JOC Article

Simple Method for the Preparation of Esters from Grignard Reagents and Alkyl 1-Imidazolecarboxylates

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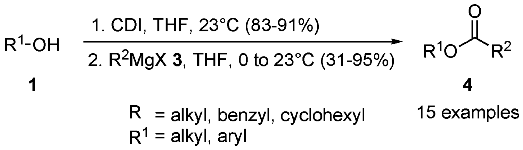

The reaction of Grignard reagents with alkyl imidazolecarboxylates, which were prepared from alcohols with carbonyl diimidazole, gave the corresponding esters in good to excellent yields. This method conveniently provides esters from alkyl halides and alcohols by C_1-carbon chain extension.

Introduction

Esters are invariably synthesized from the condensation reaction of an alcohol with the corresponding carboxylic acid. There are numerous methods for this transformation that are known and well-established.[1] During the course of our studies toward the synthesis of a variety of resorcylate natural products, we became interested in an alternative synthesis of esters from the alkoxycarboxylation reaction of Grignard reagents that were prepared from the corresponding alkyl halide.[2] We considered using alkyl chloroformates in this regard. However, such transformations have two major drawbacks. First, the synthesis of chloroformates from alcohols requires the handling of phosgene or bis(trichloromethyl) carbonate.[3] Additionally, chloroformates are inconvenient to handle and are usually prepared and directly allowed to react in situ.[3c] The reactions of chloroformates with alkynylmetallic reagents have been widely used to synthesize the corresponding 2,3-alkynyl esters.[4] Additionally, α-diazocarbonyl compounds have been metalated using Grignard reagents and subsequently allowed to react with chloroformates to produce α-diazocarbonyl-*β*-ketoesters.[5] However, there are few reports on the syntheses of esters from the reaction of chloroformates with alkyl and aryl Grignard reagents.[6] Such condensation reactions invariably provide the desired esters, only in low yields due to the concomitant formation of tertiary alcohols derived from the triple addition of the Grignard reagent.[6c] In these cases, yields of the esters were improved by converting the chloroformates to the corresponding acyl tributylphosphonium chlorides or pyrazole-1-carboxylates.[7] To the best of our knowledge, there is only one report on the addition of phenylmagnesium bromide to methyl 1-imidazolecarboxylate, which gave methyl benzoate in 51% yield.[8] This observation encouraged us to develop a simple two-step method for the preparation of esters from alcohols, Grignard reagents, and carbonyl diimidazole (CDI).

Results and Discussion

A range of 1-imidazolecarboxylates **2**, which were prepared by the reactions of primary and secondary alcohols **1** with CDI[9]

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[1] (a) Otera, J. *Esterification*; Wiley-VCH: Weinheim, Germany, 2003. (b) Larock, R. C. *Comprehensive Organic Transformations*; VCH: New York, 1989.

[2] (a) Schlingmann, G.; Milne, L.; Carter, G. T. *Tetrahedron* **2002**, *58*, 6825. (b) Schoental, R. *Adv. Cancer Res.* **1985**, *45*, 217. (c) Nozawa, K.; Nakajima, S. *J. Nat. Prod.* **1979**, *42*, 374 and references therin.

[3] (a) Holzinger, M.; Abraham, J.; Whelan, P.; Graupner, R.; Ley, L.; Hennrich, F.; Kappes, M.; Hirsch, A. *J. Am. Chem. Soc.* **2003**, *125*, 8566. (b) Pasquato, L.; Modena, G.; Cotarca, L.; Delogu, P.; Mantovani, S. *J. Org. Chem.* **2000**, *65*, 8224. (c) Cotaraca, L.; Delogu, P.; Nardelli, A.; Šunjić, V. *Synthesis* **1996**, 553.

[4] (a) Leung, L. T.; Leung, S. K.; Chiu, P. *Org. Lett.* **2005**, *7*, 5249. (b) Usuda, H.; Kuramochi, A.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2004**, *6*, 4387. (c) Taschner, M. J.; Rosen, T.; Heathcock, C. H. *Org. Synth.* **1986**, *7*, 108.

