Selective metallation of thiophene and thiazole rings with magnesium amide base

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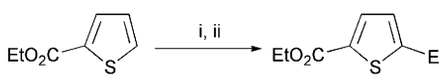
Selective hydrogen–metal exchange reaction of thiophene and thiazole proceeded smoothly with magnesium amide base ($^{i}Pr_2NMgCl$) under mild conditions.

Hydrogen–metal exchange reaction of aromatic and heteroaromatic rings such as directed *ortho* metallation or direct metallation has been developed as one of the major tools of organic synthesis.[1] Various strong bases such as alkyllithiums or lithium dialkylamides have been used for hydrogen–metal exchange of aromatics. However, organolithium compounds show high reactivity toward electrophilic groups and the use of organolithium compounds as metallating reagents has unavoidable limitations. For example, electrophilic directing groups often react with the nucleophilic bases or with the aryllithium intermediates. Directed *ortho* lithiation, therefore, usually requires low temperatures such as −78 °C or lower. Besides, directed *ortho* lithiations of aromatics bearing an ester functionality have only proceeded in bulky esters such as neopentyl or isopropyl esters with less nucleophilic metallating reagents.[2]

On the other hand, organomagnesium compounds have been used at relatively higher temperatures such as 0 °C or room temperature. Magnesium amide bases such as Hauser bases (R_2NMgX) and magnesium diamides are known, but their uses in directed *ortho* magnesiation have barely been explored. In 1989, Eaton reported directed *ortho* magnesiation of both methyl benzoate and *N*,*N*-diethylbenzamide with Hauser bases ($^{i}Pr_2NMgBr$ or TMPMgBr, TMP = 2,2,6,6-tetramethylpiperidino) or magnesium diamides ($(^{i}Pr_2N)_2Mg$ or TMP_2Mg).[3] In 1995, Schlecker extended this methodology and reported regioselective magnesiation of pyridine derivatives.[4] In a study of the scope and limitations of this methodology we reported the regioselective magnesiation of 1-substituted indoles using magnesium amide bases.[5] Now we report the chemoselective magnesiation of thiophene and thiazole derivatives using (diisopropylamino)magnesium chloride ($^{i}Pr_2NMgCl$).

Results and discussion

Initially, the metallation of ethyl thiophene-2-carboxylate **1** with $^{i}Pr_2NMgCl$, which was prepared from $^{i}Pr_2NH$ and BuMgCl, was investigated. The results are summarized in Scheme 1 and Table 1. When two mole equivalents of $^{i}Pr_2NMgCl$ for **1** were used, the metallation proceeded smoothly at room temperature within 10 min and the arylmagnesium intermediates thus prepared were treated with electrophiles to give **2a**–**c** without nucleophilic attack of $^{i}Pr_2NMgCl$ or the arylmagnesium intermediate at the ethoxycarbonyl group. Hydrogen–magnesium exchange reaction of ethyl thiophene-2-carboxylate with $^{i}Pr_2NMgCl$ is considered to proceed at the 5-position of the thiophene ring.[6] Similarly, the metallation of ethyl thiophene-3-carboxylate **3a** proceeded to give 2,3-disubstituted thiophenes **4a**,**b** with metallation at the 2-position selectively (Scheme 2, Table 2). Reaction of unsubstituted thiophene **3b** proceeded to give monosubstituted thiophenes



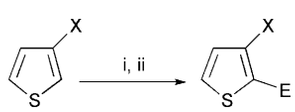
1 **2a-c**

Scheme 1 *Reagents and conditions*: i, $^{i}Pr_2NMgCl$, THF, rt; ii, Electrophile, THF, rt.

Table 1 Magnesiation of ethyl thiophene-2-carboxylate **1**

$^{i}Pr_2NMgCl$ (mol equiv.)	Reaction time	Electrophile	E	Yield (%)[a]
1.0	1 h	I_2	I	21 (73)
1.0	24 h	I_2	I	0 (90)
2.0	10 min	I_2	I	77
2.0	30 min	I_2	I	60
2.0	1 h	I_2	I	52
2.0	24 h	I_2	I	0
2.0	10 min	NFP[b]	CHO	52
2.0	10 min	PhCHO	CH(OH)Ph	60

[a] Values in parentheses are recovery yields of **1**. [b] NFP = *N*-formylpiperidine.



