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A novel direct *N*-alkenylation of nitrogen-containing heterocycles with magnesium alkylidene carbenoids

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Abstract—Treatment of magnesium alkylidene carbenoids, which were generated from 1-chlorovinyl *p*-tolyl sulfoxides with isopropylmagnesium chloride at −78 °C in toluene, with *N*-lithio nitrogen-containing heterocycles (e.g., indole, indazole, phenothiazine, and phenoxazine) gave *N*-alkenylated products in moderate to good yields. The intermediate of this reaction was found to be the alkenyl anion, which could be trapped with iodoalkanes using CuI as a catalyst to give the heterocycles having fully substituted alkenes on the nitrogen. The alkenyl anion intermediate could be trapped also with benzoyl chloride and phenyl isocyanate. This reaction offers a quite novel and direct *N*-alkenylation of nitrogen-containing heterocycles.

Nitrogen-containing heterocycles are widely distributed in natural products and in pharmaceuticals, and numerous studies for their chemistry and synthesis have been reported. From the synthetic viewpoint, however, direct arylation[1] and alkenylation of the nitrogen in nitrogen-containing heterocycles are not an easy task. For example, even though *N*-vinylindole is a very important compound as a monomer for the poly(1-vinylindole)[2] only few methods have been published for their synthesis from indole.[3] Quite recently, palladium-catalyzed amination of vinyl chloride with amines to give enamines or imines is reported by Barluenga et al.[4]

Previously, we reported the generation of magnesium alkylidene carbenoids **3** from 1-chlorovinyl *p*-tolyl sulfoxides **2**, which were synthesized from ketones **1** and chloromethyl *p*-tolyl sulfoxide in high yields, with Grignard reagent.[5] The magnesium alkylidene carbenoids **3** were found to be quite interesting reactive carbon species and some new synthetic methods have been realized.[5,6]

Recently, we found that the reaction of the magnesium alkylidene carbenoids **3** with *N*-lithio arylamines resulted in the formation of *ortho*-alkenylated arylamines **4** (Scheme 1).[7] In continuation of our interest in the development of a new synthetic method with the magnesium alkylidene carbenoid **3**, we investigated the reaction of *N*-lithio nitrogen-containing heterocycles with the carbenoids **3** and quite interesting results were obtained.

Thus, the reaction of **3** with *N*-lithio phenothiazine, as an example of the nitrogen-containing heterocycles, gave *N*-alkenylated phenothiazine **6** (E=H). The intermediate of this reaction was found to be the alkenyl anion **5** and it could be trapped with several electrophiles such as iodoalkanes and benzoyl chloride to afford the phenothiazine having a fully substituted olefin on the nitrogen **6** (E=electrophile).

The development of this reaction is reported by using indole as an example of nitrogen-containing heterocycles (Scheme 2). At first, magnesium alkylidene carbenoid **8** was generated from l-chlorovinyl *p*-tolyl sulfoxide **7** with *i*-PrMgCl at −78 °C in toluene.[7] To a solution of the magnesium alkylidene carbenoid, 3 equiv of *N*-lithio indole, generated from indole with *n*-butyllithium in toluene, was added through a cannula and the reaction mixture was slowly allowed to warm to −10 °C. We obtained the product having the molecular formula $C_{17}H_{19}NO_2$ in 53% yield. At this point of time, formation of 3-alkenylated indole **10** was expected from our previous experience.[7]

