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Efficient synthesis of α,β-dichlorinated ketone from α,β-dichlorinated Weinreb amide through simple work-up procedure

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An efficient synthesis of α,β-dichlorinated ketones from α,β-dichlorinated Weinreb amides is described. Quenching with nonaqueous HCl avoided side reactions associated with typical work-up procedures. The amide reacted with various nucleophiles to give the corresponding ketones in high yields. A novel reactivity of the Weinreb amide is also discussed.

Weinreb amide,[1] a compound having the *N*-methoxy-*N*-methylcarbamoyl group, is employed as a useful precursor for preparation of ketones[2] and aldehydes[3] by treatment with nucleophiles. A unique property of the Weinreb amide is that it accepts only one equivalent of a nucleophile to form intermediate **A**, making addition of a second equivalent difficult.[4] In contrast, two nucleophile equivalents can be added to other carboxylic acid derivatives such as esters due to *in situ* formation of the corresponding ketone or aldehyde (Fig. 1, eq 1). Strategies utilizing the Weinreb amide have successfully been applied to the total syntheses of various natural products.[5] In addition to the preparation of ketones and aldehydes, the Weinreb amide is used as a directing group for C-H activation reactions.[6] Despite these many uses of the Weinreb amide as a synthetic building block, to the best of our knowledge, the addition of a nucleophile to an α,β-dihalogenated Weinreb amide has not been reported, except for amides with a fluorine atom at the β-position[7] or without an α-proton.[8] This is because the basicity of the nucleophile induces an undesired β-elimination reaction between the α-proton and β-halogen (Fig. 1, eq 2). As new halogenated natural products are being isolated with greater frequency,[9] such as chlorosulfolipids (CSLs), an intriguing family of natural products featuring highly chlorinated linear hydrocarbon skeletons,[10,11] new methodology for the addition of nucleophiles to Weinreb amides functionalized with chlorine atom(s) would enable rapid access to the scaffolds of these halogenated natural products. Herein, we describe a simple procedure toward the synthesis of α,β-dichlorinated ketones through nucleophilic addition to the corresponding α,β-dichlorinated Weinreb amides.

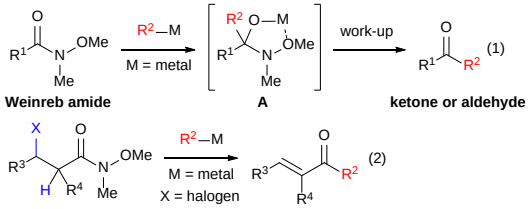

Fig. 1 Reactivity of Weinreb amide

First, reaction conditions were optimized using *anti*-dichloroamide **2** as a model substrate with *n*BuC≡CLi (**1a**) generated from 1-hexyne and *n*BuLi. The optimization results are shown in Table 1. Treatment of **2** with 3.0 equivalents of **1a** at –78 °C, –40 °C or 0 °C followed by an acidic quench using saturated aqueous NH_4Cl provided the undesired α,β-unsaturated ketone **4a** without any formation of the desired *anti*-dichloroketone **3a** (entries 1-3). Although the reaction at –78 °C resulted in partial recovery of **2** (entry 1), **4a** was obtained in high yield at –40 °C or 0 °C (entries 2 and 3). Clearly, the nucleophilic addition itself cleanly took place in these reactions. Thus, we envisioned that abstraction of the α-proton from **3a** could occur by basic substances generated during the acidic work-up, such as *N*-methoxy-*N*-methylamine, LiOH, and/or NH_3, due to the weak acidity of NH_4Cl (Fig. 2). When the reaction was quenched with 5.0 equivalents of CH_3COOH, as expected, **3a** was obtained along with **4a** in a 58:42 ratio (entry 4). Eventually, the ratio of **3a** to **4a** was considerably improved up to 85:15 through work-up with commercially available 4 M HCl in

