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CONVENIENT METHOD FOR THE PREPARATION OF THE 2-METHYL THIOPHEN-3-YL MAGNESIUM BROMIDE LITHIUM CHLORIDE COMPLEX AND ITS APPLICATION TO THE SYNTHESIS OF 3-SUBSTITUTED 2-METHYLTHIOPHENES

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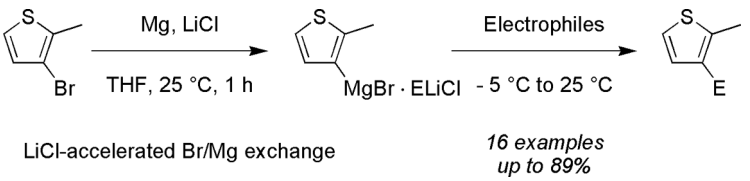
GRAPHICAL ABSTRACT



Abstract *Lithium chloride was found to accelerate formation of the Grignard reagent from inactive 3-bromo-2-methylthiophene (**1**) and commercial magnesium metal. Based on this finding, a convenient and potentially scalable preparation of ethyl 2-methylthiophene-3-carboxylate (**3**) was achieved. In addition, this process has been found to provide a new, general approach to 3-substituted 2-methylthiophenes.*

Keywords Activator; 3-bromo-2-methylthiophene; Grignard reagent; lithium chloride

INTRODUCTION

Thiophenes serve as the central pharmacophore in drug discovery and their bioisosteric replacement of a benzene ring is widely accepted as a powerful strategy to improve biological activity and pharmacodynamic and pharmacokinetic properties.[1] Therefore, use of thiophenes as building blocks undoubtedly continues to receive much attention in the pharmaceutical industry.

In the course of our program for development of a new and convenient method for preparation of 3-substituted 2-methylthiophenes, we reported a safe and efficient process for preparation of ethyl 2-methylthiophene-3-carboxylate (**3**).[2] This process relies on the LiCl-catalyzed halogen–metal exchange reaction of 3-bromo-2-methylthiophene (**1**) with *i*-PrMgCl, wherein the highly reactive 3-(2-methylthienyl)magnesium chloride

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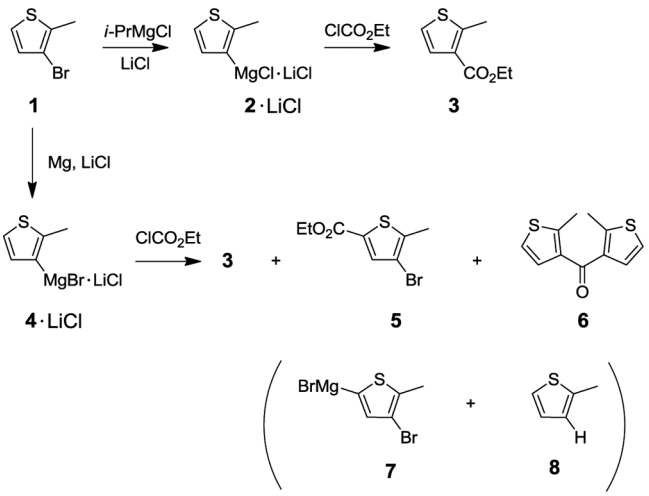


Scheme 1. Synthesis of **3** via Grignard reagents **2** or **4**.

LiCl complex (**2**·LiCl) was generated, and has successfully been applied to the 5-kg input-scale production of **3** at a yield of 63% and a purity of 91% by high-performance liquid chromatography (HPLC). As a logical extension, we were interested in application of the process to preparation of 3-substituted 2-methylthiophenes. Herein, we are pleased to report a more efficient procedure for the preparation of **4**·LiCl and the scope and limitations of this methodology.