Keywords: Sulfoxide; Sulfoxide–magnesium exchange reaction; Magnesium alkylidene carbenoid; Alkenylation; *N*-Alkenylation of heterocycles.
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0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
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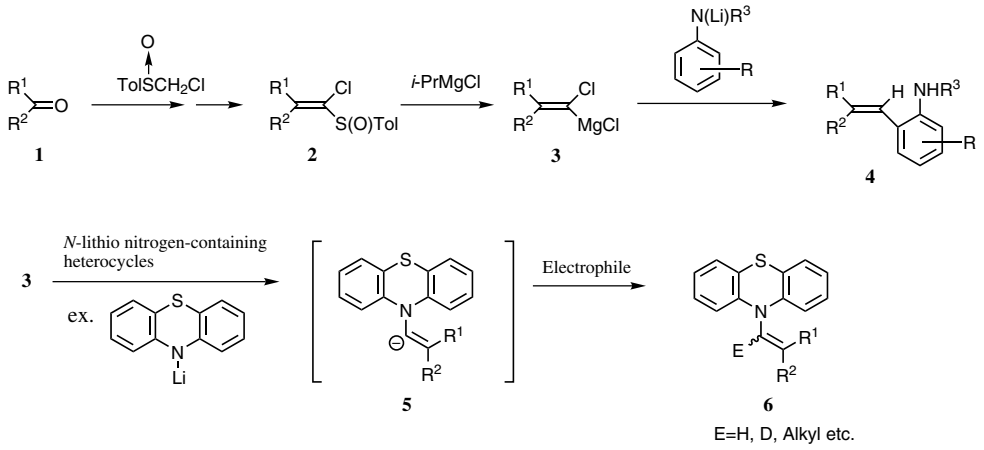
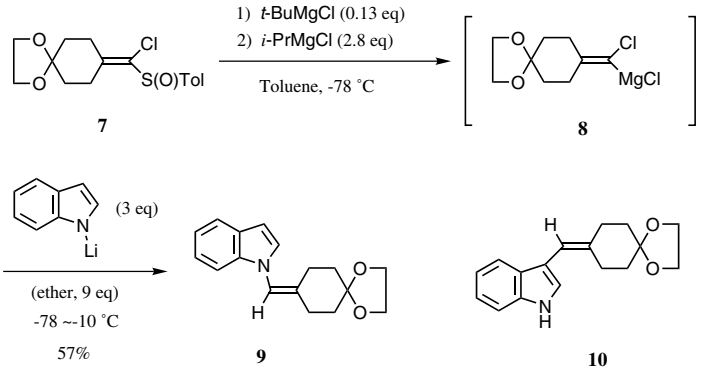


Scheme 1.



Scheme 2.

However, the product did not have N–H absorption in its IR spectrum. ^{1}H NMR showed seven protons in the aromatic and olefinic region. ^{13}C NMR showed four quaternary carbons in its DEPT spectrum. All these data suggested that the product should be the *N*-alkenylated indole **9**.

As we recognized that this is a quite interesting and novel direct *N*-alkenylation of nitrogen-containing heterocycles, improvement of the yield was undertaken. After some investigation, it was found that when this reaction was conducted with 9 equiv of ether (corresponding to the indole) as an additive the yield was improved to 57%. Under the improved conditions, generality of this reaction was studied with the magnesium alkylidene carbenoid **8** and various kinds of *N*-lithio nitrogen-containing heterocycles and the results are summarized in Table 1.

Indazole gave the desired *N*-alkenylated product in 51% yield (entry 1); however, pyrazole gave only 15% yield of the desired product (entry 2). Phenothiazine and phenoxazine gave quite good yields of the *N*-alkenylated products (entries 3 and 4). Interestingly, carbazole, expected to be a quite similar compound with phenoxazine and phenothiazine, gave only a complex mixture in this reaction (entry 5). In contrast to the results described above, the simplest heterocycles, pyrrole, gave 2-alkenylated pyrrole as a main product in 56% yield with *N*-alkenylated pyrrole in only 14% yield (entry 6).

Based on our previous studies,[5] the intermediate of this reaction was thought to be the alkenyl anion. To ascertain that the intermediate was the alkenyl anion, the reaction between the magnesium alkylidene carbenoid **8** and *N*-lithio phenothiazine was quenched with CH_3OD. This reaction gave the deuterated *N*-alkenylated product **12** (E=D) in 71% yield with 98% deuterium incorporation (see Table 2, entry 1). From this result, the existence of the alkenyl anion **11** was confirmed.

