Palladium-Catalyzed Reactions of *N*-Allylbenzotriazoles with Amines and Sulfonamides: A Facile Route to Functionalized Allylamines and *N*-Allylsulfonamides

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Received April 24, 2000

A variety of functionalized *N*-allylamines and *N*-allylsulfonamides are synthesized by Pd(II)-catalyzed intermolecular amination of the corresponding *N*-allylbenzotriazoles.

Introduction

Compounds containing the allylamino moiety are abundant in nature and very often reveal significant biological activity.[1,2] This, and the obvious importance of allylamines as precursors and intermediates in the organic synthesis of a wide variety of naturally occurring compounds,[3−5] has caused extensive development of methods for their preparation in the last two decades. The most general approach is based on transition metal catalyzed amination of various allylic derivatives, preferentially allyl acetates,[6−11] but also allyl halides,[12,13] allyl carbonates,[9] allyl ethers,[9] diethyl allyl phosphates,[8] and *N*-allyl-2,4,6-triphenylpyridinium salts.[14]

Recently, the ring-opening of methylenecyclopropanes in the presence of Pd(II) catalyst with the formation of allyl palladium complex, which could be subsequently aminated, has been described.[15] Although a variety of transition metal catalysts have been employed, such as Cu(II)−Cu(0) system[12] or Ni(0) catalysts,[9] palladium catalysts have been the most widely exploited.

We found that the benzotriazolyl group in allyl benzotriazoles is sufficiently mobile to be substituted by aliphatic and benzylic amines in the analogous amination reaction in the presence of palladium(II) acetate.[16] It was also shown that this reaction can occur intramolecularly, providing a convenient approach to the synthesis of 2-vinyl-pyrrolidines and -piperidines, which are important construction blocks for many biologically active compounds.[17] However, in these previous reports we discussed exclusively inter- and intramolecular aminations of allylbenzotriazoles bearing no additional functionalities. Numerous naturally occurring allylamines, for example, piperidine-based alkaloids micropine and epimicropine,[2] contain additional functional groups, most often hydroxy, amino, and carboxylic groups, which could possibly effect the reaction. Thus, from the point of view of the possible application of β,γ-unsaturated benzotriazolyl-containing compounds in the total synthesis of natural products, it is important to study the effects of various functionalities on the course of the reaction. A similar investigation on such reactions with allyl acetates has been recently carried out.[13]

Results and Discussion

We first investigated the influence of hydroxy groups at various positions in the allylic substrate or the amine on the course of the amination reaction and the yields of the products. For the preparation of the starting materials required for this investigation, well-known methods were used.[18] Thus, 4-hydroxy-substituted allylbenzotriazoles **2** and **4** were prepared in high yields by α-lithiation of allylbenzotriazoles **1** and **3**, respectively, and subsequent quenching with aldehydes and ketones (Scheme 1). Oxirane ring opening with lithiated **1** led to the formation of 5-hydroxy-3-benzotriazolylpent-1-ene (**5**) in 85% yield.

Based on our previously reported results,[16] we chose the catalytic system $Pd(OAc)_2-PPh_3-K_2CO_3-MeOH$, which was shown to provide the best results in the Pd-catalyzed aminations of unsubstituted 1-allylbenzotriazole. We have now found that, under such conditions, hydroxy-substituted allylbenzotriazoles **2** and **4** react readily with aliphatic and benzylic amines to afford the corresponding hydroxy-substituted allylamines **6a**−**e** in very good yields (Scheme 2). Elaboration of the allylben-

