Synlett S. Usami et al. Letter

Chelation-Based Homologation by Reaction of Organometallic Reagents with *O*-Alkyl *S*-Pyridin-2-yl Thiocarbonates: Synthesis of Esters from Grignard Reagents

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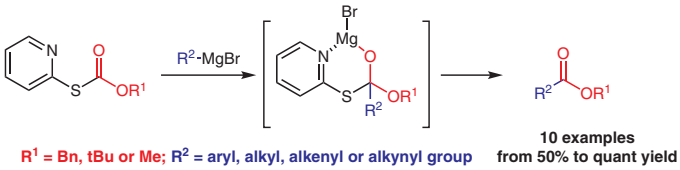
This paper is dedicated to the memory of Professor Teruaki Mukaiyama, a prominent scientist who made major contributions to the field.

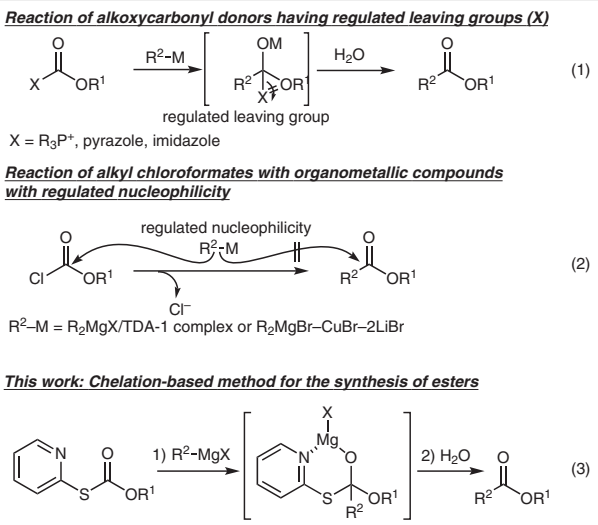


Received: 20.04.2019
Accepted after revision: 03.06.2019
Published online: 27.06.2019
DOI: 10.1055/s-0037-1611868; Art ID: st-2019-u0223-l

Abstract The one-carbon homologative esterification of Grignard reagents with *O*-alkyl *S*-pyridin-2-yl thiocarbonates has been explored. This one-step synthesis of esters from Grignard reagents is the first case to involve chelation-stabilized intermediates.

Key words alkyl pyridinyl thiocarbonates, Grignard reagents, esterification, one-step synthesis, homologation

One-carbon homologative esterification of organometallic compound, especially Grignard reagents, is an important transformation. This transformation is usually conducted by a two-step conversion through the reaction of a Grignard reagent with carbon dioxide to give a carboxylic acid, followed by esterification, because the reaction of a Grignard reagent with a carbonate derivative such as ethyl chloroformate, ethyl cyanoformate, or diethyl carbonate usually give a tertiary alcohol (three-to-one adduct) instead of an ester.[1,2] To eliminate this complexity, two categories of one-step method for the preparation of esters from Grignard reagents have been explored (Scheme 1). The first is the use of an alkoxycarbonyl donor having regulated leaving activity, such as an alkoxycarbonyl phosphonium salt,[3] a 1-(alkoxycarbonyl)pyrazole,[4] or a 1-(alkoxycarbonyl)imidazole,[5] to form a tetrahedral intermediate (Scheme 1, Equation 1). The other is the use of an alkyl chloroformate with an organometallic compound having a regulated nucleophilicity, such as a powdered Grignard reagent chelated with tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1)[6] or an organocopper reagent derived from a Grignard reagent,[7] to avoid overreaction of the ester product (Scheme 1, Equation 2). However, a chelation-based approach, as exemplified by Mukaiyama's 2-pyridyl thioesters[8] or Weinreb amides[9] in ketone syntheses, has rarely been investigated.[10] Here, we show that Grignard reagents react with *O*-alkyl *S*-pyridin-2-yl thiocarbonates to give one-carbon-homologated esters, probably via chelated intermediates (Scheme 1, Equation 3).



