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Tandem *N,N*-Dialkylation Reaction of *N*-Trimethylsilyl α-Iminoesters Utilizing an Umpolung Reaction and Characteristics of the Silyl Substituent: Synthesis of Pyrrolidine, Piperidine, and Iminodiacetate

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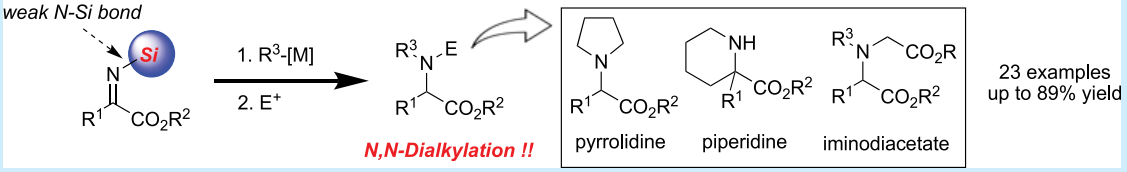
Supporting Information

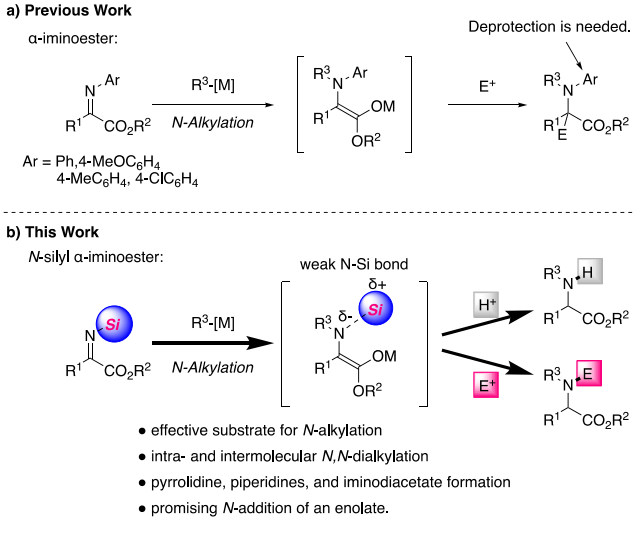


ABSTRACT: Umpolung reactions of *N*-trimethylsilyl α-iminoester with organometallics gave directly *N*-alkylaminoesters in high yields without the need for removing a protecting group at the nitrogen atom. Efficient syntheses of pyrrolidines, piperidines, and iminodiacetate derivatives were also developed via tandem *N,N*- or *N,C*-dialkylation reactions utilizing characteristics of the silyl substituent. Furthermore, under the influence of silica gel, the addition of an enolate to the imino nitrogen proceeded to give an iminodiacetate derivative.

Nitrogen-containing compounds are the most fundamental and important compounds widely existing in various fields such as pharmaceuticals, agrochemicals, and biological science. A number of efficient methods for introducing nitrogen atoms into the target molecules have been developed so far. Although the generally accepted method involves the use of imines as electrophiles, imines derived from ammonia are usually unstable and difficult to handle because they easily undergo trimerization or hydrolysis back to the starting materials. Metalloimines have attracted attention as relatively stable imine equivalents derived from ammonia. The advantage of metalloimines is that they can easily be transformed into unprotected N−H derivatives with only hydrolysis.[1] In particular, silylimine is known to exhibit intriguing reactivity as nucleophiles and electrophiles.[2]

The α-iminoester is a highly reactive imine due to the adjacent electron-withdrawing group. In general, *C*-alkylation proceeds with a nucleophile,[3] while in rare cases, an umpolung *N*-alkylation occurs under certain reaction conditions. Our laboratory has previously developed various tandem C−C bond formation reactions utilizing umpolung reactivity of α-iminoesters with organometallic reagents.[4,5] We recently reported the umpolung reaction of α-imino thioesters and syntheses of β-substituted-α-aminothioester via the unexpected alkylthio rearrangement.[4w] However, in our conventional umpolung reaction, most of substituents of the imino nitrogen were limited to aryl groups such as phenyl, 4-$MeOC_6H_4$, 4-MeC_6H_4, and 4-ClC_6H_4 (Scheme 1a). For conversion into NH-free amino acids or physiologically active compounds, it is often necessary to remove the substituent at the nitrogen.[4c] In