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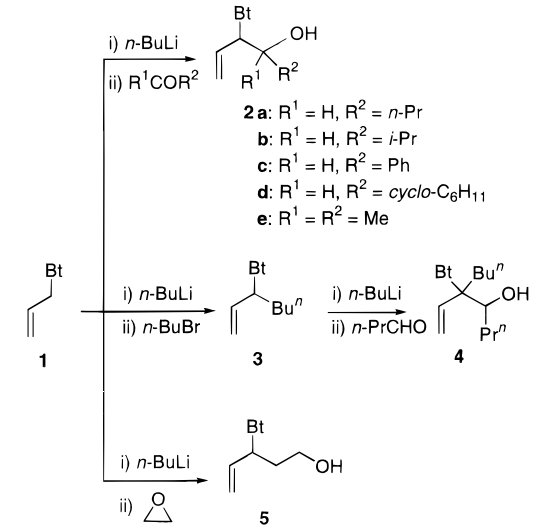
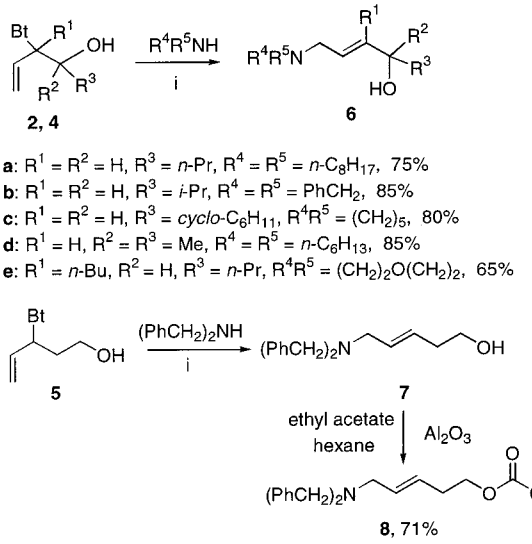
10.1021/jo0006268 CCC: $19.00
Published on Web 10/21/2000

Scheme 1



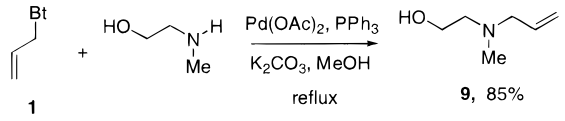
Scheme 2



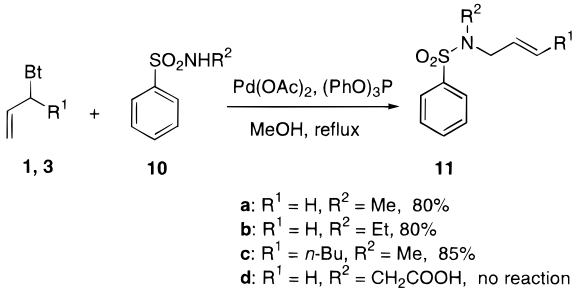
zotriazole **5** in a way similar to that described for the preparation of **6a**−**e** led to the formation of the expected primary alcohol **7**, detected in the crude product by means of ^{1}H and ^{13}C NMR spectroscopy. However, during column chromatography purification on neutral alumina using an ethyl acetate−hexane mixture as eluent, the alcohol **7** was quantitatively esterified to give in high yield the corresponding acetate **8**, which was isolated and fully characterized. Analogous acylations using ethyl acetate as an esterification reagent under similar conditions have previously been reported for a number of primary alcohols;[19,20] secondary and tertiary alcohols appear to be unreactive.

We next demonstrated that the introduction of a *C*-hydroxy group into the amine used also does not effect the course of the reaction: 2-(*N*-methylamino)ethanol reacts normally with unsubstituted allylbenzotriazole (Scheme 3). However, bulky substituents located close to the reaction centers can hinder the reaction. Thus, the

Scheme 3



Scheme 4



introduction of *n*-butyl group in the 1-position to the benzotriazolyl group somewhat decreases the product yield for **6e** (see Scheme 2), and we found that allylbenzotriazole does not react with 2-(2-hydroxyethyl)piperidine under the stated conditions.

Surprisingly, the catalytic system $Pd(OAc)_2$−PPh_3−K_2CO_3−MeOH, which showed excellent results in the reaction with reactive aliphatic and benzylic amines, proved to be ineffective for the reaction of unsubstituted allylbenzotriazole with the less nucleophilic (*N*-methyl)-benzenesulfonamide. However, we found that use of triphenyl phosphite in place of triphenylphosphine as ligand allowed the reaction to occur under neutral conditions, thus giving the corresponding *N*-allyl-*N*-methylphenylsulfonamide (**11a**) in 80% yield (Scheme 4). Moreover, a model reaction of unsubstituted allylbenzotriazole with dibenzylamine in the presence of $Pd(OAc)_2$ and $(PhO)_3P$ afforded the corresponding (allyl)dibenzylamine in 80% yield. A similar reaction of the *n*-butyl-substituted allylbenzotriazole **3** with (*N*-methyl)benzenesulfonamide gave the expected substitution product **11c** in 85% yield. However, the introduction of a carboxylic group into the sulfonamide reagent, as in **10** ($R^2 = CH_2$-COOH), blocks the amination reaction completely.