Scheme 1 Methods for the synthesis of esters from Grignard reagents

Acylating reagents **1**,[11a] **2**, and **3**[11a] were readily prepared from commercially available reagents (Scheme 2). Thus, *O*-benzyl *S*-pyridin-2-yl thiocarbonate (**1**) and the corresponding *O*-methyl derivative **2** were obtained by treatment of pyridine-2-thiol with the appropriate alkyl chloroformate in the presence of Et_3N, whereas the *O*-*tert*-

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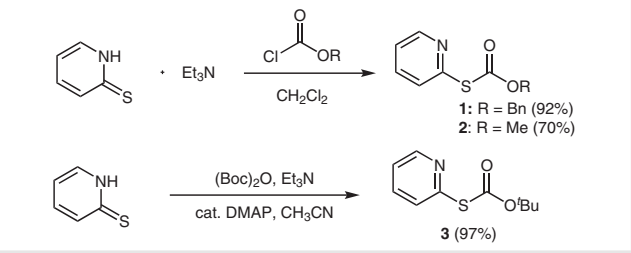
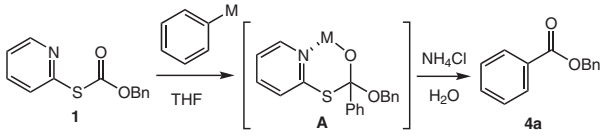
butyl derivative **3** was prepared in high yield from pyridine-2-thiol and $(Boc)_2O$ in the presence of Et_3N and a catalytic amount of DMAP.[12]



Scheme 2 Preparation of acylating reagents **1–3**

First, we examined the benzyloxycarbonylation of phenyl metal compounds by using thiocarbonate **1** (Table 1). Reaction of phenyllithium (**5**, 1.0 equiv) with **1** in THF at –78 °C gave benzyl benzoate (**4a**) in 25% yield, along with a 16% recovery of the acylating agent **1** (Table 1, entry 1). Interestingly, the use of the corresponding Grignard reagent **6a** afforded a much better yield (66%), probably due to formation of a more stable chelation intermediate **A**, although the reaction appeared to stop despite the presence of 15% of the remaining thiocarbonate **1** (entry 2). The reason for the deactivation of PhMgBr (**6a**) is unclear, but the formation of a 2:1 complex of adduct **A** with **6a** is a plausible explanation. The addition of Cu(I), which has a a high affinity for sulfur, inhibited the reaction (entry 3). Complete consumption of thiocarbonate **1** required two equivalents of PhMgBr (**6a**) at a low temperature, and these conditions afforded **4a** in high yield (88%; entry 4). Taking into account the dissociation of the putative complex, we examined several sets of conditions, and we finally found that mild heating (50 °C) was effective in providing **4a** in high yield (84%) without any recovery of **1** (entry 5).[13] In contrast, the use of the conventional acylating reagent benzyl chloroformate (**7**) resulted in a complex reaction that gave only a trace of **4a** (entry 6). Moreover, the Weinreb amide analogue **8** failed to react with **6a** and was recovered in 78% yield (entry 7).

Table 1 Reaction of Acylating Agent **1** with Phenyl Organometallic Compounds



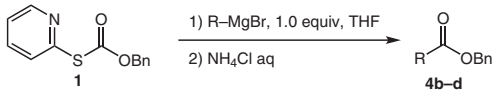
Entry	Conditions	Yield of **4a** (%)	Recovery of **1** (%)
1	PhLi (**5**) (1 equiv), –78 °C, 3.5 h	25	16
2	PhMgBr (**6a**) (1 equiv), –78 °C, 3 h	66	15
3	**6a** (1 equiv.), CuBr (1 equiv)	none	69
4	**6a** (2 equiv), –78 °C, 2 h	88	none
5	**6a** (1 equiv), 50 °C, 1 h	84	none
6	**6a** (1 equiv), $ClCO_2Bn$ (**7**, 1 equiv), 0 °C, 5 h	3	none
7	**6a** (1 equiv), $MeON(Me)CO_2Bn$ (**8**,1 equiv), 50 °C, 3 h	none	(78)[a]

[a] Acylating agent **8** was recovered.

Next, we examined the corresponding reactions of other Grignard reagents **6b–d** (Table 2). In all cases, reaction at room temperature was incomplete, with recovery of acylating agent **1**, whereas reaction at 50 °C afforded high yields of products **4b–d** without recovery of unreacted **1** (entries 1–6). Although the order of reactivity of the Grignard reagents **6b–d** at room temperature was **6b** (sp^3, 77%), **6c** (sp^2, 39%), and **6d** (sp, 0%), Grignard reagents **6b–d** all afforded satisfactory yields of the corresponding products **4b–d** at 50 °C. The use of $ClCO_2Bn$ (**7**) again afforded lower yields of products **4b–d** (entries 2, 3, 6: in parentheses).

Next, the reaction of Boc derivative **3** was examined (Table 3). The results were similar to those obtained with **1**, although the reactivity of **3** was slightly lower than that of **1**.