Scheme 1. Previous Work and This Work



order to develop a more efficient and shortcut transformation reaction utilizing umpolung of α-iminoester, we devised *N*-silyl α-iminoester as a new substrate. Herein, we would report that the umpolung reaction of *N*-silyl α-iminoester provides *N*-unprotected α-aminoesters directly without further deprotection, and the intra- and intermolecular tandem *N,N*-

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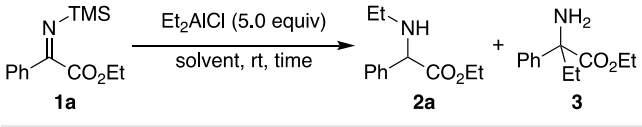
dialkylation reaction utilizing characteristics of the N−Si bond also proceeds to afford various pyrrolidines, piperidines, and iminodiacetate derivatives in high yields. Furthermore, we found an *N*-addition of an ester enolate (Scheme 1b).

As a result of various examinations into the synthesis of *N*-silyl *α*-iminoester as a new substrate, we found that *α*-iminoester **1a** could be synthesized from ethyl benzoylformate in a single step (see the Supporting Information). Initially, when we carried out *N*-alkylation of *N*-silyl *α*-iminoester **1a** with 5 equiv of diethylaluminum chloride in EtCN at room temperature for 2.5 h, the desired *N*-ethylated product **2a** was obtained in 28% yield along with a side product of *C*-ethylated compound **3** in 17% yield (Table 1, entry 1). This promising result led us to further examine several reaction parameters such as solvents, nucleophiles, and the amount of nucleophiles in this reaction (Table 1 and Tables S2 and S3). Regarding the reaction solvents shown in Table 1, we found that using polar solvents such as MeCN, DMSO, and DMF gave the *N*-ethylated product **2a** in moderate to good yields (entries 2−4), while in nonpolar solvents such as toluene, hexane, CH_2Cl_2, and $C_2H_4Cl_2$ the reaction provided the *C*-addition product **3** instead of *N*-addition counterpart in 17−35% yields (entries 5−8). Although we found that various ethers such as Et_2O, DME, dioxane, CPME, and TBME were not effective for suppressing *C*-addition reactions (entries 9−13), THF and 2-MeTHF worked well to afford the *N*-alkylated product **2a** selectively in moderate to good yields (entries 14−17).

We next investigated the scope of substrates and nucleophiles under the optimized reaction conditions (see Supporting Information), and the results are shown in Scheme 2. All of the substrates examined having various ester moieties such as Me, Et, ^{i}Pr, ^{t}Bu, and Cy groups underwent *N*-addition reaction to afford the desired products **2a−e** in good to high yields. Among them, *tert*-butyl esters gave clean reaction media, showing that a bulky substituent of the ester moiety could suppress the side reactions to increase the yields. Regarding the aryl group (R^1), *α*-aryl iminoesters with both electron-rich and electron-deficient substitutents reacted read-

