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A Versatile Protocol for the Preparation of Highly Hindered Aryl Ketones Using Organozinc Reagents

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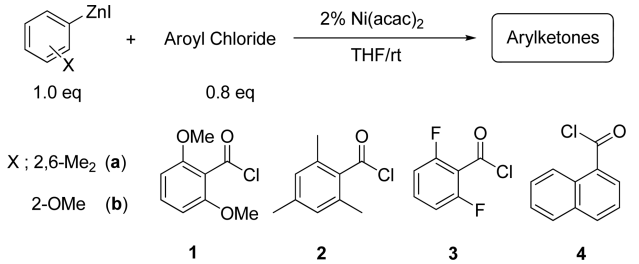
Aryl ketones containing substituents at both *ortho*-positions are found in a variety of natural products with many interesting biological activities.[1] For the construction of these sterically hindered aryl ketones, the Friedel-Crafts acylation has been successfully used, albeit with a little difficulty.[2] In addition, a nucleophilic addition-elimination reaction with acyl electrophiles has been the most frequently utilized for the preparation of the ketones. To perform this strategy, cross-coupling reactions of organometallic reagents with the appropriate carbonyl compounds such as acid chlorides, esters, anhydrides, nitriles, and amides have mostly been executed in the presence of a transition metal catalyst.[3] Despite the numerous outstanding methods for the preparation of simple aryl ketones, there are few examples, providing hindered aryl ketones. Martin and co-workers reported a convenient synthesis of sterically hindered aryl ketones utilizing the carbonylative cross-coupling reaction of *ortho*-disubstituted aryl iodides with aryl boronic acids in the presence of carbon monoxide.[4] In addition, the rhodium-catalyzed oxidative arylation of aldehydes was also proposed.[5] More recently, a selective synthetic route to hindered unsymmetrical diaryl ketones was reported by Lockhart.[6] In their study, arylstannes were coupled with aroyl chlorides under three different reaction conditions. However, as described above, a very limited number of organometallics have been employed for the preparation of highly hindered ketones. Accordingly, there is still need to develop a new efficient protocol especially for the synthesis of ketones bearing especially multiple substituents in *ortho*-positions. Herein, we report our results of utilizing organozinc reagents for the preparation of highly hindered ketones.

During the course of our ongoing research utilizing organozinc reagents, we found a reliable synthetic protocol for the preparation of the highly desirable aryl ketones. To explore the potential applicability of organozinc reagents toward the synthesis of hindered diaryl ketones, two representative organozinc reagents were chosen in the cross-coupling reactions: 2,6-dimethylphenylzinc iodide (**a**) and 2-methoxyphenylzinc iodide (**b**). For the corresponding coupling partners, we used 2,6-dimethoxybenzoyl chloride (**1**), 2,4,6-trimethylbenzoyl chloride (**2**), 2,6-difluorobenzoyl chloride (**3**) and 1-naphthanoyl chloride (**4**), all of which contain substitutents at both *ortho*-positions. Additionally, since we have found that a readily available Ni-catalyst can be effectively employed in the cross-coupling reaction of organozincs with relatively uncrowded aroyl chlorides under mild conditions,[7] this reaction conditions was directly applied to the preparation of the titled compounds in this study. The cross-coupling reactions were carried out in THF at room temperature in the presence of 2 mol % of $Ni(acac)_2$ and the results are summarized in Table 1.

We first coupled the organozinc reagent **a** bearing two methyl groups at both *ortho*-positions with 2,6-dimethoxybenzoyl chloride (**1**). Under the conditions described in Table 1, the coupling reaction was completed in 2.0 h at room temperature resulting in the formation of the corresponding *tetra-ortho*-substituted ketone in 43% isolated yield (entry 1, Table 1). By employing the same organozinc reagent, more examples of the *tetra-ortho*-substituted diaryl ketones (**1b** and **1c**) were obtained (entries 2, 3, Table 1). As shown in Table 1, higher product yield was observed with more sterically demanding 2,4,6-trimethylbenzoyl chloride (entry 2, Table 1) than 2,6-difluorobenzoyl chloride (entry 3, Table 1). The coupling reaction of **a** with 1-naphthoyl chloride (**4**) was also successfully carried out in THF at room temperature for 30 min and the expected coupling

