A Zinc Enolate of Amide: Preparation and Application in Reformatsky-like Reaction Leading to β-Hydroxy Amides

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One of the best known functionalized organic complexes is the β-hydroxy carbonyl compound. This unique functionality has been frequently found in naturally occurring bioactive derivatives.[1] Among complexes that contain two particular functionalities, β-hydroxy amides have been especially considered as valuable subunits for natural-products synthesis.[2] To construct the proper structure of 1,3-functionalities, aldol condensation is the most versatile method. In general, this methodology consists of the nucleophilic addition of enolate to carbonyl compounds. Consequently, the classical Reformatsky reaction has played a powerful role as one of the practical metallic enolates.[3] In this reaction, zinc enolates of esters, which were mostly generated from α-halo carbonyl compounds, were commonly used.

Considering the classical Reformatsky reaction, we anticipated that the coupling reaction of zinc enolates of amides with a carbonyl compound could be utilized for the synthesis of β-hydroxy amides. More interestingly, this goal could be easily achieved when the corresponding zinc enolates of amides are readily available.

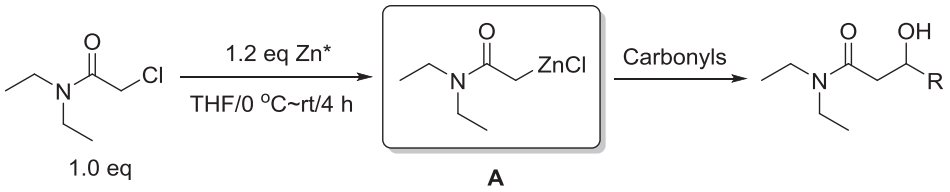
To date, very limited examples such as the use of α-bromo amide[4] and alkali metal amide enolate[5] have been reported for the preparation of zinc enolates of amides. Unfortunately, there was generally low usage of zinc enolate of amides in previous studies. Also, scattered examples of zinc enolate of amide usage have been found, and very limited numbers of β-hydroxy amide complexes have been prepared through the Reformatsky-like reaction. In the majority of cases, the reactive species, zinc enolate, was prepared *in situ*.[6]

Recently, Hartwig's group reported a study on the preparation and arylation of both isolated and *in situ* zinc enolates of amides generated from α-bromo amides.[7] Although pioneering exploration of zinc enolate of amides has been conducted in this work, coupling reactions with any carbonyl compounds has not been investigated. Instead, the study focused only on α-arylation of zinc enolates of amides.

Here, we report the easy preparation of a room-temperature-stable zinc enolate of amide in tetrahydrofuran (THF) from α-chloro amide and its subsequent coupling reactions with carbonyl derivatives – a Reformatsky-type reaction.

To execute the utility of a new organozinc reagent, our study started with *N*,*N*-diethylchloroacetamide, which is readily available, for the preparation of zinc enolate of amide. The α-chloro amide was treated with highly active zinc (Zn^*) prepared by the literature procedure.[8] The oxidative addition of zinc into the carbon–chlorine bond was completed in 4 h at ambient temperature. To confirm the formation of the corresponding (2-(diethylamino)-2-oxoethyl)zinc chloride, iodine quenching of **A** was carried out, and GC-MS analysis of the aliquot showed over 95% conversion to the corresponding *N*,*N*-diethyliodoacetamide. Delighted with this result, we further examined the reactivity of **A** by a cross-coupling reaction with carbonyl compounds (Scheme 1).

The cross-coupling reaction of **A** with aldehydes were carried out in the absence of any catalyst and completed in most cases within 1.0 h at room temperature. To our delight, the corresponding β-hydroxy amides were obtained with moderate to good isolated yields (Table 1). As expected, a variety of aromatic aldehydes (entries 1–6, Table 1) were easily coupled with **A**, resulting in the formation of the corresponding β-hydroxy amides (**1a–1f**). Regardless of the substituent on the aromatic ring, moderate isolated yields were consistently obtained. It should be emphasized that functional groups such as nitrile (entry 4, Table 1) and nitro (entry 6, Table 1) were tolerated by the novel organozinc reagent **A**. Not only aromatic aldehydes but also aliphatic aldehydes were excellent

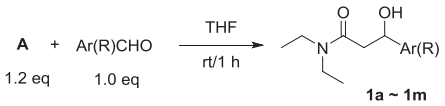


Scheme 1. Preparation and coupling reaction of zinc enolate of amide.

substrates to react with **A** under mild conditions. The corresponding products (**1g–1j**) were also achieved in moderate yields (entries 7, 9, and 10, Table 1) except *n*-pentanal (37%, entry 8). 2-Thiophene carbaldehyde coupled well with **A** to give rise to the corresponding product (**1k**) in 66% isolated yield (entry 11, Table 1). It was of interest that 2-furaldehyde and its derivatives were also suitable for the Reformatsky-like reaction, and the desired coupling products were successfully formed. Coupling of **A** with both furfural and 5-bromofurfural was executed, and the desired alcohols (**1l** and **1m**) were obtained in 50% and 71% isolated yields, respectively (entries 12, and 13, Table 1). Further study was conducted with highly conjugated furfural derivatives (entries 14–17, Table 1), leading to the complicated β-hydroxy amides (**1n–1q**) in moderate to excellent yields.

