A Convenient Synthesis of 4(5)-Alkylacyl-1*H*-imidazoles from 4(5)-Imidazolecarboxaldehyde

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Abstract: A convenient synthesis of 4(5)-acyl-1*H*-imidazoles from 4(5)-imidazolecarboxaldehyde without *N*-protecting group is described. 4(5)-Cyanoimidazole could be synthesized from commercially available 4(5)-imidazolecarboxaldehyde in one-pot. Treatment of 4(5)-cyanoimidazole with various alkylmagnesium bromides followed by addition of aqueous sulfuric acid afforded 4(5)-acyl-1*H*-imidazoles in good yield.

Key words: Grignard reaction, ketones, nitriles, alkylations

The imidazole ring is an important structure in biological and industrial chemistry; 4(5)-acyl-1*H*-imidazoles are useful intermediates in organic synthesis. For example, several compounds of the HIV-1 protease inhibitor,[1] intermediates of the P-450 enzyme aromatase inhibitor,[2] and an adreno receptor agonist[3] contain 4(5)-acylimidazoles. Anticardiac, cerebral, and tissular ischemic active compounds are also prepared from acylimidazoles.[4]

Although 4(5)-acyl-1*H*-imidazoles **3** are simple compounds, a convenient synthesis of acylimidazoles **3** is still not available because of the impossibility of direct Friedel–Crafts acylation of imidazoles.[5] Therefore, other strategies must be employed to synthesize *C*-acylimidazoles. However, these have the following drawbacks:

1. The synthesis of acylimidazoles **3** can be achieved by the metalation chemistry. This generally requires that the 2-position is suitably blocked by a protecting group or by an unreactive substituent in addition to N-protection.[6]

2. Acylimidazoles **3** can also be prepared from 4-aminoisoxazoles, however, these are not commercially available.[7]

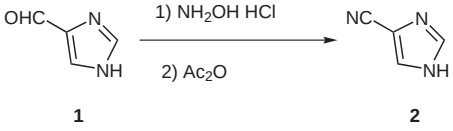
3. Recently the solid-phase synthesis of 4-substituted imidazoles was described,[8] which is not acceptable for large-scale manufacture. It was not satisfactory with respect to yield either.

4. The synthesis of acylimidazoles **3** from 4(5)-imidazolecarboxaldehyde (**1**) has been reported.[4] But, this route involves four steps; N-protection, alkylation, oxidation, and N-deprotection. In the case of alkylacylimidazoles, especially, alkylation or oxidation of imidazole derivatives suffers from low yield. In the oxidation step, manganese dioxide, which changes to industrial waste, is used.

We have therefore investigated a convenient synthesis of 4(5)-acyl-1*H*-imidazoles **3** from commercially available starting materials taking into account cost, practicability, preparation time, simplicity of purification and waste disposal. We now report that acylimidazoles **3** can be efficiently prepared from 4(5)-imidazolecarboxaldehyde (**1**) without N-protection (Equations 1 and 2).

First, the synthesis of 4(5)-cyanoimidazole (**2**) was examined. Few examples of the synthesis of **2** from other starting materials have been reported. Although 4(5)-cyanoimidazole (**2**) can be prepared from 4(5)-trifluoromethylimidazole, the use of trifluomethyl group makes this process costly.[9] The synthesis of **2** from 4(5)-imidazolecarboxylate has also been reported, however, the process consists of two steps and the reaction time of the first step is 1–7 days. Hence, this method is impractical for large-scale preparation.[10]

To explore a convenient synthesis of cyanoimidazole **2**, it was started with the commercially available 4(5)-imidazolecarboxaldehyde (**1**). Cyanoimidazole **2** could be prepared from **1** in an one-pot reaction. A pyridine solution containing **1** and hydroxylamine hydrochloride was stirred at room temperature for 2 hours, then treated with acetic anhydride, and stirred again at 110 °C for 2 hours (Equation 1). After usual workup and recrystallization, cyanoimidazole **2** was obtained in 88% yield.[11]



1 **2**

Equation 1

Most investigations have demonstrated that imidazoles should be protected in their reaction with organometallic compounds. Therefore, we examined the reaction of **2** with triphenylmethyl chloride to protect the N-1 position in the next step (Scheme 1). The products were a mixture of N-1 protected and N-3 protected cyanoimidazole. The desired N-1 protected compound **4** was obtained in only 49% yield. As the N-1 protected product was obtained in low yield and this route was not advantageous, we tried a direct Grignard reaction of cyanoimidazole **2** (Equation 2). As a result, it was found that 1-[1*H*-imidazol-4(5)-yl]-2-methylpropan-1-one (**3a**) could be synthesized in 69% yield by using 2.2 equivalents of Grignard

