Practical Preparation of Ethyl 2-Methylthiophene-3-carboxylate

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A safe and efficient process for the preparation of ethyl 2-methylthiophene-3-carboxylate (5) was devised. This process provides several advantages over the precedents, involving operational simplicity, avoidance of the use of strong bases such as *n*-butyllithium and application of noncryogenic conditions, and enabled to prepare 5 in 52% overall yield from commercially available 2-methylthiophene on a multikilogram scale.

Key words 2-methylthiophene-3-carboxylic acid ester; TurboGrignard; practical preparation

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 activities and pharmacodynamic and pharmacokinetic properties.[1)] Therefore, use of thiophenes as building blocks undoubtedly continues to receive much attention in the pharmaceutical industry.

In connection with an ongoing program, we needed kilogram quantities of 2-methylthiophene-3-carboxylic acid (**1**) and its esters as starting raw materials. A medicinal research-based route was based on C-2 methylation[2—4)] of dianion of commercially available 3-thiophenecarboxylic acid (**2**). However, because of both the expense of the reagent **2** and the use of more than 2 eq of *n*-butyllithium at low temperature, this route is far from ideal for large-scale preparation of these raw materials. Among several precedent methods for preparation of the corresponding acid or esters, the Grignard approach is thought to be a straightforward solution. In this note, we describe a practical synthesis of 2-methylthiophene-3-carboxylic acid ethyl ester, capitalizing on the LiCl-mediated halogen–magnesium exchange reactions.

This synthesis began with 2-methylthiophene, which was converted into 3-bromo-2-methylthiophene (**3**) according to literature methods.[5)] As for preparation of the Grignard reagent from **3**, the original work of Steinkopf and Jacob[6—8)] involved treatment of **3** with magnesium by an entrained method, followed by coupling with carbon dioxide. However, all our attempts failed when using an array of the usual activators such as iodine and 1,2-dibromoethane, which was consistent with the findings of Rieke.[9,10)] In recent years, there have been several publications regarding the LiCl-mediated halogen–magnesium exchange reactions (TurboGrignard reagents) of 3-bromothiophenes, and therefore we turned our attention to this technology.[11)] Exchange reaction of **3** with 1.5 eq of *i*-PrMgCl/LiCl in tetrahydrofuran (THF) reached a maximum conversion of 94% after 3 h at reflux, while reaching plateaus of 81% and 50% of the conversions after 5 h at 40 °C and room temperature, respectively. The ratios were determined by quantitative HPLC analysis of reaction aliquots after quenching with an excess of aqueous ammonium chloride. Extensive survey of other inexpensive Grignard reagents including EtMgBr and *i*-PrMgBr provided poor conversions (20—45%), illustrating the superiority of TurboGrignard. Conveniently, similar acceleration was observed when addition of LiCl to a THF solution of **3** was followed by treatment with *i*-PrMgCl.[12)]

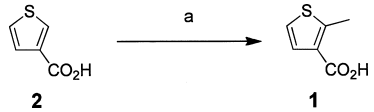
With the successful conversion of **3** into the corresponding Grignard reagent **4** in hand, several electrophiles were examined for installation of an ethyl ester group, and ethyl chloroformate was found to be the choice of electrophile in terms of cost and efficacy. It should be noted that the use of inexpensive diethyl carbonate gave a decreased yield (70%) accompanied by formation of symmetrical ketone **6** (3%).

The initial scale-up runs indicated that arbitrary, rapid temperature rise in this step would cause safety concerns about larger scale reactions. After further investigation, thermal events could be controlled by adjusting the rate of addition of ethyl chloroformate, maintaining the internal temperature below 0 °C. A demonstration batch was performed with 4.6 kg of **3**. Isopropylmagnesium chloride solution was added to **3** in the presence of LiCl for 1.5 h at ambient temperature, and then the mixture was gradually warmed to 60 °C for 1.5 h and the temperature was kept for 3 h, at which time HPLC analysis indicated that 7.9% of starting material **3** was left in the reaction mixture. Ethyl chloroformate in THF solution was added to the mixture in a linear manner for 4 h at −4 °C. Isolation by vacuum distillation gave **1** in 63% yield with 91% HPLC purity.

We devised a safe and efficient process for the preparation of ethyl 2-methylthiophene-3-carboxylate. Our work provides several advantages over the precedents, involving operational simplicity, avoidance of the use of strong bases such as *n*-butyllithium and application of noncryogenic conditions, and the process enabled us to prepare **5** in 52% overall yield from commercially available 2-methylthiophene on a multikilogram scale.

