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Preparation of aryl ketones via Ni-catalyzed Negishi-coupling reactions with acid chlorides

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ABSTRACT

A Ni-catalyst-catalyzed cross-coupling reaction of organozinc reagents with acid chlorides has been successfully developed. Mild reaction conditions were required to complete the coupling reactions affording the corresponding aryl ketones in good to excellent yields.

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The transition metal-catalyzed cross-coupling reactions of organometallics with acid chlorides have been the most widely used approach for the preparation of ketones.¹ To this end, numerous efficient synthetic methodologies using mainly organomagnesium,² -copper,³ -manganese,⁴ -lithium,⁵ -boron,⁶ -stannane,⁷ and -zinc⁸ have been developed. Among those, the most considerable effort has been devoted to utilizing organozinc reagents simply due to the highly efficient functional group tolerance. Consequently, transition metal-catalyzed coupling reactions of organozinc with acid chlorides have been considered as one of the most effective routes for the ketone synthesis. In most cases of coupling reactions, copper and palladium were the most frequently used catalysts. Unfortunately, this route contains some limitations such as inconvenience of using copper-catalyst and high price of palladium catalyst. Therefore, there is still a need to develop an economically and environmentally more efficient method for the synthesis of ketones albeit Cu- or Pd-catalyzed coupling reactions of organozincs are useful tools.

To date, relatively few outstanding studies on the coupling reaction of organozinc with acid halides have been reported to avoid these restrictions. For examples, Gosmini and co-workers⁹ reported a method for the preparation of aromatic ketones using the cobalt-catalyzed coupling reaction of organozinc prepared in situ with acid chlorides or carboxylic anhydrides. More recently, preparation of ketones using the coupling reaction of mixed organozincs with acid chlorides in the presence of tri-*n*-butylphosphine has been revealed.^{10,11} It was performed by the palladiumphosphinous acid-catalyzed cross-coupling reaction of organozinc with acid halides. Compared to other organometallics, however, there has been considerably less progress in developing effective catalytic system for producing ketone compounds using organozinc reagents. One of the more interesting routes in Negishi coupling with acid halides has been accomplished by Rovis.¹² This

* Corresponding author. E-mail address: kimsemail@dankook.ac.kr (S.-H. Kim). approach employed organozinc reagent along with Ni pre-catalyst in the presence of an appropriate ligand. In spite of good to excellent isolated yields, a limited number of organozinc reagents were used in this study.

We have developed several efficient routes for the synthesis of organozinc reagents and their subsequent coupling reactions.¹³ However, a significant improvement in this methodology would be the development of a nickel-catalyst for constructing carbonyl compounds. Thus, we herein would like to report a versatile application of readily available organozinc reagents for ketone synthesis in the presence of a nickel-catalyst.

As mentioned before, most of the coupling reactions of organozincs for the preparation of ketones were performed with copper or palladium catalyst. In search of a more efficient catalyst in terms of easy availability, we first attempted the coupling reaction of 2-(ethoxycarbonyl)phenylzinc bromide (**A**) prepared by the direct insertion of active zinc¹³ with benzoyl chloride.

To investigate the proper conditions, several nickel-catalysts were employed and the results were summarized in Table 1. Even though each catalyst required a little different reaction time (20 min to 24 h) at room temperature, the coupling product (1a) was obtained in good to excellent isolated yields in the presence of a nickel-catalyst. It was of interest that the coupling reaction was completed in the absence of any extra ligand under the given conditions with 2 mol % of a nickel-catalyst.¹⁴ As described in Table 1. among the nickel-catalysts used in this study. $Ni(acac)_2$ is shown to be a very efficient catalyst for the preparation of ketones. Generally, the coupling reaction was conducted at room temperature in THF. The subsequent cross-coupling reaction using 2 mol % of Ni(acac)₂ as a catalyst was completed in 20 min at room temperature and resulted in the formation of the product (1a) in 89% isolated yield (Table 1, entry 1). All the rest of the coupling reactions in this study were carried out with Ni(acac)₂-catalyst at room temperature.

Table 2 shows the general applications of this strategy for the preparation of highly functionalized benzophenones. As aforemen-





Table 1



Entry	Catalyst ^a	Time ^b	Result ^c (%)
1	Ni(acac) ₂	20 min	89
2	Ni(dppe)Cl ₂	24 h	80
3	Ni(PMe ₃) ₂ Cl ₂	1 h	82
4	Ni(PPh ₃) ₂ Cl ₂	30 min	85
5	Co(acac) ₂	1 h	$(20)^{d}$

^a 2 mol % used.

