this connection, we have become interested in the reaction of tri-2-thienylmethyl anion with carbon electrophiles.



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[†] Dedicated to Professor Emeritus Osamu Simamura of The University of Tokyo on the occasion of his 80th birthday.

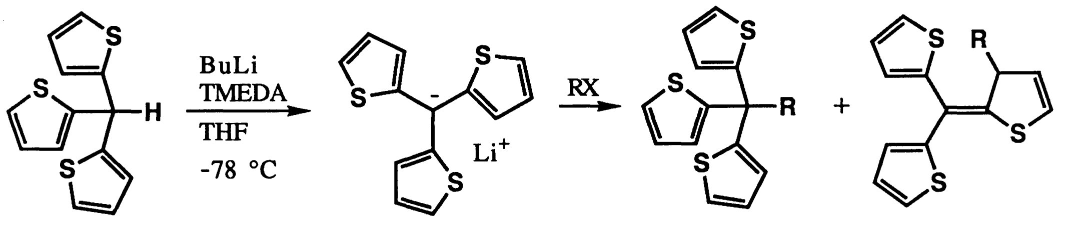
The lithiation of tri-2-thienylmethane (**7**) by alkyllithiums, the reaction used for the preparation of triphenylmethyllithium,3) is the method of our choice for generating tri-2-thienylmethyl anion. The starting material **7** is readily obtainable by condensation of 2-thiophenecarboxaldehyde with thiophene in reasonable yield.4) Addition of 1.2 equiv. of butyllithium in hexane (1.62 M) to a stirred solution of **7** in tetrahydrofuran (THF) at -78 °C under argon affords a red suspension. The mixture was quenched after 0.5 h by adding $D_2O$. The lithiation of thiophene by butyllithium is known to occur exclusively at the 2(5)-position. The lithiation of the 3(4)-position is negligible if occurs.5) Thus, deuterium content in the recovered **7** (95% purified yield) was determined by $^1H$ NMR on the assumption that no deuterium incorporation occurs on the 3- and 4-positions of thiophene rings of **7**. It revealed that deuterium content on the methine carbon is 70% and deuterium incorporation into the 5-position of thiophene rings is not detectable. Neither the elongation of reaction time nor the use of *sec*-butyllithium improve deuterium content. The use of excess butyllithium (2.7 equiv.) caused dilithiation, thus affording **7** in which 70% of the methine carbon and 15% of the 5-position of each thiophene ring are deuterated. Finally we found that the use of butyllithium (1.3 equiv.) in the presence of *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 1.5 equiv.) in THF at -78 °C for 1 h affords the optimized deuterium content (96%) on the methine carbon without deuterium incorporation into the thiophene rings. Thus, the tri-2-thienylmethyllithium (**8**) prepared under the above conditions was employed for all of the reactions of **7** with alkyl halides. Incidentally the lithiation of the methine of **7** is faster than that of triphenylmethane. When a 1:1 mixture of **7** and triphenylmethane was treated wtih 1 equiv of butyllithium at -78 °C for 5 min in THF and quenched by addition of $D_2O$, deuterium uptake occurred only on the methine carbon of **7**.

Table 1 summarizes the results of the reaction of **8** with alkyl halides. All of the reactions were carried out by adding excess alkyl halides (*ca.* 5 equiv.) at -78 °C to the red suspension of **8** prepared in the manner described above and then warming the mixture to room temperature by removing a dry ice-acetone bath.

Methyl iodide, ethyl bromide, allyl chloride, and benzyl chloride all react with **7** at the carbanion center to give **9a-d**6) in high yields. However, secondary alkyl halides, 2-bromopropane, 2-bromobutane, and bromocyclohexane react with **8** not only on the carbanion center but also on the 3-position of the thiophene ring to give the corresponding **9e-g** and **10e-g**6) in excellent combined yields. Compounds **9** and **10** cannot be separated by column chromatography and their ratio was determined by $^1H$ NMR. Structure differentiation of **10** from the products arising from substitution on the 5-position of the thiophene ring was made in the following way. Compound **7-d$_3$** whose 5-position of each thiophene ring contains 85% deuterium was synthesized by treatment of **7** with a mixture of trifluoroacetic anhydride and $D_2O$.7) The reaction of **8-d$_3$** prepared from **7-d$_3$** reacts with 2-bromopropane to give a mixture of **9e-d$_3$** and **10e-d$_3$**. In the $^1H$ NMR of **10e-d$_3$** the absorption due to the olefinic proton at the 5-position of the dihydrothiophene ring appears at d 6.30 ppm as doublet of doublet with 15% intensity compared to those of ring protons at the 3- and 4-positions. The same holds for the products resulting from the reaction of **8-d$_3$** with 2-bromobutane and bromocyclohexane. The