Table 1. Coupling reaction with arylzinc reagents



Entry	X	Aroyl chloride	Product	Yield (%)[a]
1	**a**	**1**	**1a**	43
2	**a**	**2**	**1b**	67
3	**a**	**3**	**1c**	46
4	**a**	**4**	**1d**	66
5	**b**	**1**	**1e**	28
6	**b**	**2**	**1f**	61
7	**b**	**3**	**1g**	62
8	**b**	**4**	**1h**	93

[a]Isolated yield (based on acid chloride).

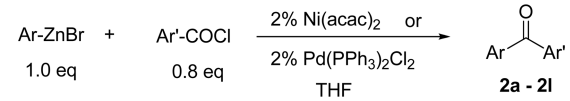
product (**1d**) was obtained in 66% isolated yield (entry 4, Table 1).

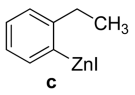
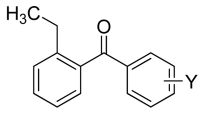
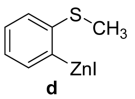
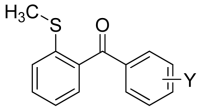
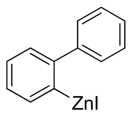
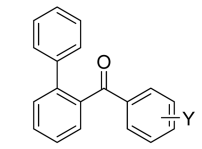
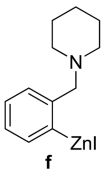
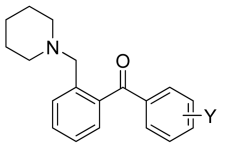
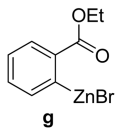
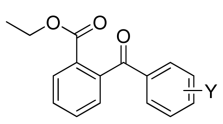
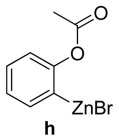
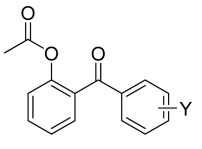
On the basis of the results obtained from the preliminary study, we examined more coupling reactions to investigate a clear-cut fact of the steric effect on the coupling reactions under the same reaction conditions used before. To this end, *mono-ortho*-substituted organozinc reagent **b** was employed in the cross-coupling reactions with the same series of aroyl chlorides (**1**, **2**, **3**, and **4**). As described in Table 1, in general, almost same steric effect was observed from this additional study. The lowest yield (28%) was obtained from the coupling reaction with 2,6-dimethoxybenzoyl chloride **1** (entry 4, Table 1). The other two couplings with **2** and **3** resulted in the moderate yields (**1f**, 61%, and **1g**, 62%, entries 6 and 7, Table 1), respectively. Interestingly, the coupling product (**1h**) was efficiently prepared from using 1-naphthoyl chloride as a coupling partner (entry 8, Table 1).

Having the prominent results summarized in Table 1, further study has been performed with several different organozinc reagents to determine the scope of this protocol. Prior to the discussion of the results in detail, it should be mentioned first that an interesting result has been observed in the selection of the catalyst to complete the coupling reaction. As depicted in Table 2, two different aroyl chlorides were coupled with a variety of organozinc reagents possessing a unique substituent in the *ortho*-position.

Since the promising results were obtained from using $Ni(acac)_2$ as a catalyst in the previous study described above, we started the first extended coupling reactions using 2-ethylphenylzinc iodide which is relatively less hindered and two different aroyl chlorides such as 2,6-difluorobenzoyl chloride (**I**) and 2,6-dichlorobenzoyl chloride (**II**). The coupling reactions were carried out in THF at room temperature in the presence of 2 mol % of $Ni(acac)_2$. In contrast to our expectation, GC-MS analysis of the reaction mixture showed that a very small amount (less than 10% by GC) of the desired cross-coupling product was formed along with lots of by-products. Among the by-products obtained in this

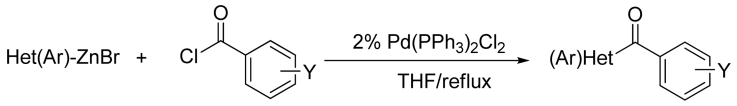
Table 2. Study on the effect of substituent