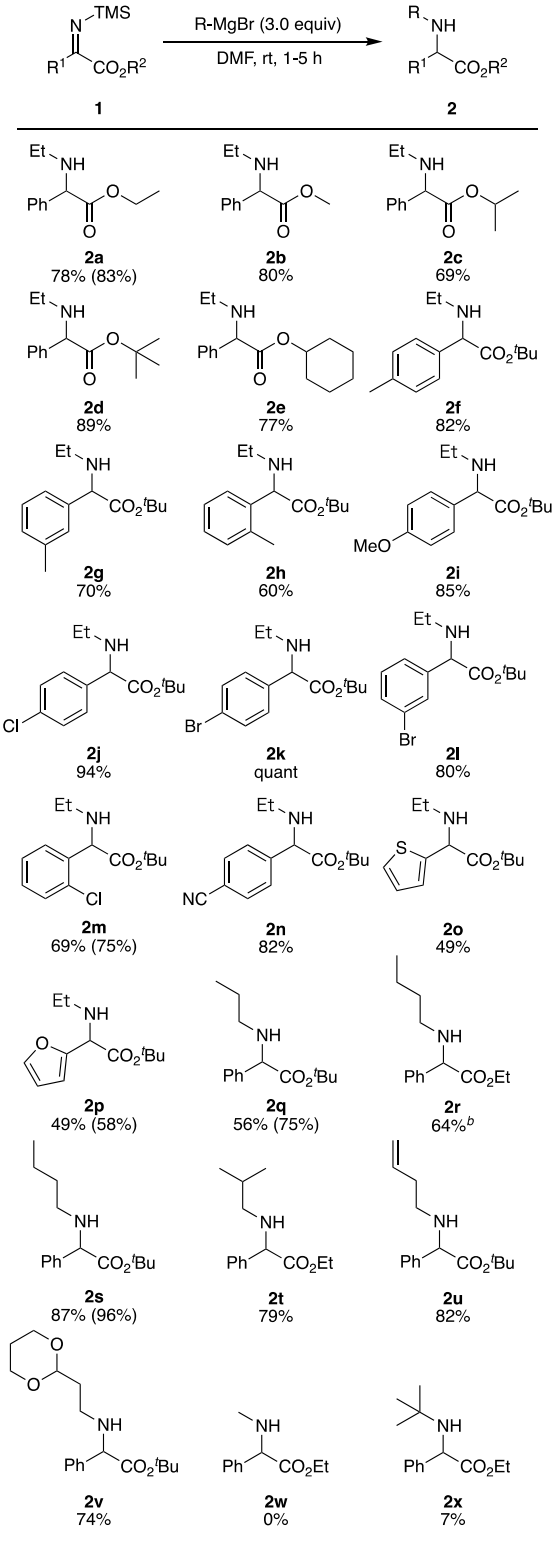
Table 1. Examination of Solvents for *N*-Alkylation of *N*-Silyl *α*-Iminoester[a]



entry	solvent	time (h)	**2a** (%)[b]	**3** (%)[b]
1	EtCN	2.5	28	17
2	MeCN	2.5	30	22
3	DMSO	3.5	42	3
4	DMF	14	59	0
5	toluene	9	7	22
6	hexane	3	8	35
7	CH_2Cl_2	3.5	3	29
8	$C_2H_4Cl_2$	3	0	17
9	Et_2O	3	15	15
10	DME	9	30	20
11	dioxane	3	44	13
12	CPME	3	24	25
13	TBME	3	26	42
14	THF	3	60	1
15	2-MeTHF	4	62	2
16[c]	2-MeTHF	3	55	4
17[d]	2-MeTHF	3	64	1

[a]The reaction was carried out according to the general procedure (see the Supporting Information). [b]Isolated yield. [c]2-MeTHF was used as received. [d]Degassed 2-MeTHF was used.

Scheme 2. Scope of Substrates for *N*-Alkylation of *N*-Silyl *α*-Iminoester[a]



[a]Yield using 5.0 equiv of Grignard reagent is shown in parentheses. [b]^{n}BuLi (5.0 equiv) was used as a nucleophile in 2-MeTHF.

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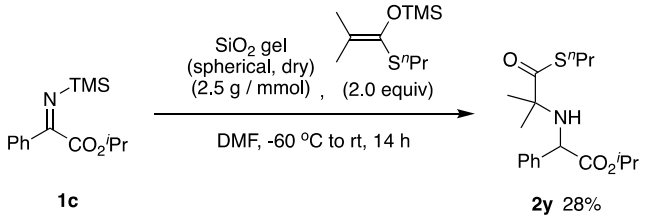
ily to provide the desired products **2f–p** in high yields. We found that *ortho-*, *meta-*, or *para-* and electron-donating or electron-withdrawing substituents were applicable (**2f–m**). It is noteworthy that even in the presence of a CN group the desired aminoester **2n** was obtained in 82% yield. Heteroaryl groups such as 2-thienyl and 2-furyl were also tolerated (**2o** and **2p**). In the case of primary Grignard reagents such as Et, ^{n}Pr, ^{n}Bu, and ^{i}BuMgX, the desired *N*-alkylated products **2a**, **2q**, **2r**, **2s**, and **2t** were obtained in good yields, while with Me and ^{t}Bu Grignard reagents the reaction did not proceed well (**2w** and **2x**). When Grignard reagents with homoallyl and primary alkyl groups having an acetal were used, the reaction products **2u** and **2v** were also obtained in good to high yields. However, aryl Grignard reagents such as PhMgBr were not effective in this reaction.