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dioxane (entries 5-8). Remarkably, the reaction of **2** with 1.5 equivalents of **1a** (entry 8) gave almost the same result as that with 3.0 equivalents of **1a** (entry 6). Quenching with aqueous 1 M HCl decreased the amount of **3a** (61:39, entry 9). On the other hand, addition of a Lewis acid was not effective toward the selective synthesis of **3a** (entries 10-12). In these reactions, α,β-unsaturated amide **5**, an elimination product from **2**, was not observed by TLC or ^{1}H NMR spectroscopy. Additionally, nucleophilic addition with an α,β-dichlorinated aldehyde instead of the corresponding amide toward the homologation reaction just provided the β-eliminated aldehyde, suggesting that the Weinreb amide is a promising precursor for the homologation reaction through the addition reaction. This is the first achievement of the preparation of α,β-dichlorinated ketones from the corresponding α,β-dichlorinated Weinreb amides.

[UT1]Fig. 2 Proposed reaction pathway to provide unsaturated ketone **4**

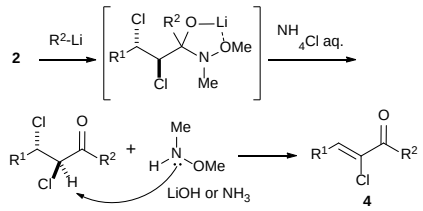
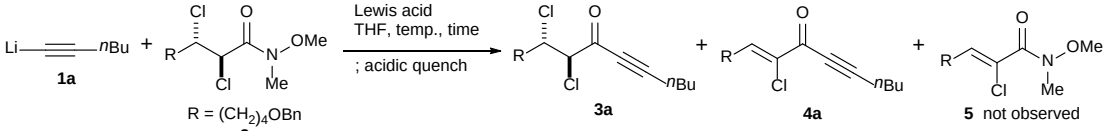


Table 1. Optimization of reaction conditions[a]



entry	**1a** (equiv.)	Lewis Acid[b]	Temp. (°C)	Time (min)	Acidic quench[c]	Ratio (**2a**:**3a**:**4a**)[d] and combined yield (**3a** + **4a**)
1	3.0	–	–78	30	*sat.* NH_4Cl	35:0:65, 59%
2	3.0	–	–40	30	*sat.* NH_4Cl	0:0:100, 94%
3	3.0	–	0	30	*sat.* NH_4Cl	0:0:100, 96%
4	3.0	–	0	30	CH_3COOH	0:58:42, 95%
5	3.0	–	0	30	4 M HCl in dioxane	0:76:24, 93%
6	3.0	–	0	10	4 M HCl in dioxane	0:85:15, 98%
7	3.0	–	–20	10	4 M HCl in dioxane	0:81:19, 95%
8	1.5	–	0	10	4 M HCl in dioxane	0:79:21, 94%
9	3.0	–	0	30	1 M HCl in H_2O	0:61:39, 92%
10	1.5	$BF_3 \cdot OEt_2$	0	30	4 M HCl in dioxane	64:26:10, 30%
11	1.5	$MgBr_2 \cdot OEt_2$	0	30	4 M HCl in dioxane	58:32:10, 39%
12	1.5	$CeCl_3$	0	30	4 M HCl in dioxane	10:60:30, 81%

[a] 0.3 mmol of **2** was used. [b] 1.5 equiv. of Lewis acid was used. [c] 5.0 equiv. of acid was used except for NH_4Cl. [d] ratio of **2**, **3a** and **4a** was estimated by crude ^{1}H NMR.

