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Synthesis of 2-azabicyclo[2.1.0]pentanes by the intramolecular nucleophilic substitution of cyclopropylmagnesium carbenoids with magnesium anilide

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ABSTRACT

A variety of 2-azabicyclo[2.1.0]pentanes were synthesized by the intramolecular nucleophilic substitution of cyclopropylmagnesium carbenoids with magnesium anilide. The 1-chlorocyclopropyl *p*-tolyl sulfoxides possessing an *N*-aryl-substituted aminomethyl group were prepared from dichloromethyl *p*-tolyl sulfoxide, α,β-unsaturated carboxylic acid esters, and anilines in four steps. The deprotonation of the amine with *t*-BuMgCl followed by sulfoxide/magnesium exchange of the sulfoxides with *i*-PrMgCl led to the generation of the cyclopropylmagnesium carbenoids possessing a magnesium anilide moiety. Subsequent intramolecular nucleophilic substitution of the cyclopropylmagnesium carbenoids occurred in a *4-exo-tet* manner to give the 2-azabicyclo[2.1.0]pentanes. The optically active 2-azabicyclo[2.1.0]pentane was synthesized using a *p*-tolylsulfinyl group as a chiral auxiliary.

1. Introduction

2-Azabicyclo[2.1.0]pentanes are a class of highly strained bicyclic compounds in which cyclopropane and azetizine are fused across a C–C bond. The 2-azabicyclo[2.1.0]pentane skeleton is found in SF-1836 and attracts attention as a conformationally restricted pyrrolidine analog in the field of drug development.[1,2] 2-Azabicyclo[2.1.0]pentanes are also used as synthetic intermediates in the total synthesis of natural products.[3] Despite their potential utility, the chemistry of 2-azabicyclo[2.1.0]pentanes is scarce mainly due to the lack of efficient synthetic method of 2-azabicyclo[2.1.0]pentanes. One of the most straightforward synthetic methods of 2-azabicyclo[2.1.0]pentanes is the nucleophilic substitution of halocyclopropanes with intramolecular nitrogen nucleophiles in a *4-exo-tet* manner. However, in general, the nucleophilic substitution at the carbon atom of small rings does not proceed efficiently because of the inaccessibility of nucleophiles to the C–X antibonding orbital and a disadvantageous highly strained transition state structure.[4] Nevertheless, cyclopropyl- and cyclobutylmagnesium carbenoids react with nucleophiles such as (α-sulfonylalkyl)lithiums, Grignard reagents, lithium phenolates and naphtholates, and lithium anilides to give multi-substituted cyclopropanes and cyclobutanes.[5,6] If cyclopropylmagnesium carbenoids possessing a nitrogen nucleophile can be generated, intramolecular nucleophilic substitution is expected to occur to give 2-azabicyclo[2.1.0]pentanes. Herein, we report the synthesis of 2-azabicyclo[2.1.0]pentanes by the *4-exo-tet* cyclization of cyclopropylmagnesium carbenoids possessing a magnesium anilide moiety.

2. Results and discussion

2.1. Preparation of cyclization precursors

As cyclization precursors, we designed the 1-chlorocyclopropyl *p*-tolyl sulfoxides **1** possessing *N*-aryl-substituted aminomethyl groups (Scheme 1). Deprotonation and sulfoxide/magnesium exchange of the sulfoxides **1** are expected to generate bifunctional species in which an electrophilic cyclopropylmagnesium carbenoid moiety and a nucleophilic magnesium amide moiety coexist in each molecule. A variety of *N*-aryl-substituted 2-(aminomethyl)-1-chlorocyclopropyl *p*-tolyl sulfoxides **1** were prepared from dichloromethyl *p*-tolyl sulfoxide, α,β-unsaturated carboxylic acid esters, and anilines in four steps.[7] Annulation of α,β-unsaturated carboxylic acid esters with dichloromethyl *p*-tolyl sulfoxide in the