During examination into nucleophiles, when ketene silyl thioacetal was used as an enolate-type nucleophile in the presence of silica gel, *N*-addition product **2y** was obtained in 28% yield (Scheme 3). This is a promising result of *N*-addition

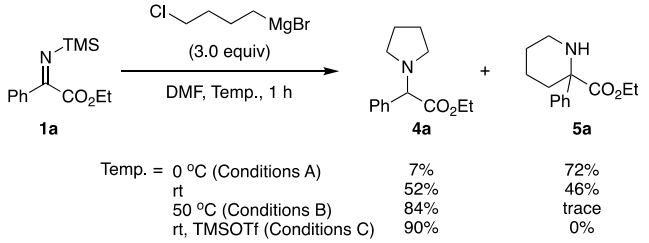
Scheme 3. *N*-Addition of Enolate for *N*-Silyl *α*-Iminoester



reaction of a sterically congested enolate onto the imino nitrogen utilizing characteristics of *N*-silyl *α*-iminoester, despite the low yields of the desired products.

Next, for the development of a tandem C–C bond formation reaction utilizing umpolung reaction of the present *N*-silyl *α*-iminoester, the reaction with haloalkyl Grignard reagents was carried out at room temperature. Not only the 6-membered ring product **5a** but also the unexpected 5-membered ring product **4a** were obtained in 46% and 52% yields, respectively (Scheme 4). This result indicates that a

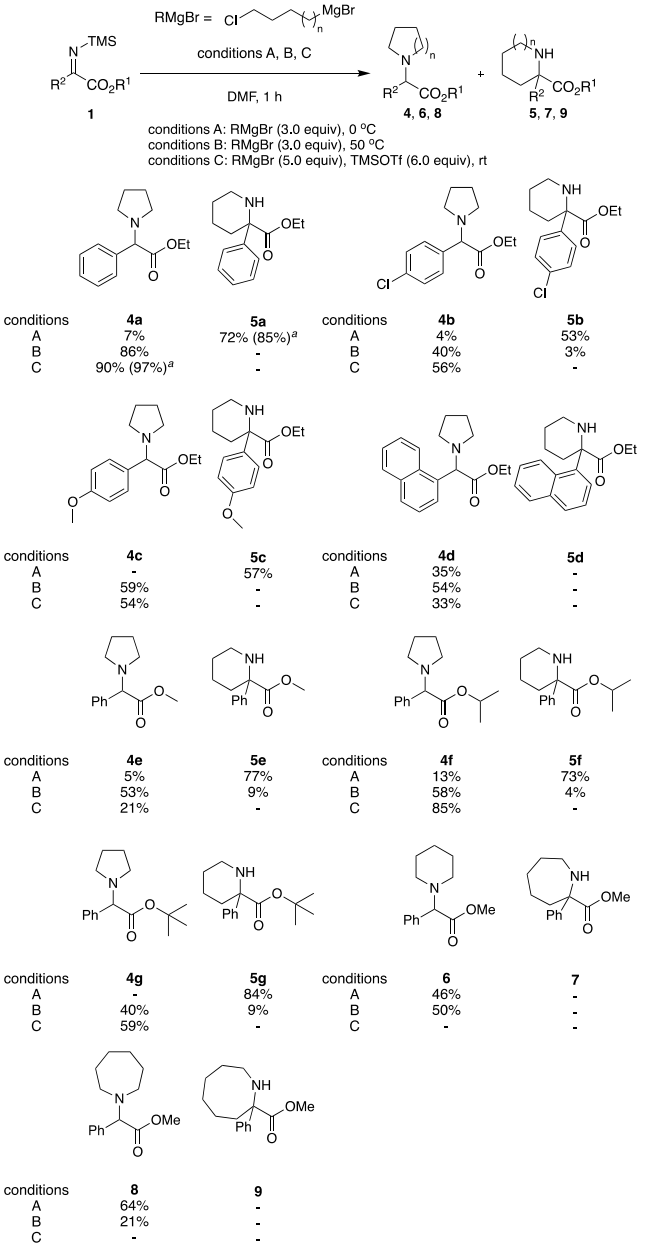
Scheme 4. Optimization of Tandem *N*-Alkylation/ Intramolecular Cyclization



