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Umpolung Reaction of α-Imino Thioesters and the Subsequent C−C Bond Formation with the Unexpected Alkylthio Rearrangement

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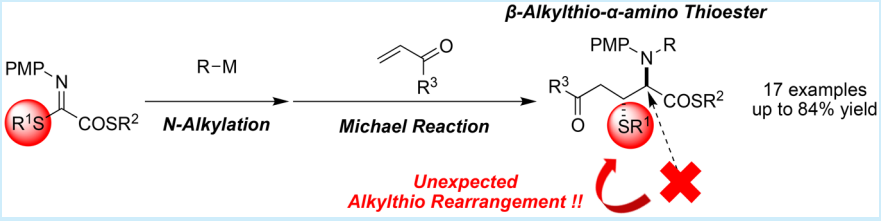
Supporting Information



ABSTRACT: An umpolung reaction of the α-imino thioester was examined, and we found that α-imino thioesters were more effective substrates for the umpolung *N*-alkylation than conventional α-imino esters and they gave *N*-alkylated amino thioesters in high yields under mild reaction conditions in a short time. A new type of C−C bond formation followed by an unexpected rearrangement of the alkylthio group took place with the unsaturated ketones to afford the β-alkylthio-α-amino thioesters in high yields with good diastereoselectivity.

Thioesters are known to have higher reactivity than their normal ester counterparts and can be utilized for further functionalizations such as the introduction of an acyl group.[1] Among them, aminothioesters are important reaction precursors utilized for enamide and aminoketone synthesis via various cross-coupling reactions.[2] Especially, β-substituted-α-amino thioesters can be transformed into β-substituted α-amino acids which can serve as known conformationaly constrained analogues of α-amino acids and can be found in several peptide natural products.[3] Although numerous efforts have been devoted to construct this framework, more useful synthetic methods are still required.

In our laboratory, we have explored the umpolung reactions of α-imino esters and developed various types of tandem *N*-alkylation/C−C bond formation reactions,[4] which include the syntheses of α-quaternary alkynyl amino esters through the use of *N*-addition to β,γ-alkynyl α-imino esters,[4n] a highly regioselective tandem *N*-alkylation/vinylogous aldol reaction of β,γ-alkenyl α-imino esters,[4o,u] and an *N,N,C*- trialkylation reaction to introduce various nucleophiles at the imino nitrogen and carbon atoms.[4r] However, regarding the *N*-alkylation reaction, an umpolung of the α-imino ester is difficult due to the electronegativity of the imino group,[5] and use of excess nucleophiles is needed; there are some limitations for the scope of substrates and nucleophiles.[6] We prepared α-imino thioesters as new substrates, and herein we report that these substrates are suitable for umpolung *N*-alkylation and have unique reactivity for the tandem C−C bond formation in good yields and diastereoselectivity to give β-alkylthio-α-amino thioesters, precursors to β-substituted α-amino acids. In most cases, umpolung reactions of α-imino thioesters proceed more efficiently than those of conventional α-imino esters; only a small excess amount of the organometallic reagent is needed under milder reaction conditions in a short time. *N*-Methylation and *N*-phenylation reactions, which do not readily proceed with conventional α-imino esters, can be used. In addition, the tandem reaction with α-imino thioesters can create useful products utilizing the elimination ability of the alkylthio group.

Regarding the synthesis of the α-imino thioester **1a** as a new substrate, we prepared **1a** (PMP = 4-MeOC$_6$H$_4$) in four steps from oxalyl chloride in 46% overall yield (see Supporting Information). Next, an umpolung *N*-alkylation reaction was performed with α-imino thioester **1a** and 2 equiv of diethylaluminum chloride in DME at room temperature for 15 min, and we found that the reaction proceeded to afford the desired *N*-ethylated product **2a** quantitatively (Table 1, entry1). Gratifyingly, the *N*-ethylated product **2a** was also obtained quantitatively when the amount of diethylaluminum chloride was decreased to 1.2 equiv (entry 2), while the use of a stoichiometric amount of aluminum reagent decreased the yield slightly to an 89% yield (entry 3). The use of other organometallic reagents such as EtAlCl$_2$, EtMgBr, and Et$_2$Zn also gave the product **2a** in good to high yields (entries 4−6). Among the other solvents examined (toluene, EtCN, CH$_2$Cl$_2$), DME was found to be the optimal solvent (entries 7−9). It is noteworthy that, in contrast to the use of an excess of the organometallic reagent for the conventional umpolung reaction to α-imino esters,[4d] this umpolung reaction to the α-imino thioester proceeded under the mild reaction conditions in a short time with only 1.2 equiv of the organometallic reagent.

