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Sequential addition reaction of lithium acetylides and Grignard reagents to thioiminium salts from thiolactams leading to 2,2-disubstituted cyclic amines

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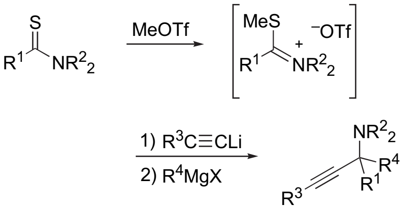
Abstract—The reaction of thioiminium salts derived from γ- and δ-thiolactams with lithium acetylides and Grignard reagents proceeded sequentially to give 2,2-disubstituted pyrrolidines and piperidines in moderate to high yields. In the initial step of the reaction, 2-(methylthio)-pyrrolidines and -piperidines may be formed. The use of lithium (trimethylsilyl)acetylide gave the products most effectively. Aryl-, alkyl-, and allylmagnesium halides were used as Grignard reagents. Silylcarbocyclization of *N*-allyl 2-ethynyl cyclic amines with $HSiMe_2Ph$ in the presence of a catalytic amount of $Rh_4(CO)_{12}$ was carried out to give trisubstituted hexahydro-1*H*-pyrrolizines and octahydroindolizines.

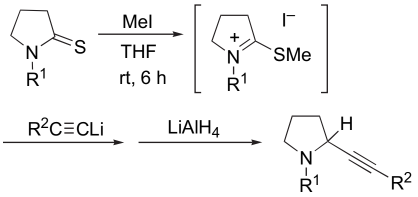
1. Introduction

The development of new carbon–carbon bond-forming reactions, in which multiple components are coupled in one operation, is needed.[1] In this context, we have recently reported the sequential addition reactions of lithium acetylides and Grignard reagents to thioiminium salts derived from acyclic thioamides[2] (Eq. 1) during the course of our studies on thioamides.[3]



(1)

In those studies, two different carbon nucleophiles were selectively introduced to thioiminium salts, and no products, to which the same carbon nucleophiles were doubly introduced, were observed. Cyclic thioamides, i.e., γ- and δ-thiolactams, can be used as a substrate in Eq. 1. In fact, the methylation of γ-thiolactams with methyl iodide has been reported to take place.[4] Alkynylation of the resulting thioiminium salts followed by reduction gives 2-alkynyl pyrrolidines (Eq. 2).[4a]



(2)

In this case, about 6 h was necessary for methylation of the thiolactams. Due to the higher reactivity of MeOTf, the methylation of thiolactams is expected to be complete within a shorter reaction time. Furthermore, the introduction of two different carbon nucleophiles to thioiminium salts derived from thiolactams can lead to 2-alkynyl-2-substituted pyrrolidines and piperidines, which are not readily available by ordinary synthetic methods. Several examples of the alkynylation of cyclic imines and iminium salts leading to 2-alkynyl pyrrolidines[5] and piperidines[6] are known, but reactions leading to 2-alkynyl-2-substituted pyrrolidines[7] and piperidines[7a,8] are rare. We report here sequential addition reactions of lithium acetylides and Grignard reagents to thioiminium salts derived from γ- and δ-thiolactams. Additionally, silylcarbocyclization was applied to the obtained *N*-allyl 2-ethynyl-2-substituted cyclic amines.

2. Results and discussion

Initially, methylation of *N*-methyl γ-thiolactam **1a** with methyl triflate (MeOTf) was carried out (Eq. 3). This reaction went to completion almost instantly to give thioiminium salt **2a**. Lithium (trimethylsilyl)acetylide (**3a**) (1.5 equiv) and phenylmagnesium bromide (**4a**) (2 equiv) were then added to an Et_2O solution of **2a** to give

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Keywords: Thiolactams; Thioiminium salts; Lithium acetylides; Grignard reagents; 2,2-Disubstituted cyclic amines; Silylcarbocyclization.

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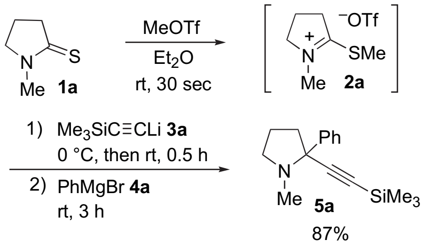
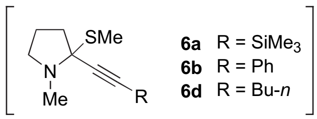
N-methyl-2-alkynyl-2-phenylpyrrolidine **5a** in 87% yield. 2-(Methylthio)pyrrolidine **6a**[9] is probably formed in the step of the addition of **3a**. In the next step, the substitution reaction occurs at the carbon atom bearing nitrogen and sulfur atoms with Grignard reagent **4a**. As expected, products derived from 2 equiv of the identical carbon nucleophiles were not observed, and 2 equiv or one more equiv of Grignard reagent **4a** was enough to efficiently substitute the MeS group in **6a**. In the first step, thioiminium salt **2a** appears to react with more ionic organolithium reagents, whereas in the second step, the coordination of the sulfur atom to the Lewis acidic magnesium metal may facilitate the reaction of Grignard reagents.