Experimental

General All reagents and solvents were commercially available and were used without further purifications. The ^{1}H- and ^{13}C-NMR spectra were recorded by a Varian-400MR spectrometer operating at 400 MHz in $CDCl_3$ at 25 °C with tetramethylsilane as an 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 singlet, m=multiplet), and coupling constant (Hz). The mass spectra were obtained using a Waters ACQUITY® SQD instrument. The following systems were used for quantitative HPLC analysis: HPLC detector, Waters 2489 UV/Visible Detector, HPLC



2 **1**

Reagents and conditions: (a) LDA, MeI, THF, −78 °C.

Chart 1

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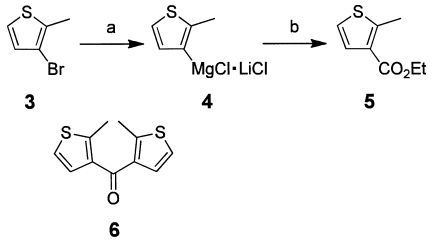

Reagents and conditions: (a) *i*-PrMgCl, LiCl, THF, reflux; (b) $ClCO_2Et$, THF, −5 °C.
Chart 2

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 the detection was performed at 254 nm.

3-Bromo-2-methylthiophene (3)[13] A three-necked 3 l round-bottom flask was charged with *N*-bromosuccinimide (355.8 g, 2.0 mol) and AcOH (500 ml). A solution of 2-methylthiophene (98.2 g, 1.0 mol) in AcOH (100 ml) was added dropwise to the suspension at room temperature for 55 min, and the mixture was stirred for an additional 5 h. The resulting mixture was poured into a mixture of *n*-heptane (500 ml) and water (500 ml) and the layers were separated. The organic layer was washed with 1 M sodium hydroxide (500 ml) and brine (500 ml) successively, and dried over anhydrous sodium sulfate. Filtration and evaporation gave 3,5-dibromo-2-methylthiophene with 92% HPLC purity (260.6 g, yield 92%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 2.33 (3H s), 6.85 (1H, s). ^{13}C-NMR (101 MHz, $CDCl_3$) δ: 14.8, 108.5, 108.7, 131.9, 136.0. MS *m*/*z*: 255 $(M+H)^+$, 99. The crude product was used in the next reaction without further purification.

A four-necked 2 l round-bottomed flask was charged with magnesium turnings (27.2 g, 1.12 mol) and tetrahydrofuran (200 ml). To the suspension, a tenth part of a solution of 3,5-dibromo-2-methylthiophene (249.5 g, *ca.* 0.899 mol) in tetrahydrofuran (550 ml) was added over 10 min at room temperature. After an exothermic reaction subsided, the remainder of the solution was added dropwise at such a rate that gentle reflux was maintained. After the addition was complete, the reaction mixture was heated at reflux for an additional 2 h. The resulting mixture was cooled to 0 °C. Water (60 ml) was added dropwise to the mixture over 20 min and 2 M hydrochloric acid was added until the mixture became clear. The biphase mixture was extracted with *n*-heptane (600 ml) and the organic layer was washed with brine (600 ml) and dried over anhydrous sodium sulfate. After solvents were removed *in vacuo*, the residue was purified by distillation under reduced pressure to afford compound **3** (148.6 g, yield 90%, purity 97% by HPLC) as a colorless oil. bp 50 °C (5 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 2.40 (3H, s), 6.89 (1H, d, J=5.4 Hz), 7.07 (1H, d, J=5.4 Hz). ^{13}C-NMR (101 MHz, $CDCl_3$) δ: 14.6, 109.4, 122.7, 129.9, 134.1. MS *m*/*z*: 200 $(M+Na)^+$, 177 $(M+H)^+$, 99. In practice, crude **3** is allowed to be used in the next reaction without further purifications.