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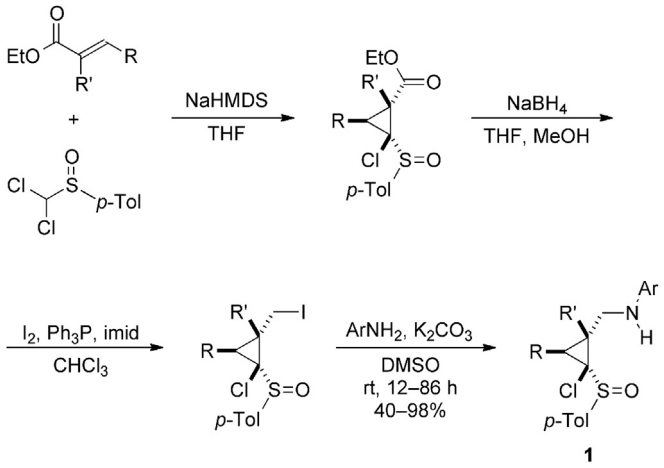
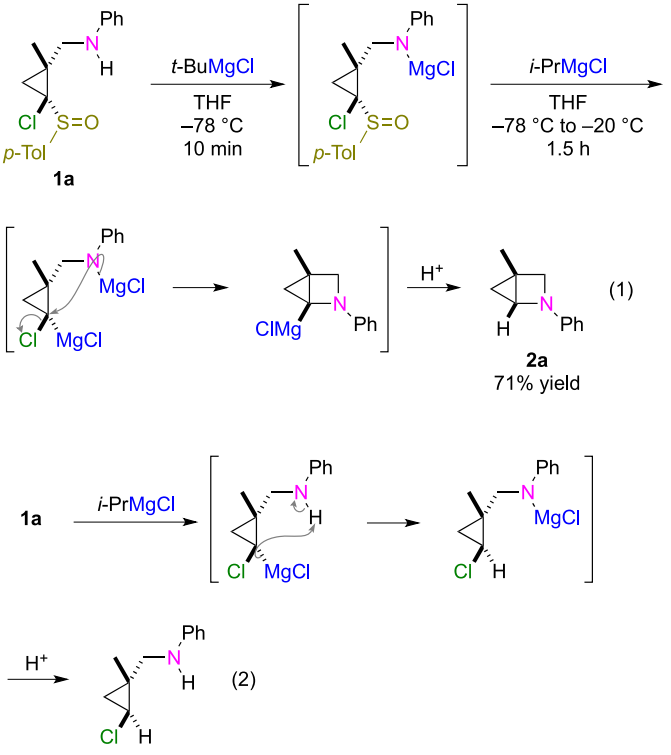


Scheme 1. Synthesis of cyclization precursors **1**.

presence of NaHMDS gave 1-chlorocyclopropyl *p*-tolyl sulfoxides possessing an ethoxycarbonyl group. Reduction of the ethoxycarbonyl group and iodination of the resulting hydroxy group afforded 1-chloro-2-(iodomethyl)cyclopropyl *p*-tolyl sulfoxides.[8] The reaction of the alkyl iodides with the anilines in the presence of K_2CO_3 gave the cyclization precursors **1** in 40–98% yields.

2.2. Cyclization reaction

With the key precursors **1** in hand, the synthesis of 2-azabicyclo[2.1.0]pentanes was examined (Scheme 2, Eq. 1). Deprotonation of the secondary amine should be carried out in advance of the sulfoxide/magnesium exchange reaction to generate the bifunctional species. Otherwise, the generated cyclopropylmagnesium carbenoids will abstract the proton of the secondary amine to give the undesirable chlorocyclopropanes (Scheme 2, Eq. 2). We chose *t*-BuMgCl, which was unreactive towards the *p*-tolylsulfinyl group, as a base. A solution of *t*-BuMgCl in THF was added to a solution of the sulfoxide **1a** in THF at −78 °C, and then, a solution of *i*-PrMgCl in THF was added to the resulting solution. The reaction mixture was warmed to −20 °C and quenched with aqueous NH_4Cl. As a result, the desired 2-azabicyclo[2.1.0]pentane **2a** was obtained in 71% yield.