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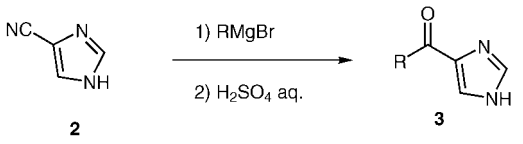
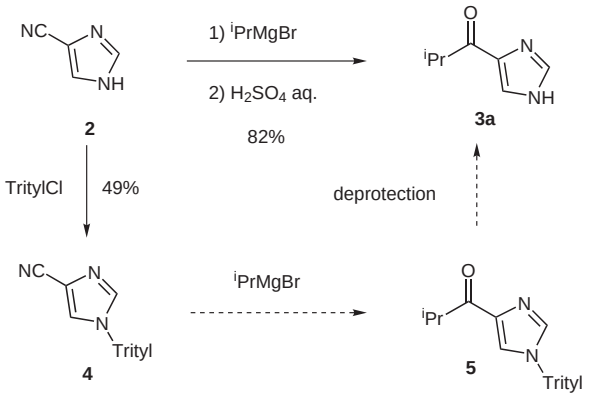
reagent. Moreover, the use of an excess of Grignard reagent (3 equiv) in this reaction successfully afforded **3a** in good yield. For example, when the Grignard reaction of cyanoimidazole **2** with isopropylmagnesium bromide (3 equiv) was carried out at room temperature for 3 hours, **3a** was obtained in a 82% yield (Scheme 1, Table 1). It was reported that the use of excess Grignard reagent in the reaction with nitrile compounds afforded amine products.[12] Interestingly, however, the alkylation of non-protected cyanoimidazole **2** with excess Grignard reagent takes place selectively to provide **3** in high yield.



2 **3**

Equation 2

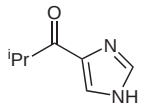
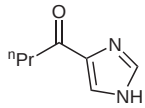
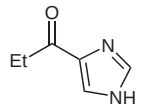
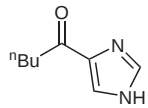
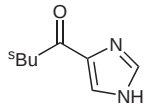
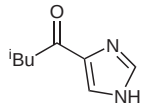
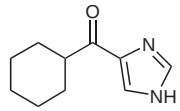


Scheme 1

Table 1 shows the results of the reaction using various alkylmagnesium bromides with cyanoimidazole **2**. The reaction with alkyl Grignard reagents such as *i*-Pr-, Pr-, Et-, Bu-, *s*-Bu-, *i*-Bu-, and *c*-C_6H_{12}MgBr proceeded smoothly to give the corresponding products **3** in good yields, respectively. This procedure allows for large-scale production without the need for oxidation by manganese dioxide and chromatographic purification.

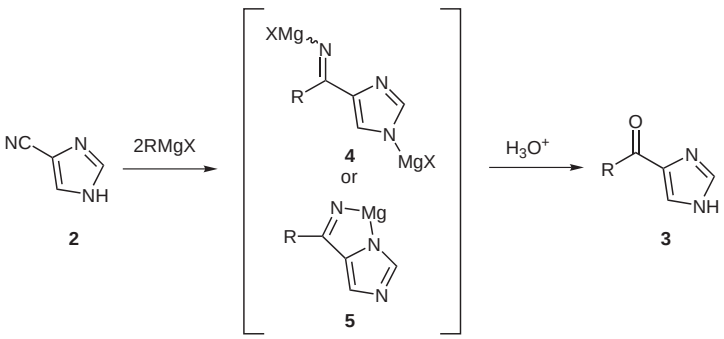
Although elucidation of the precise mechanism requires further detailed investigation, this reaction may be assumed to proceed via an intermediate of **4** or **5** as shown in Scheme 2.

Table 1 Conversion of 4(5)-Cyanoimidazole **2** to 4(5)-Acyl-1*H*-imidazoles **3**

Entry	Grignard Reagent	Product	Yield (%)[a]
1	*i*-PrMgBr	 **3a**	82
2	PrMgBr	 **3b**	83
3	EtMgBr	 **3c**	79
4	BuMgBr	 **3d**	96
5	*s*-BuMgBr	 **3e**	85
6	*i*-BuMgBr	 **3f**	90
7	*c*-C_6H_{12}MgBr	 **3g**	92

[a] Yield of isolated product.

In summary, we have found that acylimidazoles **3** could be synthesized in good yields using 3 equivalents of Grignard reagent without the troublesome processes of protec-



Scheme 2

tion and deprotection. Although most investigations have demonstrated that imidazoles were protected in the reaction of imidazoles with organometalic compounds,[6] this reaction does not need N-protection. We have developed a new process for the large-scale preparation of 4(5)-acyl-1*H*-imidazoles from 4(5)-imidazolecarboxaldehyde in good yield without using a protective group and purification by chromatography.