We thought that if this alkenyl anion intermediate **11** could be trapped with electrophiles, a new method for the synthesis of nitrogen-containing heterocycles having a fully substituted olefin would be realized. First, 9 equiv of iodomethane was added to the reaction mixture at −10 °C and the temperature of the reaction was slowly allowed to warm to room temperature; however, no expected methylated product was obtained. Next, 5 mol % of CuI[8] followed by 9 equiv of iodomethane was added to the reaction mixture and the mixture was stirred at room temperature for 1 h. Fortunately, this reaction

Table 1. The direct *N*-alkenylation of nitrogen-containing heterocycles with the magnesium alkylidene carbenoid derived from 1-chlorovinyl *p*-tolyl sulfoxide **7**

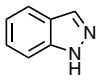
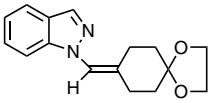
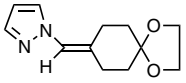
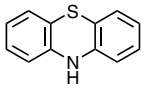
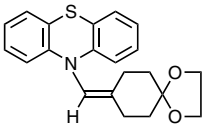
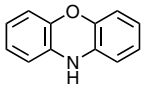
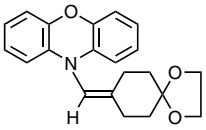
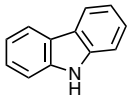
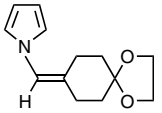
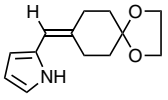
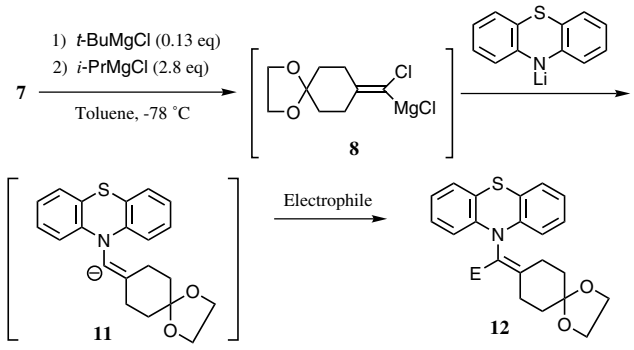
Entry	Nitrogen-containing heterocycle	*N*-Alkenylated heterocycle	Yield/%
1			51
2			15
3			71
4			70
5		Complex mixture	
6			14
			56

Table 2. Synthesis of phenothiazine having fully substituted alkene on the nitrogen **12** by the trapping of the alkenyl anion intermediate **11**



Entry	Electrophile	**12**	
		E	Yield/%
1	CH_3OD	D	71[a]
2	CH_3I[b]	CH_3	62
3	CH_3CH_2I[c]	CH_3CH_2	55
4	$CH_2{=}CHCH_2I$[b]	$CH_2{=}CHCH_2$	63
5	$PhCH_2Br$[b]	$PhCH_2$	30
6	PhCOCl[d]	PhCO	59
7	PhNCO[d]	CONHPh	39

[a] Deuterium content 98%.
[b] 9 equiv of iodoalkane and 5 mol % of CuI were used and the reaction mixture was stirred at room temperature for 1 h.
[c] 9 equiv of iodoethane and 20 mol % of CuI were used and the reaction mixture was stirred at room temperature for 6 h.
[d] The reaction was carried out without CuI.

gave the desired methylated product **12** (entry 2) in 62% yield.

The results for the trapping of the intermediate **11** with several electrophiles are summarized in Table 2. The reaction with iodoethane was found to be sluggish; however, using 20 mol % of CuI with prolonging of the reaction time to 6 h gave the ethylated product in 55% yield (entry 3). Allyl iodide gave the desired product in good yield; however, benzyl bromide gave only 30% yield of the desired product (entry 5). Secondary iodoalkane such as 2-iodopropane did not react at all with **11**.