[5] Cuevas-Yañez, E.; Muchowski, J. M.; Cruz-Almanza, R. *Tetrahedron Lett.* **2004**, *45*, 2417.

[6] (a) Boudin, A.; Cerveau, G.; Chuit, C.; Corriu, R. J. P.; Reye, C. *Tetrahedron* **1989**, *45*, 171. (b) Nunomoto, S.; Yamashita, Y. *Nippon Kagaku Kaishi* **1979**, *11*, 1615 (c) Kurtman, A. I., *Zh. Obshch. Khim.* **1952**, *22*, 1385.

[7] (a) Maeda, H.; Takahashi, K.; Ohmori, H. *Tetrahedron* **1998**, *54*, 12233. (b) Kashima, C.; Tsuruoka, S.; Mizuhara, S. *Tetrahedron* **1998**, *54*, 14679. (c) Maeda, H.; Okamoto, J.; Ohmori, H. *Tetrahedron Lett.* **1996**, *37*, 5381.

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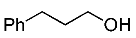
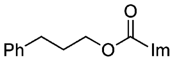
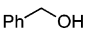
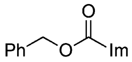
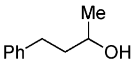
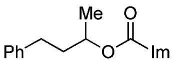
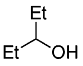
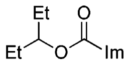
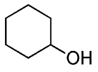
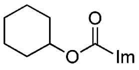
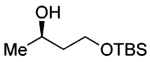
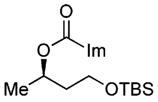
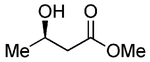
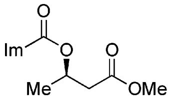
[9] (a) Bertolini, G.; Pavich, G.; Vergani, B. *J. Org. Chem.* **1998**, *63*, 6031. (b) Totleben, M. J.; Freeman, J. P.; Szuszkovicz, J. *J. Org. Chem.* **1997**, *62*, 7319. (c) Ohta, S.; Yamashita, M.; Nagai, N.; Kawasaki, I.; Maeda, K.; Miyano, Y. *Heterocycles* **1995**, *41*, 1683.

10.1021/jo060562m CCC: $33.50

TABLE 1. Synthesis of 1-Imidazolecarboxylates 2 from Alcohols 1 and CDI

Entry	Alcohol		Product		Yield (%)[a]
1		**1a**		**2a**	93
2		**1b**		**2b**	83
3		**1c**		**2c**	85
4		**1d**		**2d**	91
5		**1e**		**2e**	83
6		**1f**		**2f**	92
7		**1g**		**2g**	86

[a] All compounds were obtained analytically pure after aqueous work up. Im = 1-imidazolyl.

SCHEME 1. Synthesis of 1-Imidazolecarboxylates 2 from Alcohols 1 and their Reaction with Grignard Reagents 3 to Form Esters 4

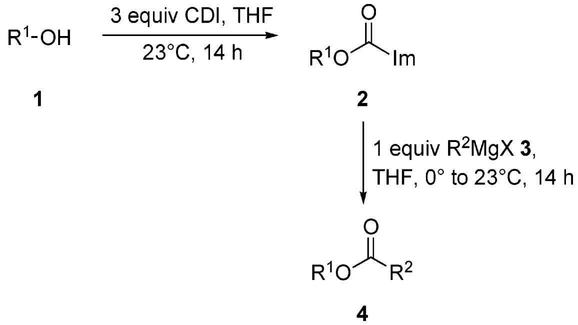
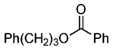
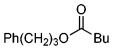
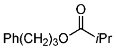
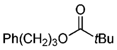
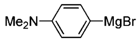
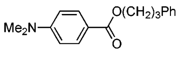
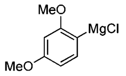
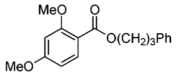
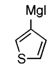
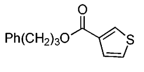
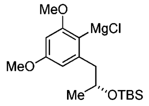
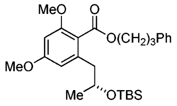
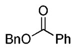
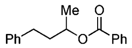
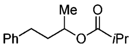
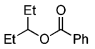
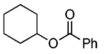
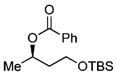
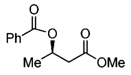