3a,b **4a-e**

Scheme 2 *Reagents and conditions*: i, $^{i}Pr_2NMgCl$, THF, rt; ii, Electrophile, THF, rt.

Table 2 Magnesiation of thiophene derivatives

Substituent X	Reaction time	Electrophile	E	Yield (%)
CO_2Et	10 min	I_2	I	94
CO_2Et	10 min	NFP	CHO	0
CO_2Et	10 min	PhCHO	CH(OH)Ph	79
H	24 h	I_2	I	52
H	24 h	NFP	CHO	84
H	24 h	PhCHO	CH(OH)Ph	93

4c–**e** (Scheme 2, Table 2). Though two mole equivalents of $^{i}Pr_2NMgCl$ for **3b** were used, a disubstituted thiophene was not detected. These results show that hydrogen–magnesium exchange reaction of thiophene derivatives with $^{i}Pr_2NMgCl$ proceeds selectively.

We turned our attention to the metallation of azoles and then that of thiazole **5** was investigated (Scheme 3, Table 3). Though thiazole **5** has three different hydrogens, the regioselective

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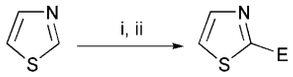

5 6a-c

Scheme 3 *Reagents and conditions*: i, $^{i}Pr_2NMgCl$, THF, rt, 24 h; ii, Electrophile, THF, rt.

Table 3 Magnesiation of thiazole

Electrophile	E	Yield (%)
I_2	I	88
NFP	CHO	51
PhCHO	CH(OH)Ph	52

metallation proceeded at the 2-position at room temperature to give 2-substituted thiazoles **6a**–**c**.

In summary, selective metallation of thiophene and thiazole derivatives including those bearing an ester functionality was realized with $^{i}Pr_2NMgCl$ as a base. In the hydrogen–metal exchange, magnesium amide bases which can be used near ambient temperature may have great potential to replace the corresponding lithium bases for heterocyclic systems.

Experimental

THF was distilled from sodium–benzophenone ketyl before use. $^{i}Pr_2NH$ was distilled from CaH_2 before use. BuMgCl was titrated using Ph_2Te_2 before use. Mps were determined on a Yazawa micro melting-point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian Gemini-2000 (300 MHz) spectrometer for samples in $CDCl_3$ solution and chemical shifts are reported in δ (ppm)-values relative to $SiMe_4$ (TMS) as internal standard. Mass spectra and high-resolution mass spectra were recorded on a JMX-DX303 and a JMX-AX500 mass spectrometer. Elemental analyses were carried out on a Yanaco CHN CORDER MT-5 apparatus.

General procedure A

Under an argon atmosphere, commercial BuMgCl in THF was added to the mixture of $^{i}Pr_2NH$ and dry THF at rt and the mixture was stirred at rt for 24 h. A heteroaromatic compound was added to the mixture at rt and the mixture was stirred at rt. I_2 in dry THF was added at rt and the mixture was stirred at rt for 1 h, diluted with saturated aq. $Na_2S_2O_3$ (20 cm^3) and saturated aq. NH_4Cl (30 cm^3), and extracted with $CHCl_3$ (50 cm^3 × 3). The organic layer was dried over dry $MgSO_4$. The solvent was removed, and the residue was purified by silica gel column chromatography. The solvent was removed to give a pure product.

General procedure B

Under an argon atmosphere, commercial BuMgCl in THF was added to a mixture of $^{i}Pr_2NH$ and dry THF at rt and the mixture was stirred at rt for 24 h. A heteroaromatic compound was added to the mixture at rt and the mixture was stirred at rt. An electrophile was added at rt and the mixture was stirred at rt, diluted with saturated aq. NH_4Cl (50 cm^3), and extracted with $CHCl_3$ (50 cm^3 × 3). The organic layer was dried over dry $MgSO_4$. The solvent was removed, and the residue was purified by silica gel column chromatography. The solvent was removed to give a pure product.

