



## Preparation of tertiary amides via aryl, heteroaryl, and benzyl organozinc reagents; scope and limitations

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### ABSTRACT

A facile synthetic protocol for the preparation of tertiary amides has been developed. The title compounds have been successfully obtained by the Pd-catalyzed cross-coupling reactions of readily available aryl and benzyl organozinc reagents with the appropriate carbamoyl chlorides.

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Amides are of special interest in synthetic organic chemistry because of their wide spectrum in natural compounds. To introduce this moiety, two general synthetic approaches have been widely utilized; the addition of an amine to the corresponding carboxylic acid derivative and the coupling reaction of an organometallic with a carbamoyl chloride. Among those, the latter has been more intensively investigated due to the wide variety of organometallic reagents that are available.

Grignard reagents have been coupled with carbamoyl chlorides to yield the corresponding amides in the presence of a Ni-catalyst.<sup>1</sup> Rouden and co-workers described the preparation of tertiary amides via the coupling reactions of organocuprates with carbamoyl chlorides.<sup>2</sup> In this study, organolithium, organomagnesium, and a limited number of organozinc reagents were used as precursors for making the organocuprates. The palladium-catalyzed cross-coupling reactions between organotin and carbamoyl chlorides also provided the corresponding amides.<sup>3</sup> Of the protocols using organometallic reagents, Suzuki-type reactions with a palladium-catalyst and an appropriate base have been the most widely employed for the coupling reaction with carbamoyl chlorides.<sup>4</sup> Direct use of benzylic halides with a carbamoylsilane is yet another approach for the preparation of tertiary amides.<sup>5</sup> In addition to these general synthetic routes, a three-component-coupling reaction, aminocarbonylation, for the preparation of a variety of amides was recently reported. It has been accomplished by employing halides (or triflates) and a Weinreb amide at atmospheric CO pressure in the

presence of a palladium catalyst along with a ligand such as Xantphos.<sup>6</sup>

In spite of the above mentioned methods, a new general approach generating highly functionalized amides would be highly desirable. As is well known, organozinc reagents have been widely utilized in organic synthesis mainly due to their general applicability.<sup>7</sup> We, herein, report a facile protocol for the preparation of tertiary amides utilizing a wide range of organozinc halides.

Our initial studies to determine the appropriate reaction conditions and the best catalyst involved the coupling reaction of 2-ethoxycarbonylphenylzinc bromide (**2**) with diethylcarbamoyl chloride (**A**). The coupling reactions were carried out in THF at refluxing temperature in the presence of 5 mol % of the following catalysts; Pd(PPh<sub>3</sub>)<sub>4</sub>, Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>, Ni(dppe)Cl<sub>2</sub>, and Ni(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>, respectively. In each case, some of the desired product (**1b**) was formed and confirmed by GC–MS analysis of the reaction mixture. Among these, it was found that the use of Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> gave the highest conversion to the corresponding coupling product (**1b**). Therefore, this catalytic system was employed in this study yielding the corresponding amides in moderate to good yields. The results are summarized in Table 1.

A substituted arylzinc reagent, 4-ethylphenylzinc bromide (**1**)<sup>8</sup> was coupled with carbamoyl chloride **A** in THF at refluxing temperature in the presence of 5 mol % Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> resulting in the formation of the corresponding amide (**1a**) in 50% isolated yield (Table 1, entry 1). As depicted above, 2-ethoxycarbonylphenylzinc bromide (**2**) was also reacted with **A** under the same conditions and the title compound (**1b**) was obtained in 52% isolated yield (Table 1, entry 2). A higher yield was observed from the coupling

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**Table 1**  
Coupling reaction of arylzinc halides

Entry	RZnX	Carbamoyl chloride <sup>a</sup>	Product	Yield <sup>b</sup> (%)
1	X: 4-CH <sub>2</sub> CH <sub>3</sub> ( <b>1</b> )	<b>A</b>	Y: 4-CH <sub>2</sub> CH <sub>3</sub>	<b>1a</b> 50
2	2-CO <sub>2</sub> Et ( <b>2</b> )		2-CO <sub>2</sub> Et	<b>1b</b> 52
3	4-CO <sub>2</sub> Et ( <b>3</b> )		4-CO <sub>2</sub> Et	<b>1c</b> 70
4	X: 4-CO <sub>2</sub> Et ( <b>3</b> )	<b>B</b>	Y: 4-CO <sub>2</sub> Et	<b>1d</b> 68
5	4-CH <sub>3</sub> ( <b>4</b> )		4-CH <sub>3</sub>	<b>1e</b> 62
6	4-Bromophenylzinc iodide ( <b>5</b> )		4-Br	<b>1f</b> 48
7	2-CH <sub>2</sub> CH <sub>3</sub> ( <b>6</b> )		2-CH <sub>2</sub> CH <sub>3</sub>	<b>1g</b> 52
8	X: 2-OMe ( <b>7</b> )	<b>C</b>	Y: 2-OMe	<b>1h</b> 66
9	2,6-Me <sub>2</sub> ( <b>8</b> )		2,6-Me <sub>2</sub>	<b>1i</b> 42