^b No acid chloride observed.

^c Isolated yield (based on benzoyl chloride).

^d Determined (conversion) by GC.

Table 2

Coupling reactions with benzoyl chlorides



^a Isolated yield (based on benzoyl chloride).

conditions were maintained during the coupling reaction in progress (1 h instead of 20 min). A bromine atom on the benzoyl chlo-

	Zr	$+$ R(Ar)-COCI $\frac{2\% N}{con}$	li(acac) ₂ ditions	
	1.2 eq	1.0 eq	THF 3a - 3h	
Entry	Acid chloride	Conditions	Product	Yield (%)
1	CH ₃ (CH ₂) ₃ COCl	rt/20 min	CO ₂ Et 3a	79
2	CICH ₂ (CH ₂) ₃ COCI	rt/20 min	Cl 3b	81
3	COCI	rt/60 min	O CO ₂ Et 3c	89
4		rt/10 min	CO ₂ Et 3d	75
5	COCI	rt/30 min	G CO ₂ Et S 3e	86
6	COCI	rt/30 min	O CO ₂ Et 3f	79
7	CINCCI	reflux/24 h	CI N 3g	68
8	CI	rt/30 min	Cl CO ₂ Et 3h	66

2 % Ni(acac)₂

^a Isolated yield (based on acid chloride).

tioned, a catalytic amount of Ni(acac)₂ was employed and the reaction was carried out at room temperature in THF. To compare the results depending upon the benzoyl chlorides, the same reaction

CO₂Et ZnBr

Table 3

Coupling reactions with acid chlorides

ride tolerated the reaction conditions (Table 2, entries 1-3) and the corresponding coupling products (2a-2c) were achieved in good yields. Interestingly, the presence of iodine on the benzoyl chloride was also not affected resulting in the formation of iodine-substituted benzophenones (2d-2f, Table 2) in excellent yields. 2-Nitroand 4-nitrobenzoyl chlorides also effectively reacted with organozinc A to give rise to the ketones (2g and 2h, Table 2) in 60% and 65% isolated yield, respectively, under the same conditions.

In order to examine the generality of this catalytic system, we expanded our study to include a wide variety of acid chlorides to be completed with **A**.¹⁵ The results are summarized in Table 3. Under the same conditions (2 mol % of Ni(acac)₂ in THF) used before, the coupling reaction with a simple alkyl acid chloride as well as chlorine-substituted acid chloride were completed in 20 min at room temperature affording the corresponding product (**3a**, **3b**) in 79% and 81% isolated yields (Table 3, entries 1 and 2). respectively. A bulky acid chloride was also reacted with A to give rise to the ketone (3c) in excellent yield (Table 3, entry 3). Significantly, ketone (3d) containing two ester functionalities was successfully prepared from the coupling reaction with ethyl 2-chloro-2-oxoacetate in good yield (Table 3, entry 4). Not only alkyl acid chlorides but other heteroaryl acid chlorides were good coupling partners to prepare heteroaryl ketones. As depicted in Table 3, thiophene, furan and pyridine carbonyl chlorides were coupled with **A** under mild conditions to afford the corresponding ketones (3e, 3f and 3g, Table 3) in good yields, respectively. Even though a slightly longer reaction time (24 h at refluxing temperature) was required in the case of pyridine carbonyl chloride, the coupling reaction occurred selectively on the acid chloride (Table 3. entry 7). Another significant result was formed in the reaction with 4-(chloromethyl)benzovl chloride (Table 3, entry 8). As noted in Table 3. a chlorine atom in the benzylic position was intact

Table 4

Preparation of functionalized ketones

		ArZnX + R(Ar)COCI	conditions	Products	
		1.2 eq 1.0 eq	THF	4a - 4h	
Entry	Organozinc	Acid chloride	Conditions	Product	Yield ^a (%)
1	Br	NC	rt/30 min	Br 4a CN	84
2	F	COCI	rt/30 min	F 4b	86
3	H ₃ CO ZnBr	NC	rt/30 min	H ₃ CO 4c	89
4	EtO ₂ C S ZnBr	COCI	rt/30 min	EtO ₂ C	81
5	Znl S	COCI	rt/30 min	S 4e	83
6	S ZnBr	COCI	rt/60 min	S Br 4f	77
7	EtO ₂ C O ZnBr	COCI	rt/30 min	EtO ₂ C 4g	78
8	X II ZnBr	COCI	rt/10 min		87 (4h)
9	X = 3-F, 4-Cl		rt/10 min	X = 3-F(4h), 4-Cl(4i)	72 (4i)
d Teeleted world	(1				