Ethyl 5-iodothiophene-2-carboxylate 2a

According to general procedure A, ethyl thiophene-2-carboxylate (165 mg, 1.06 mmol) was added to a mixture of BuMgCl in THF (0.60 mol dm^{-3}; 3.30 cm^3, 1.98 mmol), $^{i}Pr_2NH$ (0.30 cm^3, 2.14 mmol) and dry THF (10 cm^3) and the mixture was stirred at rt for 10 min. I_2 (638 mg, 2.51 mmol) in dry THF (5 cm^3) was added and the mixture was stirred at rt for 1 h before being purified by silica gel column chromatography, using *n*-hexane–AcOEt (5:1) as solvent. The solvent was removed to give **2a** (231 mg, 77%) as a *colorless oil* (Found: C, 29.89; H, 2.50; I, 44.62; S, 11.53. $C_7H_7IO_2S$ requires C, 29.80; H, 2.50; I, 44.99; S, 11.36%); δ_H 1.36 (3H, t, *J* 7.2 Hz), 4.33 (2H, q, *J* 7.2 Hz), 7.25 (1H, d, *J* 3.9 Hz), 7.43 (1H, d, *J* 3.9 Hz); *m*/*z* (EI) 282 (M$^+$).

Ethyl 5-formylthiophene-2-carboxylate 2b

According to general procedure B, ethyl thiophene-2-carboxylate (159 mg, 1.02 mmol) was added to a mixture of BuMgCl in THF (0.60 mol dm^{-3}; 3.30 cm^3, 1.98 mmol), $^{i}Pr_2NH$ (0.30 cm^3, 2.14 mmol) and dry THF (10 cm^3) and the mixture was stirred at rt for 10 min. 1-Formylpiperidine (NFP) (288 mg, 2.54 mmol) was added and the mixture was stirred at rt for 30 h before being purified by silica gel column chromatography, using *n*-hexane–AcOEt (5:1) as solvent. The solvent was removed to give **2b** (99.8 mg, 52%) as *colorless prisms*, mp 57–58 °C (Found: C, 52.24; H, 4.30; S, 17.53. $C_8H_8O_3S$ requires C, 52.16; H, 4.38; S, 17.40%); δ_H 1.40 (3H, t, *J* 7.2 Hz), 4.40 (2H, q, *J* 7.2 Hz), 7.75 (1H, d, *J* 4.2 Hz), 7.84 (1H, d, *J* 3.9 Hz), 9.98 (1H, s); *m*/*z* (EI) 184 (M$^+$).

Ethyl 5-[hydroxy(phenyl)methyl]thiophene-2-carboxylate 2c

According to general procedure B, ethyl thiophene-2-carboxylate (228 mg, 1.46 mmol) was added to a mixture of BuMgCl in THF (0.83 mol dm^{-3}; 3.60 cm^3, 2.99 mmol), $^{i}Pr_2NH$ (0.46 cm^3, 3.28 mmol) and dry THF (10 cm^3) and the mixture was stirred at rt for 10 min. Benzaldehyde (241 mg, 2.27 mmol) was added and the mixture was stirred at rt for 23 h before being purified by silica gel column chromatography, using *n*-hexane–AcOEt (2:1) as solvent. The solvent was removed to give **2c** (228 mg, 60%) as a *yellow*, *viscous oil*, δ_H 1.34 (3H, t, *J* 7.1 Hz), 4.30 (2H, q, *J* 7.1 Hz), 6.00 (1H, s), 6.86 (1H, d, *J* 3.8 Hz), 7.32–7.44 (6H, m), 7.83 (1H, d, *J* 3.8 Hz); *m*/*z* (EI) 262 (M$^+$) (Found: M$^+$, 262.0665. $C_{14}H_{14}O_3S$ requires *M*, 262.0663).