<sup>a</sup> **A**: Diethylcarbamoyl chloride, **B**: morpholinecarbonyl chloride; **C**: piperidinecarbonyl chloride.<sup>b</sup> Isolated yield (based on carbonyl chloride).

reaction of **A** with an organozinc reagent (**3**) producing 70% isolated yield (Table 1, entry 3). Interestingly, a similar result was achieved from the coupling reaction with carbamoyl chloride **B**. As shown in entry 4 (Table 1), the coupling reaction of organozinc **3** with morpholinecarbonyl chloride (**B**) led to the desired product (**1d**) in the highest yield. Again, alkyl-substituted organozinc reagents (**4** and **6**) were readily coupled with **B** affording the amides (**1e** and **1g**) in 62% and 52% isolated yields (Table 1, entries 5 and 7), respectively. Significantly, a bromine atom remained intact under the conditions used in this study. As described in Table 1, the coupling reaction of 4-bromophenylzinc iodide (**5**) with **B** proceeded smoothly producing 4-(bromophenylmorpholino)methanone (**1f**) in moderate yield (Table 1, entry 6). Piperidinecarbonyl chloride (**C**) can also be used as a coupling partner for the synthesis of tertiary amides. The cross-coupling reaction of 2-methoxyphenylzinc bromide (**7**) with **C** took place under the same conditions used in previous reactions yielding the amide (**1h**) in 66% isolated yield (Table 1, entry 8). Even with a sterically hindered organozinc, 2,6-dimethylphenylzinc bromide (**8**), the desired coupling product, 2,6-(dimethylphenylpiperidin-1-yl)methanone (**1i**), was obtained in moderate yield (Table 1, entry 8).

With these promising results in hand, our studies were expanded to see if this protocol could be used for a much broader range of amides. Initial studies included several heteroaromatic organometal reagents, and the results are summarized in Table 2. The first attempts were conducted with the readily available organozinc 3-bromo-2-thienylzinc bromide (**9**) and 3-thienylzinc iodide (**10**) under the same reaction conditions used in previous coupling reactions. The expected coupling products (**2a** and **2b**) were successfully obtained in 61% and 51% isolated yields (Table 2, entries 1 and 2), respectively. Diethylcarbamoyl chloride (**A**) was also effectively coupled with the organozinc **10** to give rise to the amide **2c** in 68% yield (Table 2, entry 3). Unfortunately, other heteroarylzinc reagents, pyridyl- and coumarinylzinc halides,

failed to yield useful results.<sup>9</sup> No reasonable amounts of the desired product were observed by switching the metal catalyst to Pd(PPh<sub>3</sub>)<sub>4</sub>, Ni(dppe)Cl<sub>2</sub>, and Ni(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>. Instead, byproducts from the ring opening of THF by carbamoyl chloride were the major components in the reaction mixture (confirmed by GC-MS).<sup>10</sup>

Cunico and Pandey reported the palladium-catalyzed preparation of  $\alpha$ -aryl tertiary amides using benzylic halides and carbamoylsilane<sup>5</sup> and, in this report, a disadvantage of using aminocarbonylation of benzylic halides was also described.<sup>11</sup> Accordingly, to expand the scope of our strategy, we next focused on the use of benzylic organometal reagents to develop a facile route for the synthesis of  $\alpha$ -aryl tertiary amides. Since the appropriate benzylzinc halides were easily prepared via the direct insertion of highly active zinc, they were immediately employed in the coupling reaction. As depicted below, the coupling reactions were carried out under the conditions (5 mol % Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>/THF/reflux) used in the previous reactions, and the results are summarized in Table 3.

As we expected, benzylzinc halides were readily coupled with carbamoyl chlorides to give rise to the desired amides in moderate yields. Coupling reactions of 2-chloropyridin-5-yl-methylzinc chloride (**11**) with several carbamoyl chlorides (**B**, **C**, and **D**) were converted to the corresponding amides (**3a**, **3b**, and **3c**) in moderate yields (Table 3, entries 1–3). However, the expected product was not observed from the coupling with diethylcarbamoyl chloride (**A**) (Table 3, entry 4). Again, the ring-opening byproduct of THF was the only product formed in this reaction. It was of interest that the coupling reaction of **A** with benzylzinc chloride (**12**) proceeded smoothly providing an amide (**3d**) in 68% isolated yield (Table 3, entry 5). Coupling reactions of 2-fluorobenzylzinc chloride (**13**) and 2-methoxybenzylzinc chloride (**14**) with **B** took place successfully and resulted in the formation of the corresponding amides (**3e** and **3f**) in moderate yields (50% and 52%, Table 3, entries 6 and 7), respectively. A bulky benzylzinc reagent (**15**) was

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