4(5)-Cyanoimidazole (2)

To a solution of 4(5)-imidazolecarboxaldehyde (**1**; 50 g, 0.52 mol) in pyridine (150 mL) was added hydroxylamine hydrochloride (40.5 g, 0.585 mol). After stirring the mixture for 2 h at r.t., the mixture was heated to 80 °C, and Ac_2O (92.3 mL, 0.978 mol) was added dropwise at 80–110 °C. The mixture was further stirred until the temperature reached r.t., and then the pH of the mixture was brought to 7.9 with 30% aq NaOH solution. EtOAc (380 mL) was added for extraction, and the aqueous layer was extracted with EtOAc (250 mL). The organic layers were combined, washed with brine (2 ×), and concentrated under reduced pressure. Toluene was added to the residue and the mixture was concentrated under reduced pressure (twice). The crystals formed were collected by filtration and washed with diisopropyl ether. The crystals were dried in vacuo (40 °C) to give **2**[9] (42.7 g, 88%).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.91 (s, 1 H), 8.10 (s, 1 H).

MS (EI): *m*/*z* = 93 (M^+·), 66 (M^+· – HCN).

1-[1*H*-imidazol-4(5)-yl]-2-methylpropan-1-one (3a); Typical Procedure

A solution of 4(5)-cyanoimdazole (**2**; 42.7 g, 0.458 mol) in THF (500 mL) was added dropwise over 30 min to a solution of 1.1 M of isopropylmagnesium bromide in THF (1.4 L, 1.47 mol) below 10 °C under N_2.[13] The mixture was stirred at r.t. for 3 h, H_2O (430 mL) and 10% aq H_2SO_4 (860 mL) were added dropwise, and the mixture was stirred at 30 min and then brought to pH 8 with 30% aq NaOH solution. After the organic layer was separated, the aqueous layer was extracted with EtOAc (2 × 300 mL). The organic layer was combined, and the mixture was washed with aq $NaHCO_3$ and brine, and concentrated under reduced pressure. The crystals formed were collected by filtration and washed with diisopropyl ether. The crystals were dried in vacuo (40 °C) to give **3a** (51.9 g, 82%).

1-[1*H*-imidazol-4(5)-yl]-2-methylpropan-1-one (3a); Large-Scale Procedure

To a solution of 4(5)-imidazolecarboxaldehyde (**1**; 635 g, 6.61 mol) in pyridine (1.85 kg) was added hydroxylamine hydrochloride (516.4 g, 7.43 mol). After stirring the mixture for 2 h at 27–43 °C, the solution was heated to 78 °C, and Ac_2O (1.27 kg, 12.4 mol) was added dropwise at 78–110 °C. The mixture was further stirred until r.t. was attained, and brought to pH 7.9 with 30% aq NaOH solution. EtOAc (4.3 kg) was added for extraction and the aqueous layer was extracted again with EtOAc (2.9 kg). The organic layers were combined, washed with brine (2 × 3.8 kg), and concentrated under reduced pressure. Toluene (1.0 kg) was added to the residue and the mixture was concentrated under reduced pressure (twice). The crystals formed were collected by filtration and washed with diisopropyl ether (1.86 kg). The crystals were dried in vacuo (40 °C) to give 4(5)-cyanoimidazole (**2**) (545.2 g, 89%).

A Grignard reagent was prepared from isopropyl bromide (2.31 kg, 18.8 mol), Mg (479 g, 19.7 mol), and I_2 (0.48 g, 1.88 mmol) in THF (15.9 kg). A solution of 4(5)-cyanoimdazole (**2**; 545 g, 5.85 mol) in THF (5.7 kg) was added dropwise over 35 min to the solution of isopropylmagnesium bromide in THF below 15 °C under N_2. The mixture was stirred at r.t. for 1 h. H_2O (100 mL) and 6.7% aq H_2SO_4 (16.4 kg) were added dropwise, and the mixture was stirred for 30 min and then brought to pH 8 with 30% aq NaOH solution. After the organic layer was separated, the aqueous layer was extracted with EtOAc (2 × 3.8 kg). The organic layers were combined, and the mixture was washed with aq $NaHCO_3$ (5.5 kg) and brine (5.5 kg), and concentrated under reduced pressure. The crystals formed were collected by filtration and washed with diisopropyl ether (4.8 kg). The crystals were dried in vacuo (40 °C) to give **3a** (631.7 g, 78%).

1-[1*H*-Imidazol-4(5)-yl]-2-methylpropan-1-one (3a)

Mp 106–108 °C.

IR (KBr): 1664 (C=O) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (d, *J* = 6.9 Hz, 6 H), 3.31–3.41 (m, 1 H), 7.81 (s, 1 H), 7.87 (s, 1 H), 11.39 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.9, 138.5, 135.9, 127.9, 36.7, 19.2.