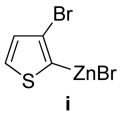
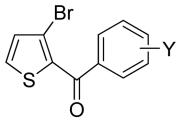
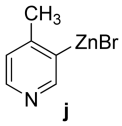
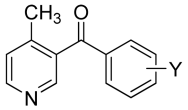
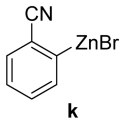
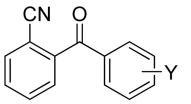
Entry	RZnX	Catalyst[a]	Ar'COCl[b]	Product			Yield (%)[c]
1	 c	B	I		Y = 2,6-$(F)_2$	**2a**	62
2			II		Y = 2,6-$(Cl)_2$	**2b**	41
3	 d	B	I		Y = 2,6-$(F)_2$	**2c**	72
4			II		Y = 2,6-$(Cl)_2$	**2d**	69
5	 e	A	I		Y = 2,6-$(F)_2$	**2e**	25
6			II		Y = 2,6-$(Cl)_2$	**2f**	19
7	 f	A	I		Y = 2,6-$(F)_2$	**2g**	16
8		B	II		Y = 2,6-$(Cl)_2$	**2h**	NR[d]
9	 g	A	I		Y = 2,6-$(F)_2$	**2i**	65
10			II		Y = 2,6-$(Cl)_2$	**2j**	54
11	 h	B	I		Y = 2,6-$(F)_2$	**2k**	32
12			II		Y = 2,6-$(Cl)_2$	**2l**	28

[a]**A**: $Ni(acac)_2$/rt, **B**: $Pd(PPh_3)_2Cl_2$/reflux. [b]**I**: 2,6-Difluorobenzoyl chloride, **II**: 2,6-Dichlorobenzoyl chloride. [c]Isolated yield (based on acid chloride). [d]Trace amount of product was formed (by GC-MS).

Table 3. Expansion of the coupling reaction



1.0 eq 0.8 eq **3a - 3f**

Entry	RZnX	Y	Product		Yield (%)[a]
1		Y = 2,6-$(F)_2$	 Y = 2,6-$(F)_2$	**3a**	36
2	**i**	Y = 2,6-$(Cl)_2$	Y = 2,6-$(Cl)_2$	**3b**	25
3		Y = 2,4,6-$(Me)_3$	Y = 2,4,6-$(Me)_3$	**3c**	84
4		Y = 2,6-$(F)_2$	 Y = 2,6-$(F)_2$	**3d**	0^b
5	**j**	Y = 2,6-$(Cl)_2$	Y = 2,6-$(Cl)_2$	**3e**	0^b
6	 **k**	Y = 2,6-$(Cl)_2$	 Y = 2,6-$(Cl)_2$	**3f**	85

[a]Isolated yield (based on acid chloride). [b]Trace amount of coupling product was formed (confirmed by GC-MS).

reaction, 4-halobutyl benzoate resulted from the ring opening of THF by an acid chloride was the major product in both cases.[8] This type of by-product formation has been observed throughout this study when the coupling reaction did not proceed well. This unexpected result immediately prompted us to find out the proper reaction conditions. After several attempts, Pd(II)-catalyst was turned out to be an efficient catalyst leading the reaction to completion. Once again, the organozinc reagents shown in Table 2 were easily prepared by the direct oxidative addition of highly active zinc into the corresponding halides.

