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A novel synthesis of functionalized ketones via a nickel-catalyzed coupling reaction of zinc reagents with thiolesters

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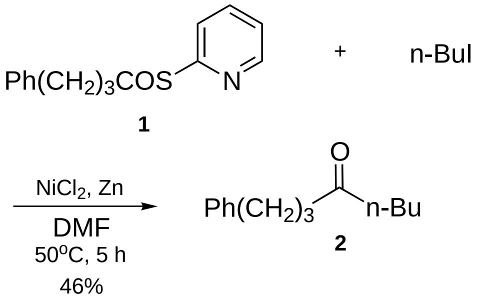
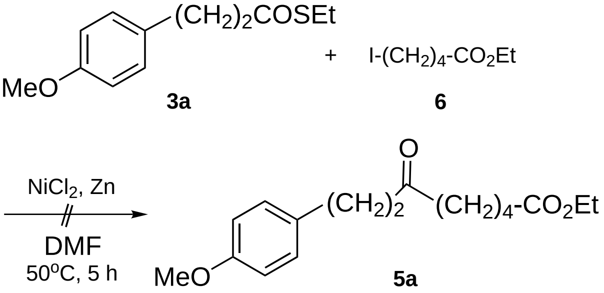
Abstract—Treatment of thiolesters with zinc reagents in the presence of Ni(acac)$_2$ provided a variety of functionalized ketones in good yields. This new protocol was successfully applied to the synthesis of (+)-biotin to allow for a practical installation of the carboxybutyl chain. © 2002 Elsevier Science Ltd. All rights reserved.

The transformation of carboxylic acids into ketones has received considerable attention because of its significance in synthetic organic chemistry.[1] As most of the target molecules have functional groups, a methodology, which permits the synthesis of the functionalized ketones without the use of protection–deprotection sequence as well as functional group transformations, has been highly desirable. Among the organometallic compounds, organozinc reagents[2] are stable to a wide range of the functional groups, and, when activated by certain kinds of transition metals, become sufficiently reactive toward activated carboxylic acid derivatives to give the desired functionalized ketones. Such transformations have hitherto been realized through copper-[3a] or palladium-mediated coupling reaction[3b–f] of the organozinc reagents with acid chlorides or their activated analogs. Although various kinds of functionalized ketones have been prepared by the synthetic methods, they suffer from some of the following drawbacks: (1) stoichiometric amount of toxic copper metal is required; (2) acid-sensitive functional groups cannot tolerate the reaction conditions for the preparation of the acid chloride; (3) palladium catalyst is very expensive if not recovered.

The coupling reaction using a nickel catalyst offers an inexpensive and practical alternative to that using a palladium catalyst.[4] A pioneering work by Mukaiyama and co-workers has shown that, in the presence of nickel chloride and zinc dust, *n*-butyl iodide can be metallated and react with a *S*-2-pyridyl thiolester **1** to afford a *n*-butyl ketone **2** (Eq. (1)).[5] We applied the one-pot procedure to the reaction of ethyl 4-iodobutylate **6** with a simple and inexpensive *S*-ethyl thiolester **3a** (Eq. (2)). However, any coupling product **5a** was



(1)



(2)

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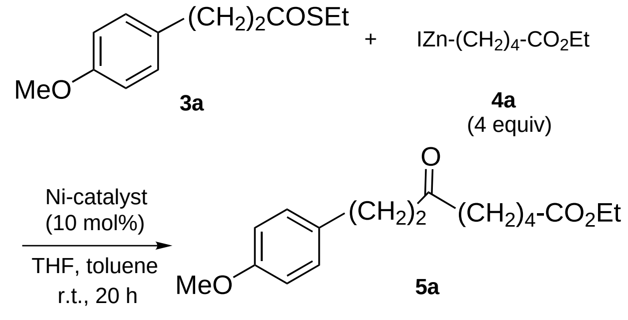
detected in the reaction using such an inactivated thiolester **3a**.[6] Fujisawa and co-workers have reported a coupling reaction of an in situ generated benzylzinc bromide with benzoyl chloride using $NiCl_2(PPh_3)_2$.[3b] While the desired ketone was obtained by the reaction, the yield was poor (24%) and a considerable amount of a homocoupling side product, i.e. dibenzyl (50%) was formed in the reaction.