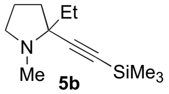
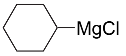
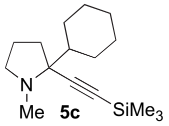
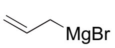
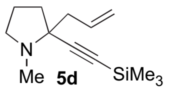
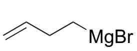
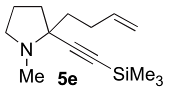
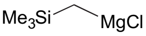
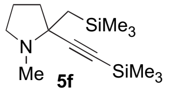
(3)



Next, a variety of Grignard reagents **4** were used for the sequential reaction. The results are summarized in Table 1. Ethyl-, cyclohexyl-, 2-propenyl-, 3-butenyl-, and silylmethylmagnesium halides **4b–4f** were used as aliphatic Grignard reagents. In all cases, the reaction proceeded smoothly to give the corresponding 2-alkynyl-2-alkylpyrrolidines **5b–5f** in good to high yields. The usual aqueous workup of the reaction mixture followed by concentration of the organic layers gave products **5** with high purity except for the reaction with **4f**.

Lithium acetylides **3b–3e** derived from phenylacetylene, 2-methyl-1-butene-3-yne, 1-hexyne, and 1-ethynylcyclohexene were also used for the sequential addition reaction to **2a** (Eq. 4). The results are summarized in Table 2. As in the reaction with lithium silylacetylide **3a**, thioiminium salt **2a** was stirred with lithium phenylacetylide (**3b**) at 0 °C–room temperature for 30 min. To the reaction mixture was then added Grignard reagents **4a**, **4b**, and **4f**, and the mixture was stirred at room temperature for 3 h, but the desired products **5g–5i** were obtained in at most 40% yield (entries 1, 3, and 4). To confirm the efficiency of the generation of 2-(methylthio)pyrrolidine **6b** from **2a** and **3b**, the reduction of in situ-generated **6b** was carried out with $LiAlH_4$ to give 2-phenylethynylpyrrolidine (**5j**) in 59% yield (entry 5). Thus, the addition of **3b** to **2a** occurs efficiently, and lower yields in entries 1, 3, and 4 may be due to a less efficient reaction of **6b** with Grignard reagents **4**. Attempts to enhance the yields of **5g–5i** by raising the reaction temperature or by using a large excess of Grignard reagents **4** were not successful, but the reaction with **4a** under reflux in THF gave the product **5g** in slightly better yield (entry 2). The use of lithium acetylides **3c–3e** gave 2-alkynyl-2-alkyl or -aryl pyrrolidines **5k–5m** and **5o**, albeit in low to moderate yields (entries 6–8 and 10). The sequential reaction of **2a** with **3d** and $LiAlH_4$ gave the product **5n** in 59% yield, which suggested the efficient formation of **6d** and the lower efficiency of the reaction of **6d** with Grignard reagents **4**.

Table 1. Sequential reaction of thiolactam **1a** with MeOTf, lithium silylacetylide **3a**, and Grignard reagents **4**[a]

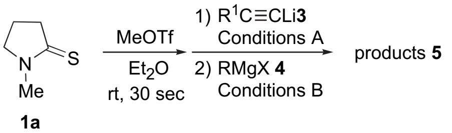
Grignard reagent **4**	Product **5**	Yield (%)[b]
EtMgBr, **4b**	 **5b**	58
 **4c**	 **5c**	70
 **4d**	 **5d**	96[c]
 **4e**	 **5e**	88[c]
 **4f**	 **5f**	51[d]

[a] Reaction was carried out as follows, unless otherwise noted: to thiolactam **1a** (1 mmol) in Et_2O (5 mL) were added MeOTf (1 equiv), lithium silylacetylide **3a** (1.5 equiv), and Grignard reagents **4** (2 equiv).

[b] Yields of crude product **5** with purity higher than 95%.

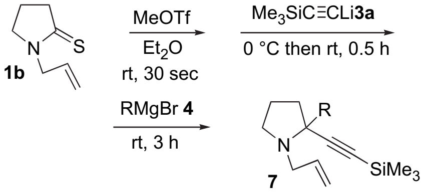
[c] Thiolactam **1a** (5 mmol) was used.

[d] Product **5f** was purified by column chromatography on silica gel, and the isolated yield is shown.



(4)

Instead of γ-thiolactam **1a**, *N*-allyl γ-thiolactam **1b** was chosen as a starting material (Eq. 5). As in the reaction of **1a**, the corresponding pyrrolidines **7** were obtained in good to high yields by reacting with lithium acetylide **3a** and Grignard reagents **4**.



(5)

7a R = Ph 94% **7c** R = Et 83%
7b R = Me 60% **7d** R = C_6H_4OMe-4 55%[a]

[a]after the purification by column chromatography on silica gel