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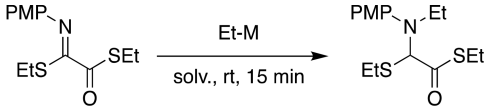
Table 1. Optimization of *N*-Alkylation to α-Imino Thioester[a]



1a **2a**

PMP = 4-MeOC$_6$H$_4$

entry	Et–M (equiv)	solv.	yield (%)[b]
1	Et_2AlCl (2)	DME	quant
2	Et_2AlCl (1.2)	DME	quant
3	Et_2AlCl (1)	DME	89
4	$EtAlCl_2$ (2)	DME	84
5	EtMgBr (1.2)	DME	78
6	Et_2Zn (1.2)	DME	74
7	Et_2AlCl (1.2)	toluene	71
8	Et_2AlCl (1.2)	EtCN	87
9	Et_2AlCl (1.2)	CH_2Cl_2	64

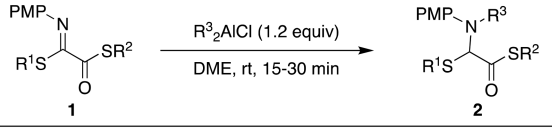
[a]The reaction was carried out according to the general procedure (see the Supporting Information). [b]Isolated yield.

We next examined the scope of substrates and nucleophiles under the optimized conditions (Table 1, entry 2), and the results are shown in Scheme 1. *N*-Alkylation of substituted *S*-ethyl iminothioates bearing a primary and secondary alkylthio such as isopropyl and cyclopropyl afforded the corresponding *N*-alkylated products **2a–c** in good to high yields. Phenyl, allyl, and benzyl groups also survived the *N*-alkylation reactions conditions (**2d–f**). An investigation into the thioester moiety was also carried out. Various substrates having primary, secondary, and tertiary alkyl thioesters, including the allyl group, provided products **2g–k** in high yields. Furthermore, reactions using various nucleophiles including Grignard reagents were carried out. Surprisingly, *N*-methylation and *N*-phenylation to the imino thioester proceeded to give the *N*-addition products **2l,t** in high to quantitative yields, where the introduction of methyl and phenyl groups was difficult in the conventional umpolung *N*-alkylation reactions. Other linear and branched alkyl Grignard reagents did not affect the reaction (**2m–p**). *N*-Addition of homoallyl and primary alkyl Grignard reagents having acetals gave the products **2q–s** in good to high yields. It is noteworthy that *N*-addition of Grignard reagents bearing electron-rich and electron-deficient aromatic substituents gave the desired product **2t–y** in low to good yields, which is contrary to our previous reports.[4o]