We next examined other nucleophiles in the addition reactions of **2**. The addition reactions were carried out with 1.5 equivalents of these nucleophiles. Results obtained after further optimizations of the reaction conditions are summarized in Table 2. As shown in entries 1 and 2, the ratio of products **2**, **3b**, and **4b** depended on the reaction temperature in the reactions with *n*BuLi (**1b**) (entries 1 and 2). *anti*-Dichloroketone **3b** was selectively formed in high yield at higher temperature (–20 °C) (entry 2). A high yield of *anti*-dichloroketone **3c** was obtained in a selective manner by using PhLi (**1c**) (entry 3). Grignard reagents were also good nucleophiles for the addition reactions. Thus, treatment of **2** with CH_3MgBr (**1d**), CH_2=CHMgCl (**1e**), or $nC_5H_{11}MgBr$ (**1f**) gave *anti*-dichloroketone **3d**, **3e** or **3f**, respectively, in high yield with high selectivity (entries 4-6). However, the reactions with PhMgBr (**1g**) and HC≡CMgCl (**1h**) proceeded with lower product ratios (entries 7-9) than those observed for the reactions with the corresponding Li reagents, PhLi (**1c**) (entry 3) and *n*BuC≡CLi (**1a**) (Table 1, entry 8), respectively. When **2** was reacted with *i*PrMgBr (**1i**), only α,β-unsaturated amide **6** was produced (entry 10). We believe that this is due to the high reducing ability of *i*PrMgBr (**1i**) toward the chlorine atom at the α-position of the carbonyl group.[12]

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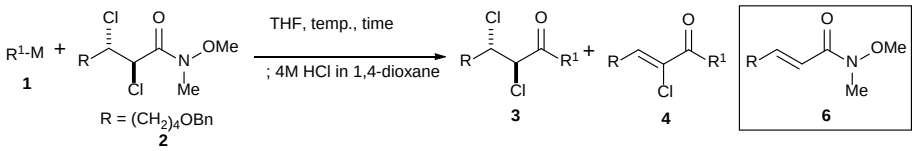
Table 2. Addition reactions of *anti*-dichloroamide **2** with various nucleophiles[a]



entry	R^1M (1.5 equiv.)	Temp. (°C)	Time (min)	Ratio (**2**:**3**:**4**)[b] and combined yield (**3** + **4**)
1	*n*BuLi (**1b**)	–40	30	19:58:23, 79%
2	*n*BuLi (**1b**)	–20	30	0:89:11, 98%
3	PhLi (**1c**)	–20	30	0:85:15, 94%
4	CH_3MgBr (**1d**)	0	120	0:91:9, 98%
5	CH_2=CHMgCl (**1e**)	0	120	0:95:5, 97%
6	$nC_5H_{11}MgBr$ (**1f**)	0	120	0:87:13, 96%
7	PhMgBr (**1g**)	0	120	13:51:36, 83%
8	PhMgBr (**1g**)	0	240	0:64:36, 96%
9	HC≡CMgCl (**1h**)	0	120	0:35:65, 90%
10	*i*PrMgBr (**1i**)	0	240	**6** (93%)

[a] 0.3 mmol of **2** was used. [b] ratio of **2**, **3** and **4** was estimated by crude ^{1}H NMR.

syn-Dichloroamide **7** was also employed in the addition reaction. Some screenings of reaction conditions with **7** were again required for efficient formation of desired *syn*-dichloroketones **8**. The results are depicted in Table 3. As shown in entries 1 and 2, during the reactions of **7** with *n*BuC≡CLi (**1a**), a higher ratio of *syn*-dichloroketone **8a** was obtained at lower temperature (–40 °C). The addition reaction with *n*BuLi (**1b**) also provided *syn*-dichloroketone **8b** in high yield (entry 3). Both of the reactions of *syn*-dichloroamide **7** with *n*BuC≡CLi (**1a**) and *n*BuLi (**1b**) smoothly proceeded with high selectivities to give **8a** and **8b** in high yields, similar to those for *anti*-dichloroamide **2** with **1a** (Table 1, entry 6) and **1b** (Table 2, entry 2). However, treatment of **7** with PhLi (**1c**) only produced elimination product **4c** (entry 3), in stark contrast to the reaction of **2** with **1c** (Table 2, entry 3). Among the Grignard reagents examined, CH_3MgBr (**1d**) was found to be a good nucleophile in the reaction of **7** at lower temperature (–20 °C) (entries 5 and 6). The addition reaction with $nC_5H_{11}MgBr$ (**1f**) produced *syn*-dichloroketone **8f** as a major product in moderate yield (entry 9). However, other Grignard reagents **1e**, **1g**, and **1h** were not effective for formation of **8** (entries 7, 8, 10, and 11). For example, treatment of **7** with CH_2=CHMgCl (**1e**) at 0 °C afforded elimination product **4e** as a single product, and the reaction at –40 °C resulted in recovery of **7** along with **4e** (entries 7 and 8). Similar to the reductive elimination reaction of **2** with *i*PrMgBr (**1i**) (Table 2, entry 10), treatment of **7** with *i*PrMgBr (**1i**) only yielded **6** (entry 12).