nucleophilic addition occurred followed by an electrophilic alkylation at the amino nitrogen to give the 5-membered ring product **4a**. After more detailed examination of the reaction conditions, we found that the 6-membered ring product **5a** was obtained in 72% yield at a low temperature (0 °C, conditions A), while the pyrrolidine **4a** was obtained selectively in 84% yield at a higher reaction temperature (50 °C, conditions B). Furthermore, pyrrolidine **4a** was formed in 90% yield as a sole product when TMSOTf was used as an additive in this reaction (conditions C). It is noteworthy that this *N,N*-dialkylation reaction is an intriguing reaction utilizing the characteristics of the silicon atom in addition to the conventional tandem umpolung reaction.

The scope of substrates and nucleophiles for the selective *N,N*-dialkylation and *N,C*-dialkylation were investigated under the optimal three sets of reaction conditions (conditions A–C) (Scheme 5). Reactions at a lower temperature of conditions A

Scheme 5. Scope of Substrates for Tandem *N*-Alkylation/ Intramolecular Cyclization



[a]The reaction was carried out on a 1 mmol scale.

produced *N,C*-dialkylated piperidines **5a–g** as major products in good to high yields, which indicates that this procedure offers a good addition to existing piperidine synthesis.[6] Under the reaction condition B, electronic and steric effects of the substituents on the aryl ring or the ester moiety of the iminoester did not exhibit a strong influence on the reactivity to afford the pyrrolidines **4a–g** in moderate to high yields. We

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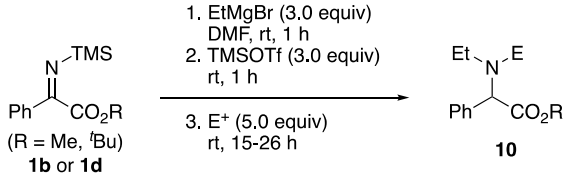
also found that the yield decreased as the ring size increased (**6**, **8**). When the substituent α- to the imino group is bulky such as 1-naphthyl or the ring size of the cyclized compound is seven or eight, *N,C*-dialkylated products were not obtained at all, but instead, the *N,N*-dialkylated products were obtained (**4d**, **6**, **8**).

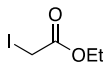
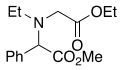
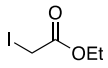
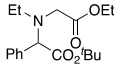
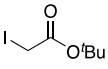
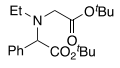
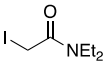
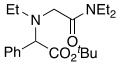
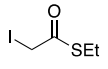
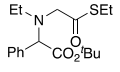
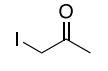
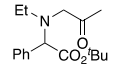
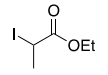
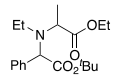
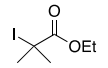
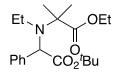
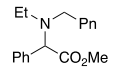
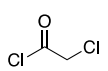
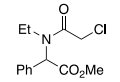
We next examined an intermolecular version of the present reaction. Optimization of the intermolecular tandem *N,N*-dialkylation reaction was carried out regarding electrophiles, additives, and the amount of reagents. As the result, we found that TMSOTf was also the most effective additive in this reaction, and iodinated compounds were suitable electrophiles to provide the desired products (see the Supporting Information). Since iminodiacetate derivatives could be synthesized by using an α-halocarbonyl compound as an electrophile, we examined the scope of electrophiles under the optimized reaction conditions, and the results are summarized in Table 2. When various α-iodocarbonyl compounds derived from esters, amides, thioesters, and ketones were used as electrophiles, the desired products **10a**–**f** were obtained in moderate to high yields. In the case of α-di- and trisubstituted iodocarbonyl compounds, the yield was drastically decreased due to their steric congestions (**10g**, **10h**). On the other hand, benzyl bromide and 2-chloroacetyl chloride worked well in this reaction to give the desired *N,N*-dialkylated products **10i** and **10j** in high yields as well. This reaction is a useful one that makes it possible to synthesize iminodiacetate derivatives, one of the most important tridentate ligands in organometallic chemistry.[7]