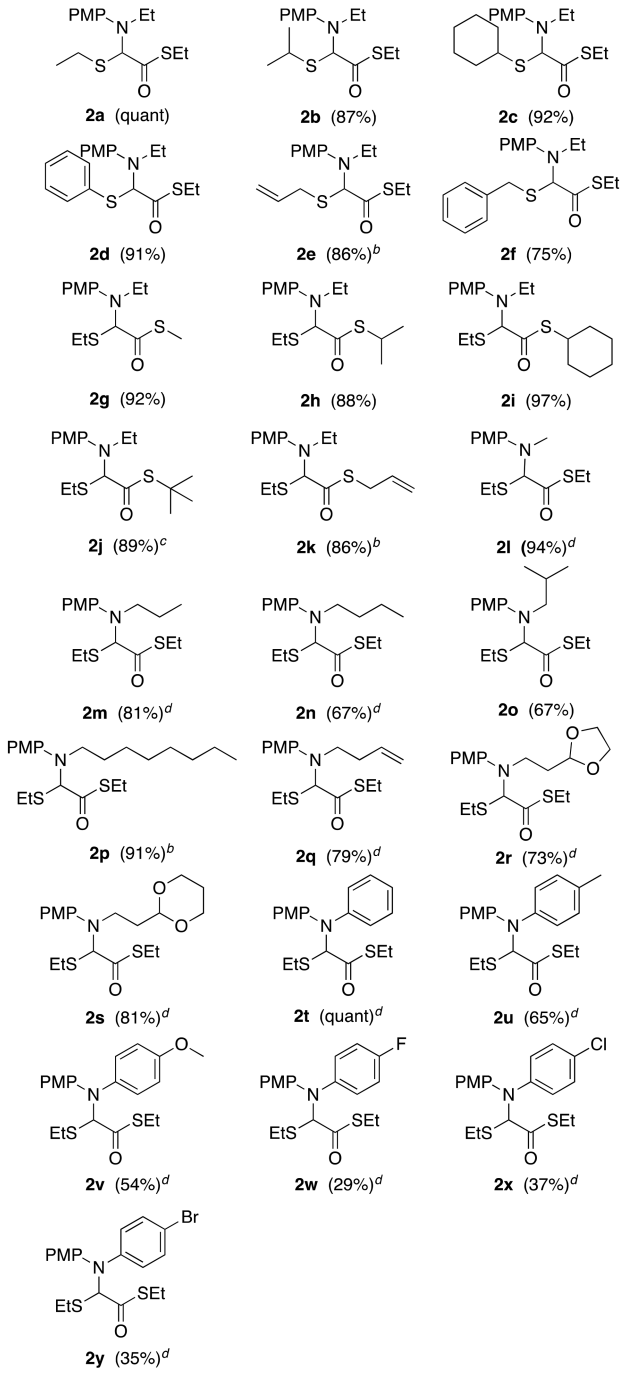
In order to ascertain the differences in reactivity between the α-imino esters and the α-imino thioesters, a comparison experiment was carried out (Scheme 2a). When the α-imino ester **3** derived from ethyl benzoylformate reacted with Et_2AlCl for 15 min, the desired *N*-ethylated product **4** was obtained in 4% yield, along with recovery of the starting material (70%), while when the α-imino thioester **5** derived from benzoyl formic acid was used, under the same reaction conditions, the *N*-ethylated product **6** was obtained in 80% yield with only 5% recovery of the starting materials. These results indicate that the α-imino thioester is extremely effective for the umpolung reaction.

To clarify the exact origin of the reactivity of these substrates, a computational study was carried out using the Gaussian 03 program[7] (Scheme 2b). All structures, **3**, **5**, and **1a**, were fully optimized followed by frequency caluculation on the stationary point performed with a 6-31G(d) basis set for all atoms, which

Scheme 1. Scope of Substrates and Nucleophiles for *N*-Alkylation to α-Imino Thioester[a]



1 **2**



[a]Purification was carried out using buffer TLC. [b]Et_2AlCl (1.5–2.0 equiv) was used. [c]Recovery of starting material. [d]R^3MgBr in THF (1.5–2.5 equiv) was used instead of R^3AlCl.

employed a B3LYP density functional theory.[8,9] After the structural optimization, we found that the LUMO energies of each molecule were −0.0627, −0.0756, and −0.0721, respectively, which means that the reactivity of α-imino

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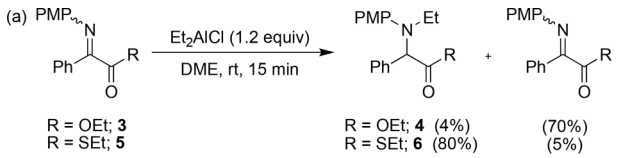
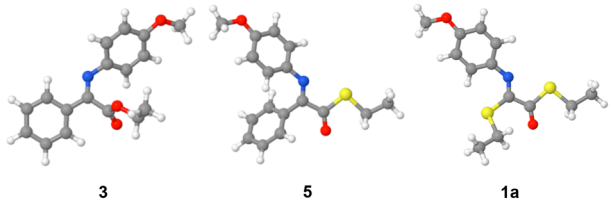
Scheme 2. Comparison Experiments and Computational Study



(b)