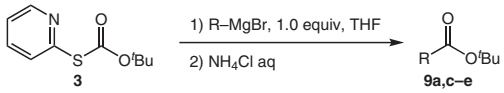
Table 2 Reaction of Thiocarbonate **1** with Various Grignard Reagents



Entry	RMgBr	Temp (°C)	Time (h)	Product	Yield (%)	Recovery of **1** (%)
1	EtMgBr (**6b**)	r.t.	15.5	**4b**	77	14
2		50 °C	1	**4b**	80 (0)[a]	–
3	(*E*)-PhCH=CHMgBr (**6c**)	r.t.	20	**4c**	39 (18)[a]	4
4		50 °C	1	**4c**	50	–
5	MeC≡CMgBr (**6d**)	r.t.	24	**4d**	–	69
6		50 °C	4	**4d**	74 (55)[a]	–

[a] Yield from reaction of RMgBr (**6**) with **7**.

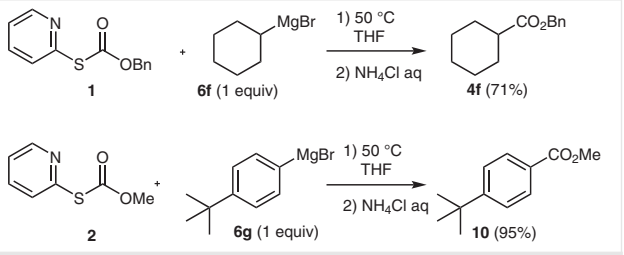
Table 3 Reaction of Acylating Agent **3** with Grignard Reagents



Entry	RMgBr	Temp (°C)	Time	Product	Yield (%)	Recovery of **3** (%)
1	PhMgBr (**6a**)	r.t.	20 h	**9a**	21	44
2		50 °C	19 h	**9a**	61	–
3	$Ph(CH_2)_2MgBr$ (**6e**)	r.t.	27 h	**9e**	78	14
4		50 °C	4 h	**9e**	79	–
5	(*E*)-PhCH=CHMgBr (**6c**)	r.t.	17 h	**9c**	18	57
6		50 °C	9 h	**9c**	62	–
7	MeC≡CMgBr (**6d**)	r.t.	1 week	**9d**	–	46
8		50 °C	2 days	**9d**	quant	–

Thus, the yields of esters **9a** and **9c–e** at room temperature were strongly associated with the s character of the Grignard reagent **6**, and the yield of **9e** (78%) was much higher than that of **9a** (21%), **9c** (18%), or **9d** (0%) (Table 3, entries 1, 3, 5, and 7). Gentle heating improved the yields of the ester products **9** (entries 2, 4, 6, and 8); in particular, **9d** was obtained in quantitative yield (entry 8).

Finally, two more reactions were conducted to illustrate the scope of the reaction (Scheme 3). Thus, the reaction of thiocarbonate **1** with the bulky reagent cyclohexylmagnesium bromide (**6f**), at 50 °C gave benzyl cyclohexanecarboxylate (**4f**) in 71% yield. A sterically less-hindered acylating agent could also be used: acylating agent **2** reacted with aromatic Grignard reagent **6g** at 50 °C without any difficulty to afford methyl 4-*tert*-butylbenzoate (**10**) in 95% yield.



Scheme 3 Illustrative scope of the alkoxycarbonylation of Grignard reagents

In conclusion, we have discovered a novel one-carbon homologation reaction of Grignard reagents via chelated intermediates. This method provides an alternative to conventional transformations of Grignard reagents into esters.

Funding Information

This work was supported by JSPSKAKENHI Grant Number 17K0821 (O.T.).

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611868.

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(12) Compound **3** was originally prepared in two steps by the reaction of phosgene with pyridine-2-thiol to give *S*,*S*-di-2-pyridyl dithiocarbonate, followed by treatment with $Cu(O^tBu)_2$.[11a] The present method provides an operationally simple one-step synthesis.

(13) **Benzyl Benzoate (4a); Typical Procedure**
A 1.0 M solution of PhMgBr (**5a**) in THF (98 mL, 98 mmol) was added to a stirred solution of **1** (24.1 mg, 98.2 μmol) in dry THF (1.0 mL) at 0 °C and the mixture was kept at 50 °C for 1 h, then cooled to 0 °C. An aqueous solution of NH_4Cl was added, and the mixture was extracted with Et_2O. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue purified by chromatography [silica gel, hexane–EtOAc (20:1)] to give *4a* as an oil; yield: 17.5 mg (84%). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.10–8.06 (m, 2H), 7.32–7.59 (m, 8 H), 5.37 (s, 2 H). This spectrum was identical with that reported.[14]

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