Ethyl 2-iodothiophene-3-carboxylate 4a

According to general procedure A, ethyl thiophene-3-carboxylate (158 mg, 1.01 mmol) was added to a mixture of BuMgCl in THF (0.90 mol dm^{-3}; 2.22 cm^3, 1.98 mmol), $^{i}Pr_2NH$ (0.30 cm^3, 2.14 mmol) and dry THF (10 cm^3) and the mixture was stirred at rt for 10 min. I_2 (666 mg, 2.62 mmol) in dry THF (5 cm^3) was added and the mixture was stirred at rt for 1 h before being purified by silica gel column chromatography, using *n*-hexane–AcOEt (5:1) as solvent. The solvent was removed to give **4a** (270 mg, 94%) as a *colorless oil* (Found: C, 30.15; H, 2.45; I, 44.63; S, 11.84. $C_7H_7IO_2S$ requires C, 29.80; H, 2.50; I, 44.99; S, 11.36%); δ_H 1.39 (3H, t, *J* 7.2 Hz), 4.34 (2H, q, *J* 7.2 Hz), 7.34 (1H, d, *J* 5.9 Hz), 7.41 (1H, d, *J* 5.9 Hz); *m*/*z* (EI) 282 (M$^+$).

Ethyl 2-[hydroxy(phenyl)methyl]thiophene-3-carboxylate 4b

According to general procedure B, ethyl thiophene-3-carboxylate (161 mg, 1.03 mmol) was added to a mixture of BuMgCl in THF (0.60 mol dm^{-3}; 3.30 cm^3, 1.98 mmol), $^{i}Pr_2NH$ (0.30 cm^3, 2.14 mmol) and dry THF (10 cm^3) and the mixture was stirred at rt for 10 min. Benzaldehyde (265 mg, 2.50 mmol) was added and the mixture was stirred at rt for 24 h before being purified by silica gel column chromatography, using *n*-hexane–AcOEt (3:1) as solvent. The solvent was removed to give **4b** (213 mg, 79%) as a *yellow*, *viscous oil*, δ_H 1.33 (3H, t, *J* 7.1 Hz), 4.31 (2H, q, *J* 7.1 Hz), 4.76 (1H, br s), 6.42 (1H, s), 7.10 (1H, d, *J* 5.4 Hz), 7.30–7.49 (6H, m); *m*/*z* (EI) 262 (M$^+$) (Found: M$^+$, 262.0684. $C_{14}H_{14}O_3S$ requires *M*, 262.0663).

2-Iodothiophene 4c

According to general procedure A, thiophene (127 mg, 1.51 mmol) was added to a mixture of BuMgCl in THF (0.61 mol dm^{-3}; 5.00 cm^3, 3.05 mmol), $^iPr_2NH$ (0.44 cm^3, 3.14 mmol) and dry THF (12 cm^3) and the mixture was stirred at rt for 24 h. I_2 (981 mg, 3.87 mmol) in dry THF (5 cm^3) was added and the mixture was stirred at rt for 1 h before being purified by silica gel column chromatography, using *n*-hexane as solvent. The solvent was removed to give **4c** (165 mg, 52%) as a *colorless oil* (Found: C, 22.56; H, 1.52; I, 60.36. C_4H_3IS requires C, 22.87; H, 1.44; I, 60.42%); δ_H 6.81 (1H, dd, *J* 3.6, 5.4 Hz), 7.25 (1H, dd, *J* 1.5, 3.6 Hz), 7.34 (1H, dd, *J* 1.5, 5.4 Hz); *m*/*z* (EI) 210 (M^+).

Thiophene-2-carbaldehyde 4d

According to general procedure B, thiophene (127 mg, 1.51 mmol) was added to a mixture of BuMgCl in THF (0.60 mol dm^{-3}; 5.00 cm^3, 3.00 mmol), $^iPr_2NH$ (0.46 cm^3, 3.28 mmol) and dry THF (12 cm^3) and the mixture was stirred at rt for 24 h. NFP (440 mg, 3.89 mmol) was added and the mixture was stirred at rt for 27 h before being purified by silica gel column chromatography, using *n*-hexane–AcOEt (5:1) as solvent. The solvent was removed to give **4d** (143 mg, 84%) as a *colorless oil*, δ_H 7.23 (1H, dd, *J* 3.9, 4.8 Hz), 7.77–7.81 (2H, m), 9.96 (1H, s); *m*/*z* (EI) 112 (M^+) (Found: M^+, 111.9949. C_5H_4OS requires *M*, 111.9983).