TABLE 2. Synthesis of Esters 4 by the Reaction of 1-Imidazolecarboxylates 2 with Grignard Reagents 3

Entry	1-imidazole-carboxylate	Grignard reagent		Ester		Yield (%)
1	**2a**	PhMgCl	**3a**		**4a**	95[a]
2	**2a**	BuMgCl	**3b**		**4b**	85
3	**2a**	*i*PrMgCl	**3c**		**4c**	96[a]
4	**2a**	*t*BuMgCl	**3d**		**4d**	94
5	**2a**		**3e**		**4e**	94[a]
6	**2a**		**3f**		**4f**	65
7	**2a**		**3g**		**4g**	80
8	**2a**		**3h**		**4h**	31
9	**2b**	PhMgCl	**3a**		**4i**	94[a]
10	**2c**	PhMgCl	**3a**		**4j**	92[a]
11	**2c**	*i*PrMgCl	**3c**		**4k**	86[a]
12	**2d**	PhMgCl	**3a**		**4l**	92[a]
13	**2e**	PhMgCl	**3a**		**4m**	95[a]
14	**2f**	PhMgCl	**3a**		**4n**	89
15	**2g**	PhMgCl	**3a**		**4o**	65

[a] After aqueous workup.

(3 equiv) in THF, were obtained as analytically pure compounds in good to excellent yields after aqueous workup (Table 1). The reaction of Grignard reagents **3** with the 1-imidazolecarboxylates **2** was optimized for the condensation of 1-imidazolecarboxylate **2a** with phenylmagnesium chloride (**3a**; Scheme 1). Superior yields of ester **4a** (95%) were obtained when the Grignard reagent **3a** was added to 1-imidazolecarboxylate **2a** at 0 °C, and the reaction mixture was subsequently warmed to 23 °C over 14 h. Phenylmagnesium chloride (**3a**) could even be added at room temperature to obtain ester **4a** in comparable yields. In contrast, the use of zinc- and lithium-centered organometallic reagents was unsatisfactory and gave little of the desired esters **4**.

The scope of the reaction with variation in the Grignard reagent was investigated. 1-Imidazolecarboxylate **2a** was allowed to react with a range of Grignard reagents **3a**−**3h** (Table 2). The reaction of **2a** with phenyl- (entry 1), electron-rich aryl- (entries 5 and 6), as well as heteroaryl Grignard reagents (entry 7) were successful and gave the desired esters **4a**, **4e**, **4f**, and **4g** in good to excellent yields. The required Grignard reagent **3h** was prepared from the corresponding aryl iodine through iodine/magnesium exchange under Knochel conditions.[10,11] The reaction of Grignard reagent **3h** with 1-imidazolecarboxylate **2a** gave ester **4h** in 31% yield (entry 8). The conversion of primary-, secondary-, and sterically demanding tertiary-alkyl Grignard reagents **3b**−**3d** also gave the esters **4b**−**4d** in good yields (entries 2−4). In contrast to these successes, the use of vinyl and allyl Grignard reagents gave complex intractable reaction mixtures.

A variation of the alcohol component was next examined (Table 2). The reaction of the benzyl derivative **2b** gave ester

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[10] The preparation of the Grignard reagent **3h** and the aryl iodine precursor from commercially available starting materials is described in the Supporting Information.

[11] (a) Krasovskiy, A.; Straub, B. F.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 159. (b) Graening, T.; Bette, V.; Neudörfl, J.; Lex, J.; Schmalz, H.-G. *Org. Lett.* **2005**, *7*, 4317. (c) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *45*, 4302. (d) Boymond, L.; Rottländer, M.; Cahiez, G.; Knochel, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 1701.