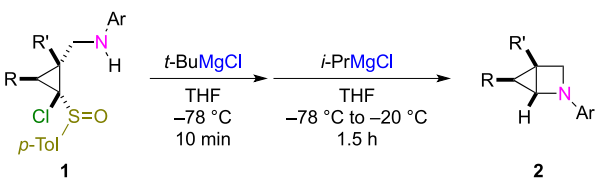


Scheme 2. Synthesis of 2-azabicyclo[2.1.0]pentane **2a**.

The scope of the cyclization was explored with a variety of sulfoxides **1b**–**h** (Table 1). When sulfoxides **1b**, **1c**, and **1e** possessing one or two methoxy groups at the *o*- or *m*-positions were subjected to the reaction with *t*-BuMgCl and *i*-PrMgCl, the corresponding 2-azabicyclo[2.1.0]pentanes **2b**, **2c**, and **2e** were formed in 59–78% yields, whereas 2-azabicyclo[2.1.0]pentane **2d** possessing a *N*-(4-methoxyphenyl) group could not be isolated because of its instability (entries 1–4). The reaction of sulfoxide **1f** possessing an electron-withdrawing trifluoromethyl group at the *m*-position also gave the bicyclic product **2f** in 58% yield (entry 5). The cyclization of the cyclopropylmagnesium carbenoid generated from sulfoxide **1g** possessing a 2-phenylethyl group on the cyclopropane ring occurred to give 2-azabicyclo[2.1.0]pentane **2g** in 74% yield (entry 6). The crude 4,5-dimethyl-2-azabicyclo[2.1.0]pentane **2h** was obtained in 60% yield after short silica gel column purification (entry 7). Further purification of the crude product by column chromatography on silica gel resulted in the decomposition of **2h**. In all cases, small amounts of the chlorocyclopropanes, which originated from the protonation of the cyclopropylmagnesium carbenoids, were formed as by-products. The 2-azabicyclo[2.1.0]pentanes **2**, except the *N*-(4-methoxyphenyl)- and 4,5-dimethyl-substituted derivatives **2d** and **2h**, were sufficiently stable and were purified by column chromatography on silica gel. For instance, neat 2-azabicyclo[2.1.0]pentane **2c** could be stored at −15 °C for several months. When a solution of 2-azabicyclo[2.1.0]pentane **2c** in $CHCl_3$ was left at room temperature for two weeks, a slight amount of decomposition occurred. Approximately half of 2-azabicyclo[2.1.0]pentane **2c** decomposed under reflux in toluene for one week.

To gain insight into the reaction mechanism, the reaction of sulfoxide **1c** with *t*-BuMgCl and *i*-PrMgCl was quenched with CH_3OD (Scheme 3). As a result, 2-azabicyclo[2.1.0]pentane **2c′** possessing a deuterium atom was formed with a high deuterium content. This result indicates the intermediacy of the organomagnesium chloride **3c**. In addition, the reaction of sulfoxide **1c** with *t*-BuMgCl did not afford 1-(*p*-tolylsulfinyl)-2-azabicyclo[2.1.0]pentane. Therefore, we speculate that the nucleophilic substitution

Table 1
Synthesis of 2-azabicyclo[2.1.0]pentanes **2**.



Entry	1	R	R′	Ar	2	Yield of **2** (%)
1	**1b**	H	Me	2-$MeOC_6H_4$	**2b**	59
2	**1c**	H	Me	3-$MeOC_6H_4$	**2c**	76
3	**1d**	H	Me	4-$MeOC_6H_4$	**2d**	0
4	**1e**	H	Me	3,5-$(MeO)_2C_6H_3$	**2e**	78
5	**1f**	H	Me	3-$CF_3C_6H_4$	**2f**	58
6	**1g**	H	$PhCH_2CH_2$	3-$MeOC_6H_4$	**2g**	74
7	**1h**	Me	Me	3-$MeOC_6H_4$	**2h**	60

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