MS (EI): *m*/*z* = 138 (M^+).

Anal. Calcd for $C_7H_{10}N_2O$: C, 60.85; H, 7.30; N, 20.28. Found: C, 60.83; H, 7.44; N, 20.21.

1-[1*H*-Imidazol-4(5)-yl]butan-1-one (3b)

Mp 121–124 °C.

IR (KBr): 1678 (C=O) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.4 Hz, 3 H), 1.60 (q, *J* = 7.3 Hz, 2 H), 3.34 (q, *J* = 7.1 Hz, 2 H), 7.77 (s, 1 H), 7.85 (s, 1 H), 11.35 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.9, 138.4, 137.0, 128.1, 40.9, 18.1, 13.8.

MS (EI): *m*/*z* = 138 (M^+).

Anal. Calcd for $C_7H_{10}N_2O$: C, 60.85; H, 7.30; N, 20.28. Found: C, 60.76; H, 7.58; N, 20.23.

1-[1*H*-Imidazol-4(5)-yl]propan-1-one (3c)

Mp 155–158 °C.

IR (KBr): 1660 (C=O) cm^{-1}.

^{1}H NMR (300MHz, $CDCl_3$): δ = 1.06 (t, *J* = 7.4 Hz, 3 H), 2.86 (q, *J* = 7.4 Hz, 2 H), 7.81 (s, 1 H), 7.84 (s, 1 H), 10.63 (br s, 1 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 196.0, 139.2, 138.2, 128.3, 33.0, 8.7.

MS (EI): *m*/*z* = 124 (M^+).

HRMS: *m*/*z* Calcd for $C_6H_8N_2O$ (M^+): 124.0637. Found: 124.0631.

1-[1*H*-Imidazol-4(5)-yl]pentan-1-one (3d)

Mp 119–121 °C.

IR (KBr): 1674 (C=O) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 (t, *J* = 7.3 Hz, 3 H), 1.35–1.47 (m, 2 H), 1.68–1.78 (m, 2 H), 2.86 (t, *J* = 7.0 Hz, 3 H), 7.79 (s, 1 H), 7.85 (s, 1 H), 11.33 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.9, 138.4, 136.4, 128.4, 38.8, 26.8, 22.4, 13.8.

MS (EI): *m*/*z* = 152 (M^+).

Anal. Calcd for $C_8H_{12}N_2O$: C, 63.13; H, 7.95; N, 18.41.Found: C, 62.97; H, 8.18; N, 18.56.

1-[1*H*-Imidazol-4(5)-yl]-2-methylbutan-1-one (3e)

Mp 102–104 °C.

IR (KBr): 1657 (C=O) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 7.4 Hz, 3 H), 1.22 (d, *J* = 6.9 Hz, 3 H), 1.47–1.61 (m, 1 H), 1.77–1.91 (m, 1 H), 3.17 (br s, 1 H), 7.81 (s, 1 H), 7.88 (s, 1 H), 11.65 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.6, 138.7, 136.0, 129.0, 43.7, 26.8, 17.0, 11.8.

MS (EI): *m*/*z* = 152 (M^+).

HRMS: *m*/*z* Calcd for $C_8H_{12}N_2O$ (M^+): 152.0950. Found: 152.0943.

1-[1*H*-Imidazol-4(5)-yl]-3-methylbutan-1-one (3f)
Mp 118–119 °C.

IR (KBr): 1672 (C=O) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (d, *J* = 6.7 Hz, 6 H), 2.23–2.37 (m, 1 H), 2.74 (d, *J* = 7.0 Hz, 2 H), 7.79 (s, 1 H), 7.88 (s, 1 H), 11.82 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.9, 138.5, 135.9, 127.9, 36.7, 19.2.

MS (EI): *m*/*z* = 152 (M^+).

Anal. Calcd for $C_8H_{12}N_2O$: C, 63.13; H, 7.95; N, 18.41. Found: C, 62.88; H, 8.12; N, 18.56.

Cyclohexyl[1*H*-imidazol-4(5)-yl]methanone (3g)[14]
Mp 177–178 °C.

IR (KBr): 1664 (C=O) cm^{-1}.

^{1}H NMR (300MHz, $CDCl_3$): δ = 1.20–1.92 (m, 10 H), 2.98 (br s, 1 H,), 7.77 (s, 1 H), 7.83 (s, 1 H), 10.76 (br s, 1 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 198.7, 139.4, 137.0, 128.2, 47.8, 30.5, 27.0, 26.7.

MS (EI): *m*/*z* = 178 (M^+).

Anal. Calcd for $C_{10}H_{14}N_2O$: C, 67.39; H, 7.92; N, 15.72. Found: C, 67.16; H, 8.20; N, 15.74.

Acknowledgments

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