Phenyl(2-thienyl)methanol 4e

According to general procedure B, thiophene (133 mg, 1.58 mmol) was added to a mixture of BuMgCl in THF (0.60 mol dm^{-3}; 5.00 cm^3, 3.00 mmol), $^iPr_2NH$ (0.46 cm^3, 3.28 mmol) and dry THF (12 cm^3) and the mixture was stirred at rt for 24 h. Benzaldehyde (404 mg, 3.80 mmol) was added and the mixture was stirred at rt for 24 h before being purified by silica gel column chromatography, using *n*-hexane–AcOEt (5:1) as solvent. The solvent was removed to give **4e** (279 mg, 93%) as *colorless prisms*, mp 47 °C (Found: C, 69.19; H, 5.46; S, 16.99. $C_{11}H_{10}OS$ requires C, 69.44; H, 5.30; S, 16.85%); δ_H 2.40 (1H, br s), 6.09 (1H, s), 6.82–6.96 (2H, m), 7.25–7.47 (6H, m); *m*/*z* (EI) 190 (M^+).

2-Iodothiazole 6a

According to general procedure A, thiazole (130 mg, 1.53 mmol) was added to a mixture of BuMgCl in THF (0.83 mol dm^{-3}; 3.60 cm^3, 2.99 mmol), $^iPr_2NH$ (0.46 cm^3, 3.28 mmol) and dry THF (12 cm^3) and the mixture was stirred at rt for 24 h. I_2 (992 mg, 3.91 mmol) in dry THF (5 cm^3) was added and the mixture was stirred at rt for 1 h before being purified by silica gel column chromatography, using *n*-hexane–AcOEt (5:1) as solvent. The solvent was removed to give **6a** (284 mg, 88%) as a *yellow*, *viscous oil*, δ_H 7.34–7.35 (1H, m), 7.61–7.62 (1H, m); *m*/*z* (EI) 211 (M^+) (Found: M^+, 210.8995. C_3H_2INS requires *M*, 210.8951).

Thiazole-2-carbaldehyde 6b

According to general procedure B, thiazole (127 mg, 1.49 mmol) was added to a mixture of BuMgCl in THF (0.83 mol dm^{-3}; 3.60 cm^3, 2.99 mmol), $^iPr_2NH$ (0.46 cm^3, 3.28 mmol) and dry THF (12 cm^3) and the mixture was stirred at rt for 24 h. NFP (255 mg, 2.25 mmol) was added and the mixture was stirred at rt for 24 h before being purified by silica gel column chromatography, using *n*-hexane–AcOEt (5:1) as solvent. The solvent was removed to give **6b** (86.4 mg, 51%) as a colorless oil, δ_H 7.79 (1H, d, *J* 2.7 Hz), 8.15 (1H, d, *J* 2.7 Hz), 10.05 (1H, s); *m*/*z* (EI) 113 (M^+) (Found: M^+, 112.9935. C_4H_3NOS requires *M*, 112.9921).

Phenyl(thiazol-2-yl)methanol 6c

According to general procedure B, thiazole (124 mg, 1.47 mmol) was added to a mixture of BuMgCl in THF (0.83 mol dm^{-3}; 3.60 cm^3, 2.99 mmol), $^iPr_2NH$ (0.46 cm^3, 3.28 mmol) and dry THF (12 cm^3) and the mixture was stirred at rt for 24 h. Benzaldehyde (244 mg, 2.33 mmol) was added and the mixture was stirred at rt for 27 h before being purified by silica gel column chromatography, using *n*-hexane–AcOEt (1:1) as solvent. The solvent was removed to give **6c** (146 mg, 52%) as *colorless prisms*, mp 109 °C (Found: C, 62.98; H, 4.91; N, 7.28; S, 16.59. $C_{10}H_9NOS$ requires C, 62.80; H, 4.74; N, 7.32; S, 16.76%); δ_H 3.55 (1H, s), 6.08 (1H, s), 7.30–7.50 (6H, m), 7.34 (1H, d, *J* 3.3 Hz); *m*/*z* (EI) 191 (M^+).

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