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NITRONES IN ORGANIC SYNTHESIS. SYNTHESIS OF SECONDARY ALLYL AMINES

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Abstract: Nitrones **1** undergo addition of vinyl organomagnesium bromide to give the allyl hydroxylamines **3** which are easily reduced to the corresponding N-benzyl allyl amines **2**.

Nitrones have been widely used in organic synthesis as 1,3-dipoles.[1] In contrast, the use of nitrones as electrophiles capable of reacting with organometallic compounds has received only limited study in the past;[2] however these reactions are now receiving great interest.[3] In this regard, we recently reported[4] the nucleophilic addition of several metalated heterocycles, including 2-thiazolyllithium, 2-furyllithium, and 2-imidazolyllithum to nitrones. We wish to report now our findings in the vinylation of nitrones **1** towards the synthesis of secondary allyl amines **2**.

Allyl amines are highly valuable synthetic intermediates[5] and many natural products present this function in their structure.[6] The classical approaches to allyl

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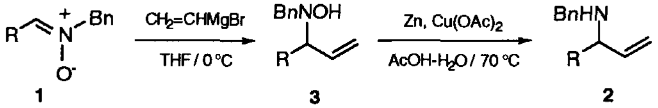


Scheme I

amines imply either the introduction of an amino function into the allylic position[7] or the olefination of α-aminoaldehydes.[8] The methodology described herein represents a different approach to the title compounds, i.e. the addition of a vinyl organometallic reagent to a nitrone. In fact, although several synthetic approaches have been described[7-9] for the preparation of allyl amines, none of these methods consist of the incorporation of a vinyl fragment to a substrate bearing a potential amino group.

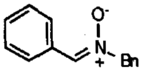
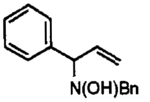
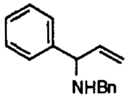
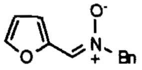
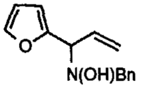
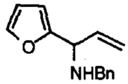
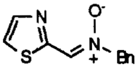
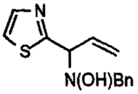
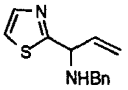
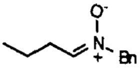
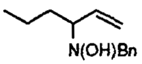
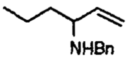
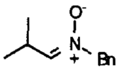
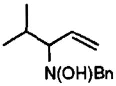
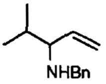
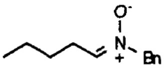
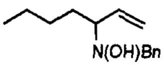
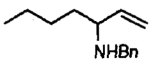
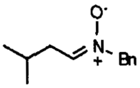
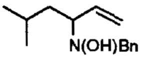
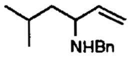
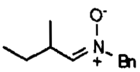
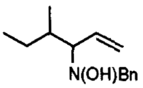
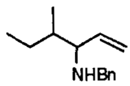
Nitrones **1**, readily available from the corresponding aldehydes (see preceding paper), react with vinyl magnesium bromide to give allyl hydroxylamines **3** in very good yields after chromatographic purification. Deoxygenation of compounds **3** can be easily achieved by using the zinc/copper couple as reducing system.[3g,10] The allyl amines **2** are obtained in good yields, with the only exception of that derived from thiazole (table 1, entry 3), and no further purification is necessary.

In conclusion, this sequence of reactions is another synthetic possibility of using nitrones as suitable precursors for the synthesis of interesting organic compounds. This preparative synthetic method to obtain allyl amines is a good new approach to such compounds since it starts from easily accesible starting chemicals. Further experiments are underway in our laboratories to determine the applicability of this methodology to chiral substrates.

Experimental

Materials: A 1.0 M solution in THF of vinyl magnesium bromide (Aldrich) was used as a source of the organometallic reagent. Tetrahydrofuran was freshly distilled from $LiAlH_4$. Acetic acid was used in commercial grade (ACS reagent, Aldrich) without further purification. Zn dust and copper (II) acetate were used in commercial grade (Aldrich) without further purification.

Table 1. Synthesis of N-benzyl allyl amines from nitrones (Scheme I).[a]

entry	nitrone[b]	hydroxylamine[b],yield(%)[c]		allyl amine[b], yield(%)[c]	
1			80		81
2			94		85
3			91		25
4			85		87
5			82		80
6			83		89
7			85		83
8			87[d]		86[d]

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[a] All compounds showed consistent physical and spectroscopic properties.[b] Bn=benzyl. [c] Isolated yield. [d] A mixture of syn:anti (1:1) isomers is obtained.

Addition of Vinyl Magnesium Bromide to Nitrones: To a solution of nitrone (2.5 mmol) in THF (30 ml), cooled at 0 °C, vinyl magnesium bromide (3 ml of an 1.0 M solution in THF, 3.0 mmol) was added, and the mixture was stirred at 0 °C for 30 min under argon atmosphere. The reaction was quenched with a saturated aqueous solution of ammonium chloride (10 ml) and diluted with diethyl ether (10 ml). The organic layer was separated, washed with brine, and dried over anhydrous magnesium sulfate. The solvent was rotatory evaporated and the crude product was chromatographed on silica gel (hexane:diethyl ether, 80:20) to yield the pure N-benzyl allyl hydroxylamines **3** (Table 1).[11]

Reduction of Allyl Hydroxylamines: To a solution of copper (II) acetate (30 mg, 0.2 mmol) in acetic acid (2.5 ml), Zn dust (0.67 g, 10.2 mmol) was added and the resulting mixture was stirred at room temperature for 15 min under argon atmosphere. Then a solution of the allyl hydroxylamine **3** (2.0 mmol) in acetic acid:water, 3:1 (3 ml) was added and the mixture was stirred at 70 °C for 1 h. After cooling at 20 °C, the disodium salt of EDTA (2.0 g) was added and the solution was made alkaline (pH=10) by the addition of 3 N NaOH. The solution was extracted with CH_2Cl_2 (3 x 25 ml); the combined organic extracts were washed with a saturated aqueous solution of the disodium salt of EDTA (2 x 25 ml), and with brine. The organic layer was dried over anhydrous magnesium sulfate and the solvent evaporated to yield the pure N-benzyl allyl amines **2** (Table 1).[11]

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11. ^{1}H and ^{13}C NMR spectra of the prepared compounds are available upon request.

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