RESULTS AND DISCUSSION

Scalability of our process was limited by the cost and volume efficiency of a commercial Grignard solution, consisting of *i*-PrMgCl in tetrahydrofuran (THF). Poor reactivity of **1**, however, had hampered the use of the traditional method utilizing Mg metal.[2,3] Nevertheless, we persisted in screening for an activator of Mg metal because there seemed to be no alternative solution, and we were gratified to find that LiCl itself could accelerate the formation of **4** from **1** and commercial Mg metal. Thus, by using 0.1 molar equivalent of LiCl, formation of the Grignard reagent was immediately initiated at room temperature and conversion was greater than 80% complete within 1 h of addition of **1**. Based on these findings, we additionally examined whether 0.1 molar equivalent of TurboGrignard reagent accelerated the formation and observed that the catalytic reagent had virtually the same effect as LiCl (data not shown). From a viewpoint of cost of the goods, we chose the use of LiCl for further investigation. In the context of Knochel protocols, the use of diisobutylaluminiumhydride (DIBAL) has usually been applied for the formation of TurboGrignard reagents with Mg metal, and potential of LiCl as the activator has not been reported. Few literature precedents drove us to confirm the performance of LiCl.[4] As shown in Table 1, the rate of formation was slightly improved with increases in LiCl loading, and 1.5 molar equivalents of LiCl led to the maximum conversion of 88% within 0.5 h. The trap experiments with ethyl chloroformate gave the

Table 1. Effect of LiCl on formation of **4** and **3**

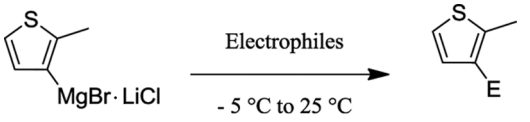
Entry	Amount of LiCl (mol eq.)	Conversion (%) 30 min 4[a]:1	Conversion (%) 60 min 4[a]:1	Product composition (area%) 3[b]:5:6
1	0.1	67:33	83:17	75 (62):19:1.7
2	0.5	80:20	87:13	78 (66):17:0.3
3	1.0	84:16	88:12	80 (68):15:0.2
4	1.5	88:12	88:12	81 (66):15:0.1

[a]Determined by HPLC analysis after conversion into **8**.
[b]Isolated yields (%) are given in parentheses.

expected product **3** accompanied by by-product **5** in 15 to 19 area% yields, which reveals formation of the more stable magnesiated species **7** in the reaction mixture. This not only would explain the observed incompleteness of the conversion of **1** to **4** but also implies that LiCl might suppress the formation of **7**. The remarkable acceleration observed with LiCl shows this process to be reliable. To demonstrate its robustness, we used LiCl to successfully implement a 300-g input-scale synthesis of **3** with a yield of 64% after vacuum distillation.

With the successful results in hand, we next investigated the scope of the process by introduction of various functional groups at C-3 of **4** (Table 2). The Grignard

Table 2. Synthesis of functionalized thiophenes **3** or **9** by the reaction of **4** · LiCl with various electrophiles



4 · LiCl **3** or **9**

Entry	Electrophile	E	Product	Yield[a] (%)
1	PhCHO	CH(OH)Ph	**9a**	76
2	*t*-BuCHO	CH(OH)Bu-*t*	**9b**	57
3	*i*-PrCHO	CH(OH)Pr-*i*	**9c**	73
4	DMF	CHO	**9d**	68
5	$MeSO_2SMe$	SMe	**9e**	56
6	I_2	I	**9f**	86
7	PhCH=NTs	PhCHNHTs	**9g**	82
8	TsCN	CN	**9h**	37
9	Boc_2O	CO_2Bu-*t*	**9i**	83
10	CO_2	CO_2H	**9j**	66
11	EtOCOCN	CO_2Et	**3**	55
12	Me_2NCOCl	$CONMe_2$	**9k**	38
13	PhCOPh	PhC(OH)Ph	**9l**	72
14	PhCOMe	PhC(OH)Me	**9m**	50
15	MeCOPr-*i*	MeC(OH)Pr-*i*	**9n**	89

[a]Isolated yield after column chromatography.

stock solution was prepared using 1.5 molar equivalents of LiCl on a 30-mmol scale and could be stored at room temperature for several days without any significant decomposition. Despite of much latitude of LiCl loadings, we chose the use of 1.5 molar equivalents of LiCl as a precaution. All electrophiles were added at −5 °C and the reaction mixtures were allowed to warm to room temperature to bring the reactions to completion. As expected, a large array of electrophiles was tolerated, especially carbonyl functional groups such as ketones or aldehydes (entries 1–3 and 13–15), resulting in relatively good yields. In addition, the hindered electrophiles (entries 2, 13, and 15) reacted with good to excellent yields. These data are thought to provide a new method for preparation of 3-substituted 2-methylthiophenes.

In summary, on the basis of the findings that LiCl accelerated the formation of Grignard reagents from inactive **1** and commercial Mg metal, we achieved a convenient and potentially scalable preparation of **3**. The process has been applied to the synthesis of 3-substituted 2-methylthiophenes and was found to be compatible with various functional groups. The underlying mechanism of the LiCl acceleration will be reported in due course.