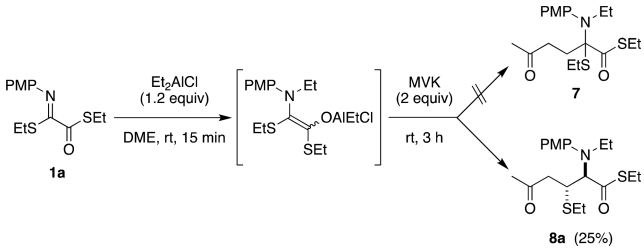


	LUMO energy	frontier electron density (N)	reactivity (N)
3	-0.0627	0.176	2.81
5	-0.0756	0.216	2.85
1a	-0.0721	0.222	3.08

thioester is higher than that of α-imino ester. In addition, we also found that the reactivity of the imino nitrogen atom of α-imino thioester was higher than that of α-imino ester since the frontier electron densities were 0.176, 0.216, and 0.222, respectively, leading to the increased reactivity of the nitrogen atom. This computational analysis supports the experimental results, which gives insights into the umpolung reaction of α-imino esters.

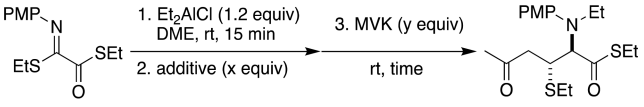
Next, we investigated the successive C−C bond formation reaction following an umpolung reaction to the α-imino thioester **1a** (Scheme 3). When methyl vinyl ketone (MVK) was used as an electrophile after the *N*-ethylation with Et_2AlCl, an unexpected product **8a** having an ethylthio group at the β-position was obtained in 25% yield, instead of the product **7**.[10] The β-alkylthio α-amino thioester can be a precursor to β-substituted α-amino acids through functionalization of the alkylthio group at the β-position.

Scheme 3. Tandem *N*-Alkylation/Nucleophilic Addition Reaction



We devised reaction conditions for the tandem *N*-alkylation/Michael reaction, and the results are shown in Table 2. As the amount of MVK was increased, the yield of product **8a** improved up to 47% (entries 1−3). To improve the yield of **8a**, other additives were also examined. When CuI and $NiCl_2$ were added to the reaction, the yields of **8a** improved to 65% and 70%, respectively (entries 4 and 5).[11,12] Screening of other Ni sources such as $NiBr_2$ and $NiCO_3$ provided the products in good to high yields (entries 6 and 8), while NiI_2 was not effective in this reaction (entry 7). We found that the optimum reaction conditions used 10 mol % of $NiBr_2$ and performed the subsequent conjugate addition for 15 min in EtCN (entry 11).

Table 2. Optimization of Tandem *N*-Alkylation/Michael Reaction[a]



entry	additive (*x* equiv)	*y* equiv	time (h)	yield (%)[b]	*anti*/*syn*
1	–	1.5	6	7	57:43
2	–	3	6	33	66:34
3	–	6	6	47	66:34
4	CuI (1)	6	1	65	69:31
5	$NiCl_2$ (1)	6	1	70	68:32
6	$NiBr_2$ (1)	6	1	85	69:31
7	NiI_2 (1)	6	1	0	–
8	$NiCO_3$ (1)	6	1	65	71:29
9[c]	$NiBr_2$ (1)	6	0.25	69	64:36
10[c]	$NiBr_2$ (0.1)	6	0.25	73	71:29
11[c,d]	$NiBr_2$ (0.1)	6	0.25	84	70:30

[a]The reaction was carried out according to the general procedure (see the Supporting Information). [b]Isolated yield. [c]The reaction of 3rd step was carried out at 0 °C. [d]EtCN was used as solvent.

Under the optimum reaction conditions, the scope of substrates and electrophiles for the tandem *N*-alkylation/Michael reaction was investigated (Scheme 4). When alkylthio- and arylthio-groups such as MeS, CyS, PhS, and BnS were evaluated at the imino carbon, we found that the desired reaction via the rearrangement of alkylthio group gave the products **8b−e** in moderate to good yields. In the case of substrates having various thioester moieties such as methyl thioester and *tert*-butyl thioester, the products **8f** and **8g** were obtained in good yields. Furthermore, reactions with various enones as the electrophiles were also examined, and we found that use of the linear alkyl substituents such as Et and *n*-Bu group did not adversely affect this reaction, thus affording the corresponding products **8h,i**, while the use of an enal and an acrylate were not effective at all in this reaction (**8j,k**).