With these promising results in hand, the investigation was expanded to see if this protocol could be used for a much broader range of carbonyl compounds. With this aim, the study was executed with a wide variety of ketones, and the results are summarized in Table 2. The initial attempts were conducted with aromatic ketones bearing either an electron-withdrawing or electron-donating group. A nice conversion into the corresponding β-hydroxy amides (**2a** and **2b**) was observed (entries 1–2, Table 2) in good yields. For nitro-

Table 1. Coupling reaction of **A** with aldehydes



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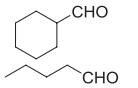
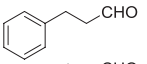
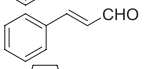
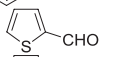
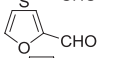
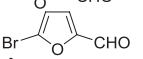
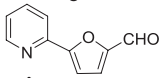
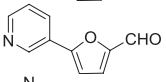
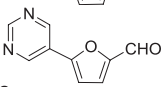
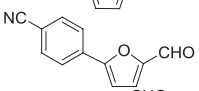
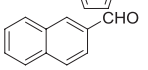
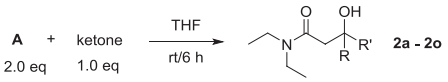
Entry	Ar(R)CHO	Product	Yield[a]
1	X= H	**1a**	55
2	3-Br	**1b**	55
3	4-Cl	**1c**	59
4	4-CN	**1d**	40
5	3,4-Cl_2	**1e**	60
6	4-NO_2	**1f**	56
7		**1g**	57
8		**1h**	37
9		**1i**	60
10		**1j**	63
11		**1k**	66
12		**1l**	50
13		**1m**	71
14		**1n**	95
15		**1o**	49
16		**1p**	65
17		**1q**	86
18		**1r**	65

[a] Isolated yield (based on aldehyde).

Table 2. Coupling reaction of **A** with ketones



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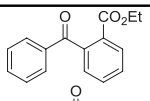
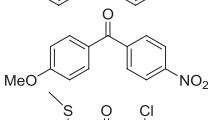
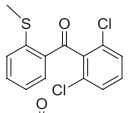
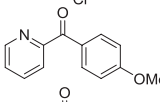
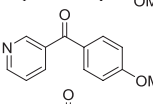
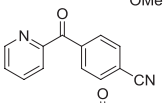
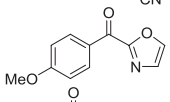
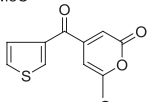
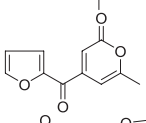
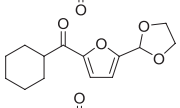
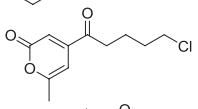
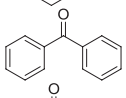
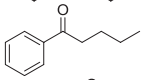
Entry	Ketone	Product	Yield[a]
1		**2a**	79
2[b]		**2b**	82
3		**2c**	nr[c]
4		**2d**	64
5		**2e**	76
6		**2f**	66
7		**2g**	94
8		**2h**	55
9		**2i**	70
10		**2j**	44
11		**2k**	43
12		**2l**	50
13		**2m**	34
14		**2n**	38
15		**2o**	85

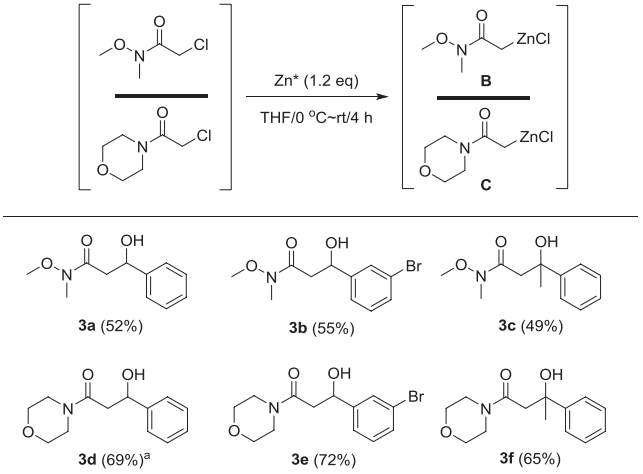
[a] Isolated yield (based on ketone).
[b] Catalytic amount of TMEDA used.
[c] No coupling took place.