EXPERIMENTAL

All reagents and solvents were commercially available and were used without further purification. The ^{1}H NMR spectra were recorded by a Bruker Avance III spectrometer operating at 400 MHz in $CDCl_3$ at 25 °C with tetramethylsilane (TMS) as the internal standard. The data are reported as follows: chemical shift in ppm (δ), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), and coupling constant (Hz). Liquid chromatography/mass spectrometry (LC/MS) data were obtained on an Agilent 1200RRLC/6140 SQ system. Gas chromatography (GC) data were obtained on an Agilent Technologies 7890A GC system coupled to a 5975C VLMSD mass spectrometer with a 7683B series injector. High-resolution mass spectra (HRMS) were obtained from a Bruker Daltonics Apex III 7.0 Tesla FTMS. Infrared (IR) spectra were recorded as a thin film on sodium chloride plates or as dilute chloroform solutions using a Shimadzu Prestige-21 instrument. The following systems were used for quantitative HPLC analysis: HPLC detector, Waters 2489 UV/visible detector, HPLC column, Capcellpak C_{18} MGII column (3.0 μM, 20 × 2.0 mm, Shiseido) at 40 °C. The flow rate of the mobile phase was 0.4 ml/min, and detection was performed at 254 nm.

Demonstration Batch on a 300-g Input Scale

A three-necked, 3-L, round-bottomed flask equipped with a reflux condenser was charged with magnesium turnings (50.3 g, 2.07 mol, >99.5% purity; Wako Pure Chemical Industries, Japan), lithium chloride (87.7 g, 2.07 mol, >99% purity; Wako Pure Chemical Industries, Japan), and THF (310 ml) at 25 °C. To this mixture, one-tenth of a solution of 3-bromo-2-methylthiophene (312.3 g, ca. 1.38 mol) in THF (620 ml) was added at 25 °C. After the transient exotherm subsided, the remaining solution was added dropwise to the mixture at such a rate that gentle refluxing was maintained. After the addition was complete, the reaction mixture was stirred for an additional 1 h at room temperature, at which time HPLC analysis indicated

that 8.6% of **1** was left. The mixture was cooled to −20 °C, and then ethyl chloroformate (197 ml, 2.07 mol) was added dropwise to the mixture over 40 min at such a rate that the internal temperature was below 0 °C during the addition. The mixture was stirred for an additional 2 h at 0 °C and then quenched with 2 M hydrochloric acid (1000 ml). The resulting mixture was stirred for 30 min and extracted with *n*-heptane (1000 ml). The organic layers were washed with H_2O (800 ml) and brine (800 ml) and dried over anhydrous sodium sulfate. After evaporation of the solvents, the residue was purified by distillation under reduced pressure to afford compound **3**[2] (168.6 g, yield 64%, purity 93% by HPLC) as a pale yellow oil. Bp 90–111 °C (6 mmHg).

Preparation of a Stock Solution of 4

A three-necked flask equipped with a reflux condenser was charged with magnesium turnings (1.09 g, 45 mmol, >99.5% purity; Wako Pure Chemical Industries, Japan), lithium chloride (1.91 g, 45 mmol, >99% purity; Wako Pure Chemical Industries, Japan), and THF (5 ml) at 25 °C. To this solution, one-tenth of a solution of 3-bromo-2-methylthiophene (5.33 g, 30 mmol) in THF (10 ml) was added at 25 °C. After the transient exotherm subsided, the remaining solution was added dropwise to the mixture at such a rate that gentle refluxing was maintained. After the addition was complete, the reaction mixture was stirred for an additional 1 h at room temperature. The yield and the concentration of the Grignard solution were calculated to be 84% and 1.25 M, respectively, by a standard titration method.[5]

Representative Procedure for Preparation of 9l

A solution of benzophenone (182 mg, 1 mmol) in THF (0.2 ml) was added dropwise to the stock solution described previously (0.8 ml, 1.25 M) over 10 min at −5 °C under a nitrogen atmosphere. The reaction mixture was allowed to warm to room temperature and stirring was continued for an additional 2 h. Then, the reaction was quenched with saturated. aqueous NH_4Cl (2 ml) and extracted with *n*-heptane (2 ml × 2). The combined organic layers were washed with brine and dried over Na_2SO_4. After evaporation of the solvents, the residue was purified by preparative TLC (PE/EA = 10/1) to give 202 mg of **9l** as white solids (yield 72%). Mp 61–63 °C. ^{1}H NMR δ 7.43–7.21 (m, 10H), 6.89 (d, J = 5.3 Hz, 1H), 6.44 (d, J = 5.3 Hz, 1H), 2.79 (s, 1H), 2.15 (s, 3H). FT-IR (film): 3473.80, 3057.17, 3026.31, 2954.95, 2920.23 cm^{-1}. MS (ESI$^+$) m/z: 280, HRMS (ESI$^+$) m/z calcd. for $C_{18}H_{16}NaOS$: 303.0820; found: 303.0820.