Although EtMgBr and Et_2Zn were primarily used for this tandem *N*-alkylation/Michael addition reaction respectively, neither of the reactions afforded the product **8a** (see the SI, Table S4). We also found that the $BF_3{\cdot}OEt_2$ was the most effective additive in this reaction, affording the product **8** in high yield with good diastereoselectivity (see the SI in detail, Tables S5, S6). Various types of Grignard reagent were examined, and the results are shown in Scheme 5. To our delight, a variety of Grignard reagents could be used under the reaction conditions to provide the corresponding products **8l−r** in moderate to high yields with good diastereoselectivity, except for the use of the phenyl Grignard.

The relative stereochemistry of the product **8** was determined as follows. Each diastereomer of the product **8a** was reduced with LAH to afford the diol **9** followed by the mesylation/cyclization to **10**, whose stereochemistry was confirmed and determined by the coupling constant of ^1H NMR of each diastereomer (Scheme 6)(see the SI in detail).

Our proposed reaction mechanism is shown in Scheme 7. First, *N*-alkylation to α-imino thioester **1** with the organometallic reagent proceeds to give the enolate intermediate **B** via the five-membered intermediate **A**, with coordination of the metal to the imino nitrogen and the carbonyl oxygen.

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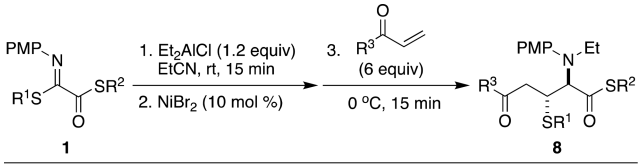
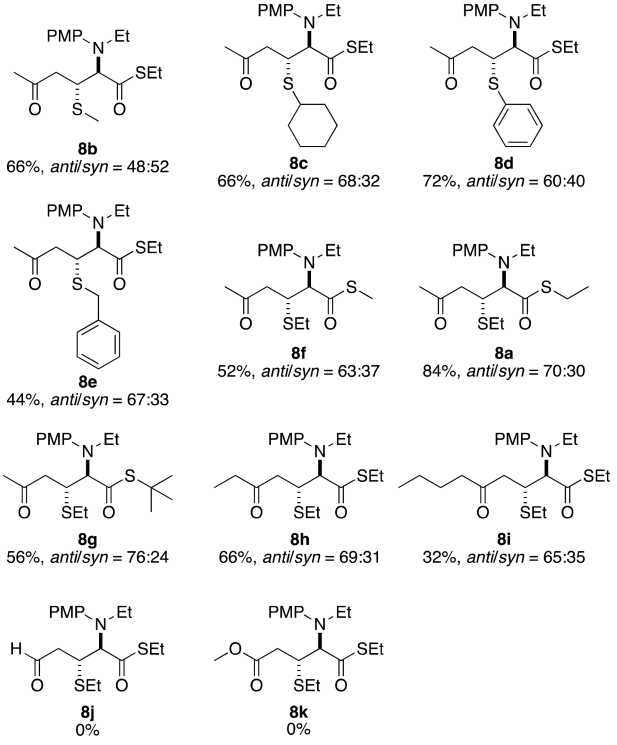
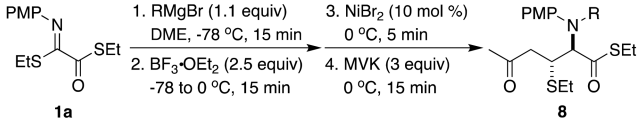
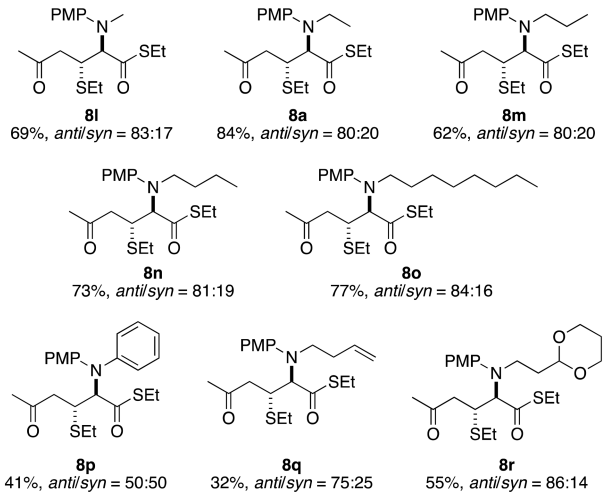
Scheme 4. Scope of Substrates and Electrophiles for Tandem *N*-Alkylation/Michael Reaction