Ethyl 2-Methyl-thiophene-3-carboxylate (5)[14] A 100 l glass-lined reactor was charged with 3-bromo-2-methylthiophene **3** (88% HPLC purity, 4.67 kg, *ca.* 23.3 mol), lithium chloride (1.66 kg, 39.2 mol, >99% purity, Wako Pure Chemical Industries, Japan), and tetrahydrofuran (7.0 l) at room temperature. Isopropylmagnesium chloride (19.6 l, 39.2 mol, 2 M solution in tetrahydrofuran, Aldrich, U.S.A.) was added dropwise over 1.5 h at such a rate that the internal temperature was maintained below 30 °C during the addition. The mixture was warmed to 60 °C over 2 h and stirred for an additional 3 h, at which time HPLC analysis indicated that 7.9% of **3** was left. The mixture was cooled below −5 °C, and then ethyl chloroformate (4.26 kg, 39.2 mol) was added dropwise to the mixture over 4 h at such a rate that the internal temperature was maintained below −2 °C during the addition. The mixture was stirred for an additional 2 h at −3 to 5 °C and then quenched with 2 M hydrochloric acid (18 l). The resulting mixture was stirred for 1 h and extracted with *n*-heptane (18 l). The organic layers were washed with brine (18 l) and dried over anhydrous sodium sulfate (300 g). After evaporation of the solvents, the residue was purified by distillation under reduced pressure to afford compound **5** (3.11 kg, yield 63%, purity 91% by HPLC) as a pale yellow oil. bp 90—111 °C (6 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 1.36 (3H, t, J=7.1 Hz), 2.74 (3H, s), 4.31 (2H, q, J=7.1 Hz), 6.97 (1H, d, J=5.4 Hz), 7.39 (1H, d, J=5.4 Hz). ^{13}C-NMR (101 MHz, $CDCl_3$) δ: 14.4, 15.4, 60.2, 120.8, 128.4, 129.2, 149.1, 163.7. MS *m*/*z*: 171 $(M+H)^+$, 142, 99.

References and Notes

1) For a recent review, see; Matsuoka H., Ohta M., *Farumashia*, **46**, 215—222 (2010).
2) The method has been most often applied in recent years, see this and the following two references; Knight D. W., Nott A. P., *Tetrahedron Lett.*, **21**, 5051—5054 (1980).
3) Oi S., Nagaya H., Inatomi N., Nakao M., Yukimasa H., U.S. Patent 5840917 (1997) [*Chem. Abstr.*, **126**, 317493 (1997)].
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5) Steinkopf W., *Jusust. Liebigs. Ann. Chem.*, **513**, 281—294 (1934).
6) Gaertner reported another Grignard reaction approach, whereby **5** was given in 72% yield from 2-chloromethylthiophene, see Gaertner R., *J. Am. Chem. Soc.*, **73**, 3934—3937 (1951).
7) However, the reaction required delicate operations, including use of a cyclic reactor, to maintain highly diluted conditions and volatile ether as solvent, which seemed to be unsuitable for large-scale preparation of **5**, see Campaigne E., Yokley O. E., *J. Org. Chem.*, **28**, 914—917 (1963).
8) Steinkopf W., Jacob H., *Jusust. Liebigs. Ann. Chem.*, **515**, 273—283 (1935).
9) Rieke R. D., Kim S.-H., Wu X., *J. Org. Chem.*, **62**, 6921—6927 (1997).
10) Very recently, an AstraZeneca group also reported difficulty in preparation of 3-thienyl Grignard reagents by an entrained method and found that the Grignard exchange reaction with *i*-PrMgCl worked well, see Alcaraz M.-L., Atkinson S., Cornwall P., Foster A. C., Gill D. M., Humphries L. A., Keegan P. S., Kemp R., Merifield E., Nixon R. A., Noble A. J., O'Beirne D., Patel Z. M., Perkins J., Rowan P., Sadler P., Singleton J. T., Tornos J., Watts A. J., Woodland I. A., *Org. Process Res. Dev.*, **9**, 555—569 (2005).
11) For a recent review, see Piller F. M., Metzger A., Schade M. A., Haag B. A., Gavryushin A., Knochel P., *Chem. Eur. J.*, **15**, 7192—7202 (2009).
12) To our best knowledge, while many examples of LiCl-mediated direct insertion of Mg into aromatic bromides have been reported, few examples featuring the *in situ* preparation of TurboGrignard reagents have been reported, see Hauk D., Lang S., Murso A., *Org. Process Res. Dev.*, **10**, 733—738 (2006) and references therein. The *in situ* preparation method described here seemed to be more convenient than the method for pre-preparation of TurboGrignard reagent.
13) Hallberg A., Liljefors S., Pedaja P., *Synth. Commun.*, **11**, 25—28 (1981).
14) Chatterjee P., Murphy P. J., Pepe R., Shaw M., *J. Chem. Soc., Perkin Trans. 1*, **17**, 2403—2405 (1994).