1-(2-Methylthiophen-3-yl)phenylmethanol (9a)

Yield 76%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.28 (m, 4H), 7.28–7.21 (m, 1H), 6.99 (d, J = 5.2 Hz, 1H), 6.89 (d, J = 5.2 Hz, 1H), 5.88 (s, 1H), 2.43 (s, 3H), 2.24 (br s, 1H). FT-IR (film): 3383.14, 3061.03, 2918.30 cm^{-1}. MS (ESI$^+$) m/z: 187 [M-OH], HRMS (ESI$^+$) m/z calcd. for $C_{12}H_{11}S$: 187.0581 [M-OH]; found: 187.0580.

2,2-Dimethyl-1-(2-methylthiophen-3-yl)propan-1-ol (9b)

Yield 57%; mp 35–37 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, J = 0.8 Hz, 2H), 4.50 (s, 1H), 2.40 (s, 3H), 1.72 (br s, 1H), 0.95 (s, 9H). FT-IR (film): 3387.00,

2954.95, 2906.73 cm^{-1}. MS (ESI^+) m/z: 167 [M-OH], HRMS (ESI^+) m/z calcd. for $C_{10}H_{15}S$: 167.0894 [M-OH]; found: 167.0890.

2-Methyl-1-(2-methylthiophen-3-yl)propan-1-ol (9c)

Yield 73%; ^1H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, $J = 5.2$ Hz, 1H), 6.98 (d, $J = 5.2$ Hz, 1H), 4.40 (d, $J = 8.0$ Hz, 1H), 2.41 (s, 3H), 2.03–1.86 (m, 1H), 1.73 (br s, 1H), 1.07 (d, $J = 6.6$ Hz, 3H), 0.76 (d, $J = 6.8$ Hz, 3H). FT-IR (film): 3385.07, 2956.87, 2870.08 cm^{-1}. MS (ESI^+) m/z: 153 [M-OH], HRMS (ESI^+) m/z calcd. for $C_9H_{14}NaOS$: 193.0663; found: 193.0660.

2-Methylthiophene-3-carbaldehyde (9d)

Yield 68%; ^1H NMR δ 10.04 (s, 1H), 7.38 (d, $J = 5.3$ Hz, 1H), 7.06 (d, $J = 5.3$ Hz, 1H), 2.79 (s, 3H). IR (film): 2924.09, 2831.50, 2736.99, 1674.21 cm^{-1}. MS (EI^+) m/z: 126, HRMS (EI^+) m/z calcd. for C_6H_6OS: 126.0139; found: 126.0137.

2-Methyl-3-(methylthio)thiophene (9e)

Yield 56%; ^1H NMR δ 7.07 (d, $J = 5.3$ Hz, 1H), 6.96 (d, $J = 5.3$ Hz, 1H), 2.47 (s, 3H), 2.36 (s, 3H). IR (film): 2922.16, 1614.42 cm^{-1}. MS (EI^+) m/z: 144, HRMS (EI^+) m/z calcd. for $C_6H_8S_2$: 144.0067; found: 144.0065.

3-Iodo-2-methylthiophene (9f)

Yield 86%; ^1H NMR δ 7.07 (d, $J = 5.3$ Hz, 1H), 6.96 (d, $J = 5.3$ Hz, 1H), 2.43 (s, 3H). IR (film): 2920.23, 2856.58, 1438.90 cm^{-1}. MS (EI^+) m/z: 223, HRMS (EI^+) m/z calcd. for C_5H_5IS: 223.9157; found: 223.9157.