As shown in Table 2, the coupling reactions of 2-ethylphenylzinc bromide with 2,6-disubstituted benzoyl chlorides were carried out in THF at refluxing temperature in the presence of 2 mol % of $Pd(PPh_3)_2Cl_2$. The corresponding coupling products (**2a** and **2b**, Table 2) were obtained in 62% and 41% isolated yields, respectively. In order to study any difference in reactivity between the oxygen atom (**a**) and the sulfur atom (**d**) in the *ortho*-position in the organozinc reagent, the coupling reactions of 2-(thiomethyl)phenylzinc iodide were performed under the same conditions. The corresponding coupling product (**2c**) was obtained in a slightly higher yield (entry 3, Table 2). And also, this catalytic system worked well with 2,6-dichlorobenzoyl chloride which has a bigger substituent in the *ortho*-position than **I** giving rise to the product **2d** in 69% isolated yield (entry 4, Table 2). It was of interest that the Ni-catalytic system worked well with phenyl-substituted organozinc reagent (**e**). In the presence of 2 mol % of $Ni(acac)_2$, coupling reactions with both **I** and **II** in THF at room temperature resulted in the formation of the products **2e** and **2f** in 25% and 19% isolated yields (entries 5 and 6, Table 2), respectively. In the case of organozinc **f** bearing a cyclohexyl amine moiety in the benzylic position, coupling product **2g** was obtained from the reaction with $Ni(acac)_2$ in very low yield (entry 7, Table 2). Unfortunately, the coupling reaction of **f** with **II** was unsuccessful even under the Pd(II)-catalyzed reaction conditions (entry 8, Table 2). A more significant difference in the reactivity of the catalyst was observed from the following reactions (entries 9-12, Table 2). Two organozinc reagents (**g** and **h**, Table 2) have similar functionality at the *ortho*-position. However, as depicted in Table 2, each reaction required a different catalytic system for the completion of the coupling reaction. The coupling reaction of **g** with both **I** and **II** underwent well in the presence of 2 mol % of $Ni(acac)_2$ at room temperature and the products (**2i** and **2j**) were obtained in moderate yields (entries 9 and 10, Table 2). In contrast, Pd(II)-catalyst system should be used for the coupling of **h** to achieve the desired ketones. Obtaining a lower yield of **2k** (32%, entry 11, Table 2) than **1g** (62%, Table 1) was presumably attributed to the steric effect of the aroyl chloride.

To investigate the scope and limitation with respect to the use of the Pd(II)-catalytic system, more coupling reactions were examined with *ortho*-disubstituted benzoyl chlorides. The results are summarized in Table 3.

3-Bromo-2-thienylzinc bromide (**i**) was also readily prepared with highly active zinc. The resulting organozinc was coupled with several aroyl chlorides in the presence of 2 mol % $Pd(PPh_3)_2Cl_2$ in THF at refluxing temperature. The first attempt was made with 2,6-difluorobenzoyl chloride (**I**), which led to the product (**3a**) in 36% isolated yield (entry 1, Table 3). As expected from the previous experience, a slightly lower yield (**3b**, 25%, entry 2, Table 3) was appeared in the coupling reaction with 2,6-dichlorobenzoyl chloride. It was of interest that the product **3c** was isolated in excellent yield (entry 3, Table 3). Unfortunately, no isolable amount of coupling product was observed from the coupling reaction

of the pyridylzinc bromide (**j**) under the same conditions (entries 4 and 5, Table 3). As denoted in Table 3, a trace amount of the desired ketones were formed in the reaction mixture. Instead, undesired products, 4-halobutyl benzoates, were the major components in the reaction mixture. Additionally, 2-cyanophenylzinc bromide (**k**), which contains a unique functional group, was also coupled with aroyl chloride **II** providing the product **3f** in 85% isolated yield (entry 6, Table 3).

In conclusion, we have demonstrated a new facile route for the preparation of highly substituted ketones by utilizing readily available organozinc reagents. From a variety of coupling reactions, it has been observed that an effective catalytic system of the reaction depends on the substituent at the *ortho*-position of the organozinc reagents. Therefore, selection of the appropriate catalyst plays a significant role in achieving satisfactory results in the coupling reaction. Although the Pd(II)-catalytic system did suffer from a few limitations, the present study represents the first example of utilizing organozinc reagents in the synthesis of *ortho*-multiple substituted ketones. Further study on optimization and expansion is currently underway.