4i in 94% yield (entry 9). The reaction of the secondary 1-imidazolecarboxylates **2c**−**2g** with phenylmagnesium chloride (**3a**) gave the corresponding esters **4j** and **4l**−**4o** in good yields (entries 10 and 12−15). Although the reaction of 1-imidazolecarboxylate **2c** with *iso*-propylmagnesium chloride (**3c**) is sterically quite demanding, ester **4j** was obtained in 86% yield (entry 11). However, no conversion was observed with further increase in steric bulk with *tert*-butylmagnesium chloride (**3d**). Especially remarkable is the reaction of 1-imidazolecarboxylate **2g** to give ester **4o** (entry 15, 65%), a reaction in which E$_1$cb elimination to form methyl crotonate or addition to the methyl ester were not observed.

In summary, we have developed a simple two-step procedure to prepare esters from alcohols, CDI, and a Grignard reagent.

Experimental Section

3-Phenyl-1-propyl 1-Imidazolecarboxylate (2a).[9c] General Procedure for the Synthesis of 1-Imidazolecarboxylates 2. CDI (3.63 g, 22.4 mmol) was added with stirring to 3-phenyl-1-propanol (**1a**; 1.02 g 7.47 mmol) in dry THF (5.0 mL). After 14 h at 23 °C, the mixture was diluted with Et$_2$O (26 mL) and washed with H$_2$O (2 × 15 mL). The organic layer was dried (MgSO$_4$) and rotary evaporated to afford 1-imidazolecarboxylate **2a** (1.60 g, 93%) as a colorless oil: IR (neat) 1756, 1471, 1393, 1289, 1241, 1177 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.07−2.16 (m, 2H), 2.75 (t, J = 7.5 Hz, 2H), 4.40 (J = 6.5 Hz, 2H), 7.03 (s, 1H), 7.16−7.30 (m, 5H), 7.35 (s, 1H), 8.04 (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 29.5, 31.7, 67.3, 116.8, 126.0, 128.0, 128.3, 130.2, 136.8, 140.2, 148.3; LRMS (CI, NH$_3$) 231 (100%; (M + H)$^+$), 154 (4%), 118 (5%), 69 (12%). Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.12. Found: C, 67.82; H, 6.10; N, 12.15.

3-Phenyl-1-propyl Benzoate (4a).[12] General Procedure for the Formation of Esters 4. PhMgCl (**3a**; 0.37 mL, 0.74 mmol, 2 M in THF) was added dropwise with stirring to 1-imidazolecarboxylate **2a** (167 mg, 0.725 mmol) in dry THF (5.0 mL) at 0 °C. The reaction mixture was warmed to 23 °C over 14 h, poured on ice, and extracted with Et$_2$O (3 × 10 mL). The organic layers were combined, dried (MgSO$_4$), and rotary evaporated to afford ester **4a** (165 mg, 95%) as a colorless oil: IR (neat) 1719, 1452, 1380, 1115 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.04−2.13 (m, 2H), 2.77 (t, J = 7.6 Hz, 2H), 4.32 (t, J = 6.5 Hz, 2H), 7.18−7.29 (m, 5H), 7.39−7.44 (m, 2H), 7.52−7.56 (m, 1H), 7.99−8.02 (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 30.2, 32.2, 64.1, 125.9, 128.2, 128.3, 128.4, 129.4, 130.2, 132.8, 141.0, 166.5; LRMS (CI, NH$_3$) 258 (81%; (M + NH$_4$)$^+$), 231 (61%; (M + H)$^+$), 135 (40%), 118 (100%). Anal. Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.96; H, 6.65.

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Supporting Information Available: Specific experimental conditions, product characterization data, and copies of ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO060562M

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(12) Kwon, D. W.; Kim, Y. H. *J. Org. Chem.* **2002**, *67*, 9488.