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Tetrahedron Letters 46 (2005) 4855–4858

Tetrahedron Letters

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

Tsuyoshi Satoh,* Jo Sakurada and Yumi Ogino

Department of Chemistry, Faculty of Science, Tokyo University of Science, Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan

Received 25 April 2005; revised 12 May 2005; accepted 16 May 2005

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.

* Corresponding author. Tel.: +81 3 5228 8272; fax: +81 3 3235 2214; e-mail: tsatoh@ch.kagu.tus.ac.jp

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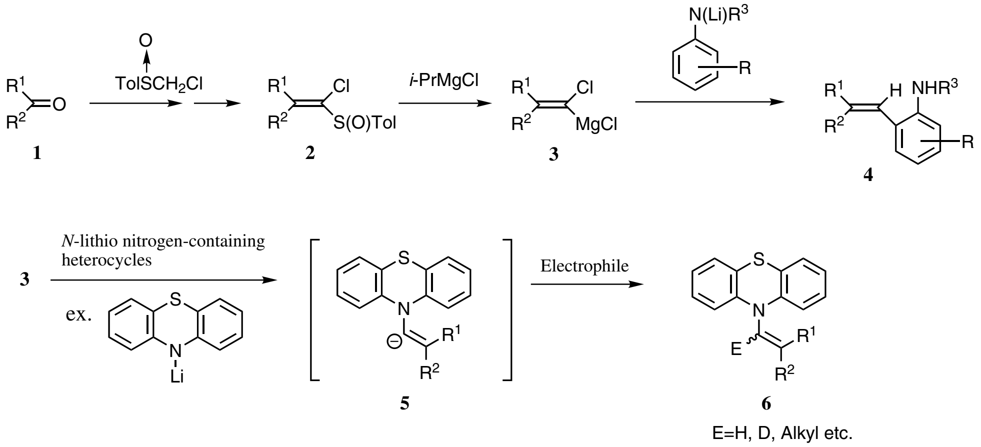
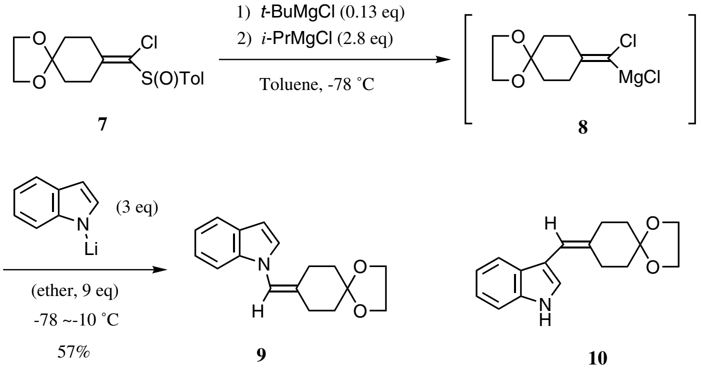
doi:10.1016/j.tetlet.2005.05.058



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