Experimental Section

A Representative Procedure for Compounds 1a-1h: 2-Methoxyphenyl 1-Naphthalenyl Ketone (1h). In a 25 mL round-bottomed flask, $Ni(acac)_2$ (0.03 g, 2 mol %) and 10 mL of 0.5 M solution of 2-methoxyphenylzinc iodide (**b**) in THF (5.0 mmol) were added into the flask at room temperature. Next, 1-naphthoyl chloride (0.76 g, 4.0 mmol) was added. The resulting mixture was stirred at room temperature for 30 min. The reaction mixture was quenched with 3 M HCl solution and extracted with ethyl ether (30 mL × 3). The combined organic layers were washed with saturated $NaHCO_3$(aq), $Na_2S_2O_3$(aq) solution and brine, successively, and dried over anhydrous $MgSO_4$, filtered and concentrated. A flash column chromatography (5% EtOAc/95% Heptane) gave 0.97g of **1h** as a white solid in 93% isolated. mp 78-79 °C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.54 (d, J = 7.2 Hz, 1H), 7.91-7.79 (m, 2H), 7.53-7.30 (m, 6H), 6.99-6.87 (m, 2H), 3.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 188.9, 158.3, 136.9, 133.9, 133.0, 132.4, 131.0, 130.9, 130.1, 129.9, 128.4, 127.8, 126.4, 126.0, 124.5, 120.6, 112.0, 56.1.

All other spectroscopic data of the compounds in Table 1 were consistent with the published results.[6]

A Representative Procedure for Compounds 2a-2l: 2,6-Dichlorophenyl 2-Methylthiophenyl Ketone (2d). In a 25 mL round-bottomed flask, $Pd(PPh_3)_2Cl_2$ (0.07g, 2 mol %) and 10 mL (5 mmol) of 0.5 M solution of 2-(thiomethyl)-phenylzinc iodide (**d**) in THF was added into the flask at room temperature. Next, 2,6-dichlorobenzoyl chloride (0.84 g, 4 mmol) was added. The resulting mixture was refluxed for 6 h, then cooled down to room temperature. The reaction mixture was quenched with saturated 3 M HCl solution, then extracted with ethyl ether (30 mL × 3). The combined organic layers were washed with saturated $NaHCO_3$(aq), $Na_2S_2O_3$(aq) solution and brine, successively, and dried over anhydrous $MgSO_4$, filtered and concentrated. A flash column chromatography (20% EtOAc/80% Heptane) gave 0.82 g of **2d** as a light yellow solid in 69% isolated. mp 153-154 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.53 (t, J = 7.2 Hz, 1H), 7.42 (d, J = 7.2 Hz, 1H), 7.39 (d, J = 7.2 Hz, 1H), 7.35 (m, 3H), 7.11 (t, J = 7.2 Hz, 1H), 2.51 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 192.4, 145.6, 138.3, 133.9, 133.7, 132.3, 131.6, 130.8, 128.3, 124.7, 123.5, 15.6; GC-MS (EI, 70 eV) *m/z* (*rel ratio*): 296 (M^+, 20), 283 (33), 261 (100), 246 (42), 218 (16), 173 (8).

A Representative Procedure for Compounds 3q-3f: 3-Bromothiophenyl 2,6-Dichlorophenyl Ketone (3b). In a 25 mL round-bottomed flask, $Pd(PPh_3)_2Cl_2$ (0.07g, 2 mol %) and 10 mL (5 mmol) of 0.5 M solution of 3-bromo-2-thienylzinc bromide (**i**) in THF were added into the flask at room temperature. Next, 2,6-dichlorobenzoyl chloride (0.84 g, 4 mmol) was added then the resulting mixture was heated to reflux for 24 h, then cooled down to room temperature. The reaction mixture was quenched with saturated 3 M HCl solution, then extracted with ethyl ether (30 mL × 3). The combined organic layers were washed with saturated $NaHCO_3$(aq), $Na_2S_2O_3$(aq) solution and brine, successively, and dried over anhydrous $MgSO_4$, filtered and concentrated. A flash column chromatography (1% EtOAc/99% Heptane) gave 0.34 g of **3b** as a white solid in 25% isolated yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.68 (d, J = 6.0 Hz, 1H), 7.32-7.38 (m, 3H), 7.12 (d, J = 6.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 183.9, 137.6, 135.1, 134.1, 132.3, 131.4, 128.4, 117.3; GC-MS (EI, 70 eV) *m/z* (*rel ratio*): 336 (M^++1, 56), 335 (M^+, 33), 191 (100), 173 (33), 145 (13).

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