Carbonyl compounds were investigated as the electrophiles. So far, benzoyl chloride and phenyl isocyanate reacted to give the desired products (entries 6 and 7). Acetaldehyde and acetone did not react at all with **11**. Although there are some reports for direct *N*-alkenylation of nitrogen-containing heterocycles,[3] our method described above is quite unique. In addition, this is the first example for the synthesis of compounds having a fully substituted olefin on the nitrogen in the nitrogen-containing heterocycles.

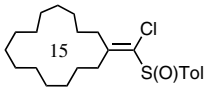
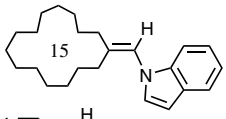
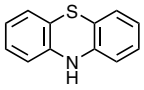
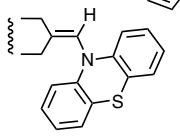
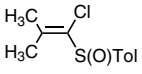
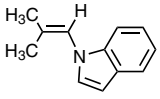
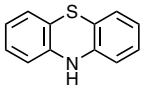
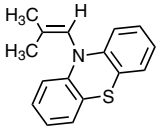
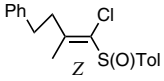
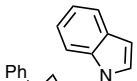
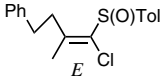
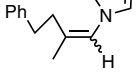
Generality and stereochemistry of this reaction were investigated using 1-chlorovinyl *p*-tolyl sulfoxides derived from cyclopentadecanone, acetone, and 4-phenyl-2-butanone and the results are summarized in Table 3. Entries 1–4 show that this reaction could be generally applied to other 1-chlorovinyl *p*-tolyl sulfoxides; however, in these cases, the yields were found to be moderate to low.

The stereochemistry of this reaction is interesting (entries 5 and 6). First, both isomers of the *Z*- and *E*-1-chloro-2-methyl-4-phenyl-1-(*p*-tolylsulfinyl)-1-butenes (Table 3, entries 5 and 6) were synthesized from 4-phenyl-2-butanone. The *Z*-isomer was treated with *i*-PrMgCl followed by *N*-lithio indole to give the desired product in 64% yield. The product was found to be a mixture of two isomers,[9] and the ratio is shown in Table 3, entry 5. In the same manner, the *E*-isomer gave the desired *N*-alkenylindole in 65% yield and the ratio is shown in Table 3, entry 6.

Interestingly, both *Z*- and *E*-1-chlorovinyl *p*-tolyl sulfoxides gave mainly *Z*-*N*-alkenylindole stereoselectively, though the selectivity was low. These results implied that the configuration of the generated magnesium alkylidene carbenoids **3** from the 1-chlorovinyl *p*-tolyl sulfoxides synthesized from 4-phenyl-2-butanone is not stable and isomerization would occur rapidly even at −78 °C.

In conclusion, we have found a quite interesting and novel reaction for direct *N*-alkenylation of nitrogen-containing heterocycles. By using this procedure even an *N*-alkenylated product in which the alkenyl group is fully substituted can be synthesized. We are continuing

Table 3. The direct *N*-alkenylation of nitrogen-containing heterocycles with the magnesium alkylidene carbenoid derived from 1-chlorovinyl *p*-tolyl sulfoxides

Entry	1-Chlorovinyl *p*-tolyl sulfoxide	Nitrogen-containing heterocycle	*N*-Alkenylated heterocyle	Yield/%
1				44
2				44
3				46
4				29
5			 *E*/*Z* = 44/56	64
6			 *E*/*Z* = 29/71	65

to study the scope and limitation and the detailed mechanism of this reaction.

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9. The stereochemistry of the *N*-alkenylindoles was determined by ^{1}H NMR-NOESY spectrum.