Fukuyama and co-workers have recently reported an elegant coupling reaction of zinc reagents with thiolesters in the presence of a homogeneous palladium catalyst $[PdCl_2(PPh_3)_2]$.[3e] The method, however, has difficulty in recovering the catalyst. We have reported an improvement, use of heterogeneous Pd/C in place of $PdCl_2(PPh_3)_2$ to accomplish the high-yielding recovery of the palladium.[3f] However, the method creates the following drawbacks: (1) pyrophoric Pd/C should be added to the anhydrous and flammable solvent; (2) while Pd/C was recovered with high palladium content (>95% recovery) by simple filtration, the recovered Pd/C was not used as such, and, prior to re-use, should be subjected to a recovering process involving combustion.

We envisioned a possible use of an inexpensive nickel catalyst for the coupling reaction of zinc reagents with thiolesters and report herein a successful result that allows, for the first time, the coupling reaction using readily accessible $Ni(acac)_2$.

Preliminary experiments were performed in the reaction between a zinc reagent **4a** and a thiolester **3a** in the presence of various nickel catalysts in THF–toluene at room temperature (Scheme 1). Although $NiCl_2$ did not exert any catalytic activity, $Ni(acac)_2$, $NiCl_2(PPh_3)_2$ and $NiBr_2(PPh_3)_2$ were found to be effective to provide **5a** in satisfactory yields (74, 71, and 63% yield, respectively). Considering the yield and the accessibility, $Ni(acac)_2$ was chosen as the catalyst for further investigation.



Ni-catalyst	Yield (%)[a]
$NiCl_2$	0
$NiCl_2(dppp)$	49
$NiBr_2(PPh_3)_2$	63
$NiCl_2(PPh_3)_2$	71
$Ni(acac)_2$	74

a: Isolated yield.

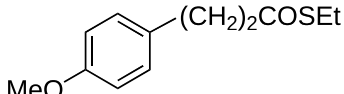
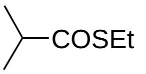
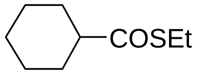
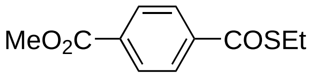
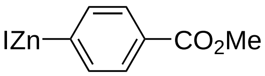
Scheme 1.

The $Ni(acac)_2$ catalyst was then applied to the reaction of other zinc reagents and thiolesters (Table 1).[7] The reaction of alkylzinc iodide **4a** with various thiolesters **3b–d** involving primary and secondary aliphatic thiolesters as well provided the corresponding functionalized ketones **5b–d** in good yields (Table 1, entries 2–4). However, the reaction between **4a** and an aromatic thiolester **3e** failed (Table 1, entry 5). Although this can be a limitation of the present methodology, the desired aryl alkyl ketones **5f–h** were found to be accessible through the reaction of arylzinc iodides **4b**,**c** with aliphatic thiolesters **3b**,**d** (Table 1, entries 6–8). The reaction between phenylzinc iodide **4c** and an aromatic thiolester **3e** was also problematic to afford an aryl aryl ketone **5i** in a poor yield (39% yield) (Table 1, entry 9). Since carbon–sulfur oxidative addition of the thiolester **3** to nickel(0) complex is fast due to the high thiophilicity of nickel, the rate-determining step of the coupling reaction should be the transmetallation of the zinc reagent **4** to the acylnickel thiolate **7** (Scheme 2).[9] An *S*-phenyl thiolester **3f** carrying a phenylthio group of a good leaving group ability was thus tested to accelerate the transmetallation and to improve the coupling reaction. As expected, the use of **3f** considerably shortened the reaction period and remarkably increased the yield (85% yield) (Table 1, entry 10). Some improvement of the coupling reaction between the alkylzinc iodide and the aromatic thiolester was also observed when an *S*-phenyl thiolester **3f** was employed as the substrate (Table 1, entry 11 versus 5). In the absence of $Ni(acac)_2$, the coupling reaction between **3** and **4** did not take place to any appreciable extent even by the use of the reactive *S*-phenyl thiolester **3f**.