substituted ketone, a catalytic amount of TMEDA was required to complete the reaction. A drawback was observed from the coupling reaction of **A** with a heavily hindered ketone (entry 3, Table 1). No coupling reaction took place under the conditions depicted in Table 1. To expand the general applicability of this protocol, we next sought to perform a more challenging coupling, which was accomplished with heteroaromatic ketones. Since the Mineno group[9] reported a double Reformatsky reaction especially with 2-benzoylpyridine in slightly different conditions from ours, it was of interest to compare the results. As seen in the results depicted in Table 2, we were pleased to observe the formation of the mono-adducts (**2d–2f**) in good yields. More heteroaromatic ketones (entries 7–9, Table 2) bearing thiophene, furan, pyrone, and oxazole rings were coupled well, furnishing various tertiary alcohol products (**2g–2i**).

Coupling reactions of **A** with heteroaromatic alkyl ketones (entries 10 and 11, Table 2) took place successfully and resulted in the formation of the expected β-hydroxy amides (**2j** and **2k**). From the results observed above, we anticipated that the coupling reaction of **A** with relatively simple ketones could be easily accomplished to give rise to hydroxyl amides. Thus, several readily available ketones (entries 12–15, Table 2) were employed in the coupling reactions, leading to the products (**2l–2o**) in moderate yields.

To investigate the generality of this strategy, more examples of zinc enolate of amides were prepared and coupled with carbonyl compounds. As described in Table 3, zinc enolates (**B** and **C**) were easily prepared utilizing the aforementioned conditions. Then, the obtained zinc enolates were applied to the Reformatsky-like reaction, affording the corresponding β-hydroxy amides in moderate yields. As mentioned above, 1.2 equiv and 2.0 equiv of zinc enolate (**B** or **C**) were employed in the reactions with aldehydes and ketones, respectively. The results are described in detail in Table 3.

Table 3. More examples.



Number in parenthesis is isolated yield (based on aldehyde or ketone).

In conclusion, we have developed an efficient synthetic route for the preparation of β-hydroxy amides.[10] The method involved the preparation of room-temperature-stable organozinc reagents (**A**, **B**, and **C**) in THF and their subsequent coupling reactions with various carbonyl derivatives under mild conditions. Significantly, this approach using zinc enolate of amides could expand the scope of Reformatsky-like reactions. Further studies to elucidate this synthetic protocol are currently under way in our laboratory.

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10. Representative procedures: Preparation of (2-(diethylamino)-2-oxoethyl)zinc chloride (**A**); In an oven-dried 100 mL round-

bottomed flask equipped with a stir bar was added 5.23 g of active zinc (Zn^*, 80.0 mmol). *N*,*N*-Diethylchloroacetamide (8.98 g, 60.0 mmol) was cannulated neat into the flask in an ice bath. The resulting mixture was then stirred for 4.0 h at ambient temperature. The whole mixture was settled down and then the supernatant was used for the subsequent coupling reactions. (b) Cross-coupling reaction of **A**. Into a 25-mL round-bottomed flask was placed 4-nitrobenzaldehyde (0.30 g, 2.0 mmol) and then 2.0 mL of THF was added into the flask under an argon atmosphere. Next, (2-(diethylamino)-2-oxoethyl)zinc chloride (5.0 mL, 0.5 M in THF, 2.5 mmol) was added, stirred at room temperature for 1.0 h, quenched with saturated NH_4Cl solution, extracted with ethyl ether (10 mL × 3), washed with saturated $NaHCO_3$, $Na_2S_2O_3$ solution, and brine, and then dried over anhydrous $MgSO_4$. Purification by column chromatography on silica gel (10% ethyl acetate/90% heptane) afforded 0.30 g of *N*,*N*-diethyl-3-hydroxy-3-(4-nitrophenyl)propanamide (**1f**) in 56% isolated yield as an off-white solid (m.p. 103–105 °C); ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 8.21 (d, *J* = 8.5 Hz, 2H), 7.59 (d, *J* = 8.5 Hz, 2H), 5.29 (br s, 1H), 5.24 (d, *J* = 10.0 Hz, 1H), 3.40 (dq, *J* = 7.5, 2.0 Hz, 1H), 3.25 (dq, *J* = 7.5, 2.0 Hz, 1H), 2.73 (dd, *J* = 16.0, 3.0 Hz, 1H), 2.58 (dd, *J* = 16.0, 10.0 Hz, 1H), 1.16 (t, *J* = 7.5 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 170.72, 150.62, 147.20, 126.60, 123.94, 69.86, 42.00, 41.32, 40.35, 14.09, 13.29. IR (KBr): ⊠ = 3320 (br), 2950, 2900, 1630, 1500, 1340 cm^{-1}.