2 % Ni(acac)

Isolated yield (based on acid chloride).

during the coupling reaction under the conditions used in this study and was not attacked in the cross-coupling reaction (3h, Table 3).

The utility of this methodology in the preparation of a number of ketones was extended to the coupling reactions with a variety of organozinc reagents. Again, all of the organozinc reagents used in this study were prepared by the direct insertion of active zinc to the corresponding halides and the results obtained from this study are described in Table 4. For most of the cases, the coupling reactions were conducted in the presence of $2 \mod \%$ Ni(acac)₂ at room temperature in THF and completed within 30 min except in the case of 3-bromothiophene-2-ylzinc bromide (Table 4, entry 6). Halogen-substituted phenylzinc iodide underwent the coupling reaction with aryl acid chlorides under mild conditions and successfully gave the aryl ketones (4a and 4b, Table 4). No significant effect on the coupling reaction was observed when an electron-donating group was present (Table 4, entry 3). Again, the aforementioned mild conditions worked well for the coupling reactions with heteroarylzinc reagents. 5-(Ethoxycarbonyl)thiophene-2-ylzinc bromide reacted with 2-thiophenecarbonyl chloride to give rise to the formation of heteroaryl ketone (4d, Table 4) in 81% yield. The coupling reactions of similar organozincs, 3-thienylzinc iodide and 3-bromothien-2-ylzinc bromide, led to the formation of ketones 4e and 4f in 83% and 77% yields (Table 4, entries 5 and 6), respectively. It is also significant that 5-(ethoxycarbonyl)furan-2-ylzinc bromide was coupled with benzoyl chloride to yield ethyl 5-benzoylfuran-2-carboxylate (4g) in 78% yield (Table 4, entry 7). Additionally, it was found that treatment of benzylzinc reagents under the same conditions generated functionalized coupling products 4h and 4i in 10 min at room temperature (Table 4, entries 8 and 9).

From these results, it can be concluded that the mild conditions and nickel catalyst have resulted in a wider tolerance of functional groups and a greater scope of the reaction. Significantly, this strategy affords a more economically and environmentally useful and valuable synthetic procedure for the preparation of ketones utilizing organozinc reagents, which are readily available. Additional studies using the nickel catalyst are underway.

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- 15. A representative procedure of coupling reaction; In a 25 mL round-bottomed flask, Ni(acac)₂, (0.06 g, 2 mol%) and 10 mL (5 mmol) of 0.5 M solution of 2-(ehtoxycarbonyl)phenylzinc bromide in THF was added into the flask at room temperature. Next, 6-chloronicotinoyl chloride (0.70 g, 4 mmol) dissolved in 5.0 mL of THF was added. The resulting mixture was refluxed overnight, then cooled down to room temperature. Quenched with saturated NH₄Cl solution, then extracted with ethyl acetate $(30 \text{ mL} \times 3)$. Combined organics were washed with saturated Na₂S₂O₃ solution and brine. Dried over anhydrous MgSO₄. A flash column chromatography (50% EtOAc/50% Heptane) gave 0.78 g of **3g** as yellow solid in 68% isolated. Mp = 48-51 °C. ¹H NMR (CDCl₃, 500 MHz): δ 8.59 (s, 1H), 8.11 (d, 2H, J = 10 Hz), 7.69 (t, 1H, J = 5 Hz), 7.62 (t, 1H, J = 5 Hz), 7.43 (d, 1H, J = 5 Hz), 7.38 (d, 1H, J = 10 Hz), 4.17 (q, 2H, J = 5 10 Hz), 1.19 (t, 3H, J = 10 Hz); ¹³C NMR (CDCl₃, 125 MHz): δ 194.8, 165.6, 155.6, 151.2, 140.6, 138.8, 133.0, 131.9, 130.6, 130.4, 129.2, 127.5, 124.6, 61.9, 14.0.