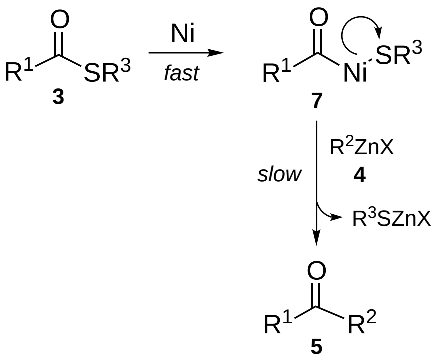
We have already reported an efficient synthesis of (+)-biotin through the reaction of thiolactone **8** with **4a** in the presence of a homogeneous[10] or a heterogeneous[3f] palladium catalyst $[PdCl_2(PPh_3)_2$ or 10% Pd/C]. To avoid a problem of the high cost of the palladium catalyst, we examined the application of the present nickel-catalyzed reaction to the installation of the carboxybutyl chain of (+)-biotin. As shown in Table 2, the standard procedure, even by the use of a large excess of the zinc reagent **4a** (6 equiv.), provided the desired vinyl sulfide **9** in only 13% yield after dehydration with *p*-toluenesulfonic acid (Table 2, entry 1). The use of $NiBr_2(PPh_3)_2$ did not affect the yield (14% yield) (Table 2, entry 2). Considerable improvement of the yield was eventually accomplished by the addition of DMF (0.5 equiv. relative to **4a**) to afford **9** in 81% yield (Table 2, entry 3).

Table 1.

$$\underset{\textbf{3a-f}}{R^1COSR^3} + \underset{\substack{\textbf{4a-c}\\(4\text{ equiv})}}{R^2ZnI} \xrightarrow[\substack{\text{THF, toluene}\\\text{r.t., 20 h}}]{\substack{\text{Ni(acac)}_2\\(10\text{ mol\%})}} \underset{\textbf{5a-j}}{R^1COR^2}$$

Entry	Thiolester (**3**)	Zinc Reagent (**4**)	Ketone (**5**)	Yield (%)[a]
1	 **3a**	IZn-$(CH_2)_4$-CO_2Et **4a**	**5a**	74
2	$CH_3(CH_2)_6COSEt$ **3b**	**4a**	**5b**	79
3	 **3c**	**4a**	**5c**	73
4	 **3d**	**4a**	**5d**	89
5	 **3e**	**4a**	**5e**	-[b]
6	**3b**	 **4b**	**5f**	86
7	**3d**	**4b**	**5g**	77
8	**3b**	PhZnI **4c**	**5h**	81
9	**3e**	**4c**	**5i**	39
10[c]	PhCOSPh **3f**	**4c**	**5j**	85
11	**3f**	**4a**	**5k**	33

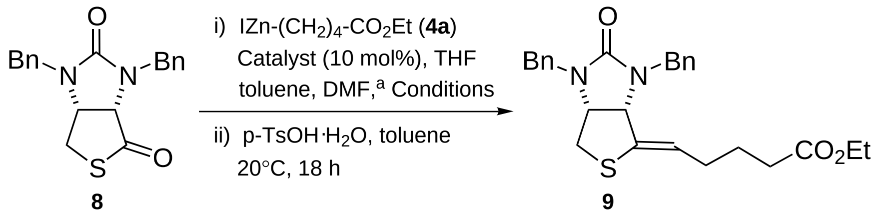
a: Isolated yield; b: multi-spots were observed on TLC; c: the reaction was conducted at r.t. for 2 h.