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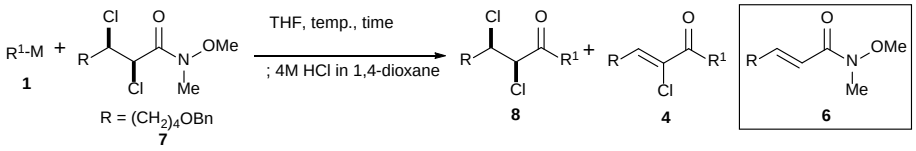
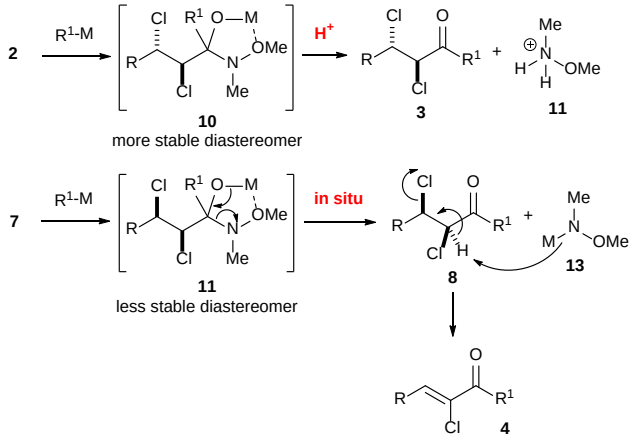
Table 3. Addition reactions of *syn*-dichloroamide **7** with various nucleophiles[a]



entry	R^1M (1.5 equiv.)	Temp. (°C)	Time (min)	Ratio (**7**:**8**:**4**)[b] and combined yield (**8**+**4**)
1	*n*BuC≡CLi (**1a**)[c]	–20	10	0:81:19, 94%
2	*n*BuC≡CLi (**1a**)[c]	–40	10	0:91:9, 95%
3	*n*BuLi (**1b**)	–40	30	0:83:17, 95%
4	PhLi (**1c**)	–20	30	0:0:100, 78%
5	CH_3MgBr (**1d**)	0	120	0:0:100, 94%
6	CH_3MgBr (**1d**)	–20	120	0:88:12, 95%
7	CH_2=CHMgCl (**1e**)	0	120	0:0:100, 90%
8	CH_2=CHMgCl (**1e**)	–40	30	45:0:55, 51%
9	$nC_5H_{11}MgBr$ (**1f**)	–20	120	0:54:46, 90%
10	PhMgBr (**1g**)	–20	120	26:0:74, 74%
11	HC≡CMgCl (**1h**)	0	120	100:0:0, 0%
12	*i*PMgBr (**1i**)	0	240	**6** (90%)

It has been revealed that the diastereomers, *anti*-dichloroamide **2** and *syn*-dichloroamide **7**, showed different reactivities in the addition reaction. We propose the rationale for this shown in Fig. 3 based on the stability of five-membered ring intermediates **10** and **11**, which are formed by the addition of a nucleophile to **2** and **7**, respectively. As shown in Table 4, when carrying out the addition reaction of **2** with 1.5 equivalents of *n*BuLi (**1b**) at 0 °C (entry 1), the amount of elimination product **4b** significantly increased as compared to the reaction of **2** with **1b** at –20 °C (Table 2, entry 2). It thus seems feasible that **4b** was generated via *in situ* formation of *anti*-dichloroketone **3b** and subsequent elimination before acidic treatment with anhydrous HCl in dioxane. Therefore, we believe that **11** is less stable than **10** and releases *syn*-dichloroketone **8** and lithium or magnesium *N*,*O*-dimethylhydroxyamide **13**, which then acts as a base for abstraction of the α-proton of **8**, giving elimination product **4**. Incidentally, we also performed the addition reaction of **2** with **1b** at room temperature (entries 2-4). To our surprise, α,β-unsaturated ketone **14** without a chlorine atom was obtained along with **4b**, although **3b** was not detected in the