4-Methyl-*N*-((2-methylthiophen-3-yl)(phenyl)methyl)benzenesulfonamide (9g)

Yield 82%; mp 136–138 °C. ^1H NMR δ 7.52 (d, $J = 8.3$ Hz, 2H), 7.28–7.16 (m, 5H), 7.12 (d, $J = 8.0$ Hz, 2H), 6.85 (d, $J = 5.3$ Hz, 1H), 6.57 (d, $J = 5.3$ Hz, 1H), 5.65 (d, $J = 7.0$ Hz, 1H), 5.11 (d, $J = 7.0$ Hz, 1H), 2.37 (s, 3H), 2.22 (s, 3H). IR (film): 3439.08, 3271.27, 2918.30, 1323.17, 1157.29 cm^{-1}. MS (ESI^+) m/z: 380 [M + Na], HRMS (EI^+) m/z calcd. for $C_{19}H_{19}NNaO_2S_2$: 380.0755; found: 380.0759.

2-Methylthiophene-3-carbonitrile (9h)

Yield 37%; ^1H NMR δ 7.06 (d, $J = 5.4$ Hz, 1H), 7.03 (d, $J = 5.4$ Hz, 1H), 2.58 (s, 3H). IR (film): 3115.04, 2924.09, 2223.92 cm^{-1}. MS (EI^+) m/z: 123, HRMS (EI^+) m/z calcd. for C_6H_5NS: 123.0143; found: 123.0143.

tert-Butyl 2-methylthiophene-3-carboxylate (9i)

Yield 83%; ^{1}H NMR δ 7.27 (d, $J = 5.4$ Hz, 1H), 6.87 (d, $J = 5.4$ Hz, 1H), 2.63 (s, 3H), 1.50 (s, 9H). IR (film): 3001.24, 2929.87, 1707.00 cm^{-1}. MS (EI$^+$) m/z: 198, HRMS (EI$^+$) m/z calcd. for $C_{10}H_{14}O_2S$: 198.0715; found: 198.0717.

2-Methylthiophene-3-carboxylic Acid (9j)

Yield 66%; mp 112–115 °C. ^{1}H NMR δ 7.45 (d, $J = 5.4$ Hz, 1H), 7.00 (d, $J = 5.4$ Hz, 1H), 2.77 (s, 3H). IR (film): 3122.75, 2922.16, 2619.33, 2536.39, 1676.14, 1533.41, 1282.66 cm^{-1}. MS (ESI$^+$) m/z: 142, HRMS (ESI$^+$) m/z calcd. for $C_6H_5O_2S$: 141.0010; found: 141.0016.

N,N,2-Trimethylthiophene-3-carboxamide (9k)

Yield 38%; ^{1}H NMR δ 7.00 (d, $J = 5.2$ Hz, 1H), 6.84 (d, $J = 5.2$ Hz, 1H), 2.95 (d, $J = 59.1$ Hz, 6H), 2.40 (s, 3H). IR (film): 2922.16, 2682.36, 1633.71 cm^{-1}. MS (ESI$^+$) m/z: 169, HRMS (ESI$^+$) m/z calcd. for $C_8H_{11}NNaOS$: 192.0459; found: 192.0459.

1-(2-Methylthiophen-3-yl)-1-phenylethanol (9m)

Yield 50%; ^{1}H NMR δ 7.40–7.34 (m, 2H), 7.34–7.27 (m, 2H), 7.25–7.20 (m, 1H), 7.09 (d, $J = 5.3$ Hz, 1H), 7.00 (d, $J = 5.3$ Hz, 1H), 2.14 (s, 4H), 1.92 (s, 3H). IR (film): 3450.65, 2974.23, 2924.09 cm^{-1}. MS (ESI$^+$) m/z: 200 [M-OH], HRMS (ESI$^+$) m/z calcd. for $C_{13}H_{14}NaOS$: 241.0663; found: 241.0659.

3-Methyl-2-(2-methylthiophen-3-yl)butan-2-ol (9n)

Yield 89%; ^{1}H NMR δ 6.92 (d, $J = 5.4$ Hz, 1H), 6.85 (d, $J = 5.4$ Hz, 1H), 2.56 (s, 3H), 2.10 (hept, $J = 6.8$ Hz, 1H), 1.74 (br s, 1H), 1.51 (s, 3H), 0.88 (dd, $J = 14.3$, 6.8 Hz, 6H). IR (film): 3471.87, 2968.45, 2933.73 cm^{-1}. MS (ESI$^+$) m/z: 167 [M-OH], HRMS (ESI$^+$) m/z calcd. for $C_{10}H_{15}S$: 167.0894; found: 167.0896.

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