**reaction of 8 with 2-bromo-2-methylpropane (*t*-butyl bromide) affords 7 in 52% yield in addition to 9h (27%) and 10h (19%). The recovered 7 does not contain deuterium on quenching of the reaction with $D_2O$, thus suggesting the formation of 7 and isobutene by E2 elimination. 1-Bromo-2,2-dimethylpropane (neopentyl bromide) does not react with 8; compound 7 was recovered quantitatively even on prolonged reaction at room temperature.**

**In summary the followings are worthy to note. Although tri-2-thienylmethyl anion reacts with primary alkyl halides exclusively on the carbanion center, its reaction with bulkier**

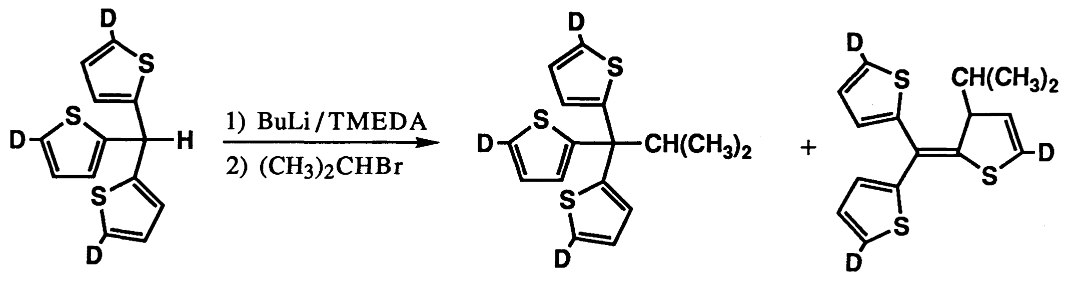


**7** **8** **9** **10**

Table 1. Reactions of Tri-2-thienylmethyllithium (8) with Alkyl Halides

| RX | Products (Yield/%) | | Ratio of **10** to **9** |
|---|---|---|---|
| $CH_3I$ | **9a** (95) | | |
| $CH_3CH_2Br$ | **9b** (95) | | |
| $CH_2{=}CHCH_2Cl$ | **9c** (96) | | |
| $C_6H_5CH_2Cl$ | **9d** (94) | | |
| $(CH_3)_2CHBr$ | **9e** (86) | **10e** (8) | 1:11 |
| $CH_3CH_2(CH_3)CHBr$ | **9f** (67) | **10f** (28) | 1:2.4 |
| *c*-$C_6H_{11}Br$ | **9g** (66) | **10g** (27) | 1:2.4 |
| $(CH_3)_3CBr$ | **9h** (27) | **10h** (19)[a)] | 1:1.4 |
| $(CH_3)_3CCH_2Br$ | no reaction | | |

a) Tri-2-thienylmethane was obtained in 52% yield.



7-$d_3$ 9e-$d_3$ 10e-$d_3$

tertiary alkyl halides occurs not only on the carbanion center but also on the less hindered thiophene ring.8) Meanwhile, triphenylmethyl anion is known to react with a secondary alkyl halide, chlorodiphenylmethane, only on the carbanion center.9) Triphenylmethyl anion usually brings about E2 elimination of secondary and tertiary alkyl halides to afford the corresponding alkenes.10) In the present case such elimination was observed only with 2-bromo-2-methylpropane. Thus, tri-2-thienylmethyl anion is softer than triphenylmethyl anion as nucleophile. This probably comes from weaker aromaticity of thiophene compared to that of benzene, which allows negative charge to delocalize more effectively over the whole molecule and thus enables substitution on the thiophene ring to occur. However, the reason why no substitution occurs on the 5-position of the thiophene ring still remains as an open question. The present reaction must proceed via an $S_N2$ mechanism. Single electron transfer mechanism via a radical pair may be ruled out since, if such mechanism is operative, the dimer of tri-2-thienylmethyl radical should be formed as observed with the reaction of the carbenium ion **1a** with *t*-butyllithium.1)

## References

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4) To a mixture of 50 ml (0.54 mol) of 2-thiophenecarboxaldehyde and 120 ml (1.5 mol) of thiophene in 150 ml of benzene heated at 50 °C was added 120 g of phosphorus pentoxide in small portions over a period of 1 h. The insoluble material was removed by filtration and washed with dichloromethane. The filtrate and washings were combined, washed with water, dried, and evaporated. The residue was chromatographed on a column of silica gel using hexane as the eluent to give 46 g (33%) of **7**, mp 50-51 °C.
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(Received February 19, 1992)