[UT2]Fig. 3 Proposed mechanism for the different reactivities of *anti*-dichloroamide **2** and *syn*-dichloroamide **7**.



^1H NMR spectrum (entry 2). A longer reaction time induced an increase in the amount of **14** with a lower combined yield (entries 3 and 4). For the generation of **14**, two reaction pathways are possible: (1) *n*BuLi reduces the chloride, or (2) **13**

acts as the reducing agent. These possibilities were explored by the following control experiments using a mixture of **3b** and **4b** (94:6), prepared under the conditions of entry 2 in Table 2 (Scheme 1). The mixture was subjected to *n*BuLi at room temperature to afford **4b** as a sole product, suggesting that *n*BuLi acted as a base (Scheme 1). By treatment of the same mixture at room temperature with **13** generated from *N*,*O*-dimethylhydroxyammonium chloride and *n*BuLi, the mixture of **3b** and **4b** was converted to that of **4b** and **14** (89:11), indicating that **13** has the potential to reduce the chlorine atom attached to the α-position of the carbonyl group. To the best of our knowledge, this is the first example of the reducing ability of lithium *N*,*O*-dimethylhydroxyamide.

Scheme 1. Reactivity of lithium *N*-methyl-*O*-methylamide **13**.

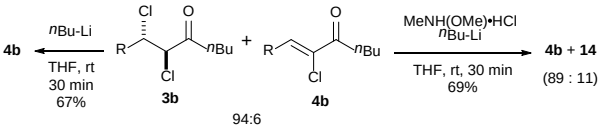
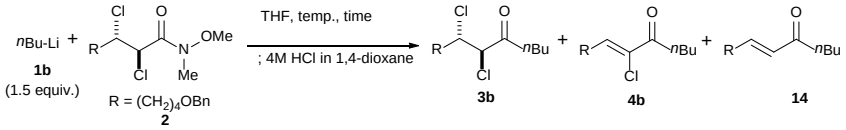


Table 4. Reactivity of **2** at higher temperature.



entry	Temp.	Time	Ratio (**3b**:**4b**:**14**) [a] and combined yield (**3b** + **4b** + **14**)
1	0 °C	10 min	62:38:0, 97%
2	rt	30 min	0:55:45, 72%
3	rt	12 h	0:49:51, 61%
4	rt	24 h	0:40:60, 39%

Conclusions

In summary, we have reported the efficient synthesis of ketones through addition of various nucleophiles to Weinreb amides containing two chlorine atoms at the α- and β-positions of the carbonyl group. Work-up with anhydrous HCl in dioxane enabled selective syntheses of α,β-dichlorinated ketones in high product ratios of up to 95:5, whereas normal aqueous quenches using saturated NH_4Cl or 1 M HCl solution resulted in the formation of elimination products. In contrast to α,β-dichlorinated Weinreb amides, nucleophilic addition with the corresponding α,β-dichlorinated aldehydes only provided α,β-unsaturated α-chloroaldehydes. Therefore, from the viewpoint of synthetic studies on chlorosulfolipids (CSLs),[11] the nucleophilic addition reaction with polychlorinated Weinreb amides would be a powerful method for elongation of hydrocarbon frameworks densely functionalized with chlorine atoms. Further studies with lithium *N*,*O*-dimethylhydroxyamides are also currently underway in our laboratory.

Authour contributions

T. U. designed and conducted the project. N. I. P. carried out the optimization, synthesis and characterization. T. U. and F. M. analyzed the data and wrote the paper.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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