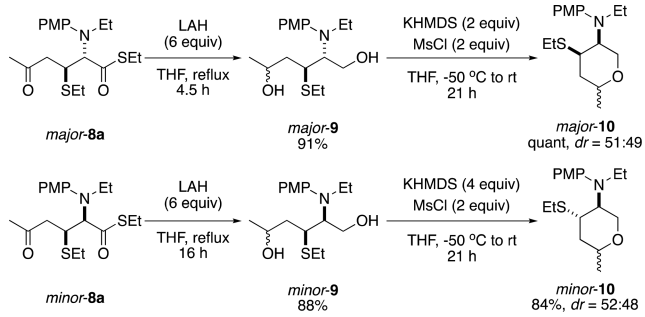
Scheme 5. Diastereoselective Tandem *N*-Alkylation/Michael Reaction



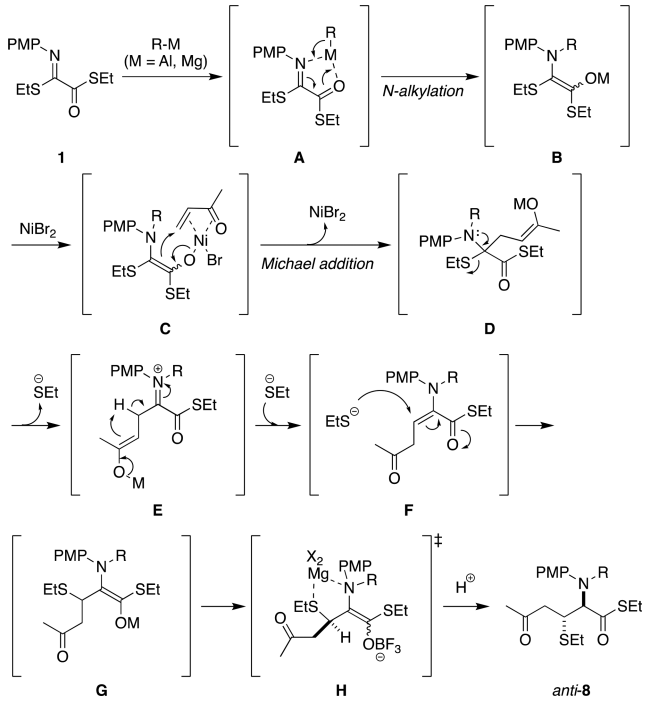


Transmetalation by a catalytic amount of $NiBr_2$ leads to the nickel enolate **C** followed by the Michael addition with MVK

Scheme 6. Determination of Relative Stereochemistry



Scheme 7. Plausible Reaction Mechanism



under the influence of the Lewis acidic nickel to form the intermediate **D**.[12] We assume that the role of the $BF_3{\cdot}OEt_2$ may be to make the transmetalation occur more readily. The formation of the iminium intermediate **E** by the elimination of the ethylthio anion followed by the isomerization to **F** causes 1,4-addition of the ethylthiolate to afford **G**.[13,14] Finally, diastereoselective protonation provides the desired product **8** via the transition state **H**.

In summary, we have developed an umpolung *N*-alkylation reaction to *α*-imino thioesters that proceeds under mild reaction conditions in a short time, which indicates that the imino thioester is an appropriate substrate for this novel *N*-alkylation reaction. In addition, we have found that the tandem *N*-alkylation/Michael addition to enones proceeds to give the *β*-alkylthio-*α*-amino thioester in good yield and diastereoselectivity, which is a new type of C−C bond formation that is followed by the rearrangement of an alkylthio group.

■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedure, 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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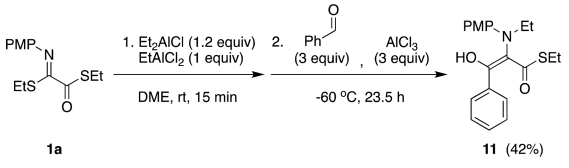
(9) Calculation of other α-imino thioesters **1** and imidoyl chlorides was carried out using B3LYP/6-31G(d). See the Supporting Information.

(10) When a benzaldehyde was used as an electrophile for the tandem N-alkylation/addition reaction, unexpected product **11** was obtained in 42% yield.



1a **11** (42%)

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