Although more detailed examination is needed, at the present stage we propose a plausible reaction mechanism for cyclization shown in Scheme 6. First, a Grignard reagent coordinates with the imino nitrogen and the carbonyl oxygen to activate the *N*-silyl α-iminoester via five-membered intermediate **I**. *N*-Alkylation proceeds to form the enolate intermediate **II**, which reacts with haloalkyl moiety of the Grignard reagent at low temperature to give the six-membered product **5** (*C*-alkylation), while at higher temperatures the formation of the pentavalent silicate intermediate **III**[8] would occur followed by that of the bromomagnesium amide **IV** via a silyl transfer, and the cyclization of the amide proceeds to provide the five-membered product **4** (*N*-alkylation). In the presence of TMSOTf, formation of the bis-silylated intermediate **V** may account for the *N*-alkylation to give the pyrrolidine **4**.[9,10]

In summary, we have found that *N*-silyl α-iminoester is a useful substrate for umpolung reactions to afford, after hydrolysis, the unprotected amino esters directly. We also developed selective intra- and intermolecular *N,N*-dialkylation reaction utilizing the characteristics of silicon atom to give pyrrolidines, piperidines, and α-amino dicarbonyls in high yields. The present method is an attractive one in terms of controlling the regioselectivity (*C* vs *N*-alkylation) only by choosing an appropriate reaction temperature or adding TMSOTf. Moreover, an enolate addition to the imino nitrogen also proceeded to give an iminodiacetate derivative possessing a bulky substituent, which is promising for the development of a new amination reaction of enolates, leading to the synthesis of iminodiacetate of importance as tridentate ligands.

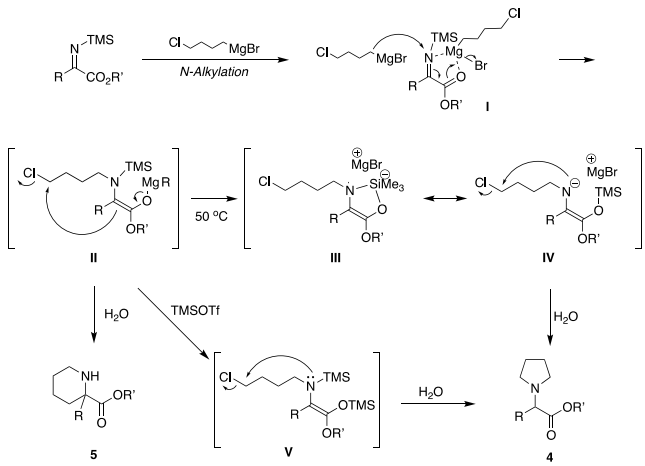
Table 2. Tandem *N,N*-Dialkylation Reaction of *N*-Silyl α-Iminoester



entry	E^+	product		yield (%)
1			**10a**	82
2			**10b**	89
3			**10c**	81
4			**10d**	51
5			**10e**	75
6			**10f**	79
7[a]			**10g**	13
8			**10h**	0
9	BnBr		**10i**	75
10			**10j**	67

[a]The reaction was carried out at 50 °C.

Scheme 6. Proposed Reaction Mechanism



■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedure and compound characterization data (PDF)

^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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