Scheme 2.

In conclusion, an efficient synthesis of the functionalized ketones has been accomplished through a Ni-$(acac)_2$-catalyzed coupling reaction of the zinc reagents with the thiolesters. Due to the low cost of the nickel catalyst, this new protocol would permit a practical access to a great variety of functionalized unsymmetrical ketones involving alkyl alkyl, aryl alkyl and aryl aryl congeners. The efficiency of the present methodology was demonstrated by the practical synthesis of (+)-biotin, where the carboxybutyl chain was installed in high yield under mild conditions.

Table 2.



Entry	DMF (equiv.)[b]	Catalyst	Zinc reagent (equiv.)[c]	Conditions	Yield (%)[d]
1	0	Ni(acac)$_2$	6.0	25°C, 48 h	13
2	0	NiBr$_2$(PPh$_3$)$_2$	6.0	20°C, 24 h	14
3	0.5	Ni(acac)$_2$	2.0	20°C, 15 h	81

a: DMF was added in the reaction shown in entry 3; b: equivalent relative to **4a**; c: equivalent relative to **7**; d: isolated yield.

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4. The price of nickel is ca. >1000 times cheaper than that of palladium on metal base.
5. Onaka, M.; Matsuoka, Y.; Mukaiyama, T. *Chem. Lett.* **1981**, 531.
6. The authors have suggested a reaction pathway where a low-valent organonickel compound is generated by the treatment of *n*-butyl iodide with nickel chloride and zinc dust.[5] While the species did react with an activated thiolester **1**, it should not be so reactive as to couple with **3a**.
7. A typical procedure for the nickel-catalyzed coupling reaction of a zinc reagent with a thiolester (Table 1, entry 1): Into a suspension of zinc powder (activated according to Ref. 8) (1.17 g, 17.90 mmol) in THF (2.7 mL) was added 1,2-dibromoethane (40 μL, 0.46 mmol), and the mixture was heated to reflux for 3 min. After cooling the mixture to 25°C, TMS-Cl (40 μL, 0.32 mmol) was added, and the slurry was stirred for 15 min. Ethyl 5-iodopentanoate (2.30 g, 8.98 mmol) was then added and the mixture was heated to 35°C and stirred for 30 min to give the zinc reagent **4a**. Into the zinc reagent **4a** were added thiolester **3a** (500 mg, 2.23 mmol), toluene (2.5 mL) and Ni(acac)$_2$ (57 mg, 0.22 mmol), and the mixture was stirred at 25°C for 20 h. The mixture was filtered through Celite, and the filtrate was evaporated. Into the residue was added ether, and the mixture was washed successively with 1N HCl, sat. aq. NaHCO$_3$ and brine, dried over MgSO$_4$ and evaporated. The residue was purified by silica-gel column chromatography (hexane:AcOEt = 10:1) to afford **5a** (481 mg, 74%) as colorless oil. IR (KBr): 1733 cm^{-1}. ^{1}H NMR (200 MHz, CDCl$_3$): δ 1.25 (t, $J=7.1$ Hz, 3H), 1.5–1.7 (m, 4H), 2.2–2.5 (m, 4H), 2.6–2.9 (m, 4H), 3.78 (s, 3H), 4.12 (q, $J=7.1$ Hz, 2H), 6.78–6.85 (m, 2H), 7.06–7.11 (m, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 14.6 (q), 23.5 (t), 24.8 (t), 29.3 (t), 34.4 (t), 42.9 (t), 44.9 (t), 55.6 (q), 60.7 (t), 114.3 (d), 129.6 (d), 133.5 (s), 158.3 (s), 173.8 (s), 210.2 (s). MS m/z 293 (M^+).
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