Conclusions

We have found that the presence of a hydroxy group (but not a carboxylic group) in either benzotriazolyl or amino reagent does not effect the course of the reaction or yields of the products. This allows the reaction of Pd-catalyzed amination of allylbenzotriazoles using $Pd(OAc)_2$−PPh_3−K_2CO_3 or $Pd(OAc)_2$−$(PhO)_3P$ catalysts to be applied as a convenient method for the preparation of allylamines bearing an additional functionality and for *N*-allylsulfonamides.

Experimental Section

General Comments. Melting points were measured on a Mel-Temp apparatus and are uncorrected. ^{1}H and ^{13}C NMR data were recorded on 300 MHz NMR spectrometer (300 and 75 MHz, respectively) in $CDCl_3$ as a solvent and with TMS as an internal standard. Column chromatography was carried out on aluminum oxide (activated, neutral, 50−200 micron). Benzotriazolyl-substituted compounds **1**-**5** were prepared by the procedures already described.[18] *N*-Alkylbenzenesulfonamides **10** were prepared by standard sulfonylation procedure.[21]

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General Procedure for the Synthesis of Substituted 4-Amino-2-buten-1-ols (6), 5-(Dibenzylamino)-3-penten-1-yl Acetate (8), or 2-(*N*-Allyl-*N*-methylamino)ethanol (9). A mixture of the corresponding *N*-allylbenzotriazole derivative **1**, **2**, **4**, or **5** (5.3 mmol), a secondary amine (7.0 mmol), K_2CO_3 (1.0 g, 7.2 mmol), triphenylphosphine (130 mg, 0.5 mmol, 10 mol %), and $Pd(OAc)_2$ (50 mg, 0.22 mmol, 4 mol %) in methanol (20 mL) was heated under reflux under nitrogen for 48 h. The reaction mixture obtained was allowed to cool, triturated with water and extracted with ethyl acetate. The organic fraction was washed with saturated aqueous NH_4Cl, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (Al_2O_3, hexane/ethyl acetate = 100:3).

(*E*)-6-(*N*,*N*-Dibenzylamino)-2-methyl-4-hexen-3-ol (6b): yellow oil; yield 85%; ^{1}H NMR δ 0.87 (d, J = 6.9 Hz, 3H), 0.9 (d, J = 6.9 Hz, 3H), 1.65−1.75 (m, 1H), 1.82 (br s, 1H), 3.06 (d, J = 5.1 Hz, 2H), 3.57 (s, 4H), 3.77−3.79 (m, 1H), 5.58−5.63 (m, 2H), 7.21−7.38 (m, 10H); ^{13}C NMR δ 18.0, 18.1, 33.6, 55.2, 57.9, 77.5, 126.7, 128.1, 128.6, 129.3, 134.1, 139.2. Anal. Calcd for $C_{21}H_{27}NO$: C, 81.51; H, 8.79. Found: C, 81.64; H, 8.91.

5-(Dibenzylamino)-3-penten-1-yl Acetate (8). Obtained as a mixture of stereoisomers in the ratio 3:1 (data for the minor isomer are given in parentheses): yellow oil; yield 85%; ^{1}H NMR δ 1.98 (s, 3H), 2.35 (dd, J = 12.6, 6.2 Hz, 2H), 3.01 (d, J = 5.3 Hz, 2H) [minor isomer 3.05 (d, J = 7.2 Hz, 2H)], 3.55 (s, 4H), 4.07 (t, J = 6.7 Hz, 2H) [4.02 (t, J = 6.6 Hz, 2H)], 5.50−5.70 (m, 2H), 7.19−7.37 (m, 10 H); ^{13}C NMR δ 20.9, 31.8, 57.6, 63.7, 126.7, 128.1, 128.6, 130.3, 139.6, 171.0; HRMS (FAB) calcd for $C_{21}H_{26}NO_2$ (M + 1) 324.1964, found 324.1949.

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2-(*N*-Allyl-*N*-methylamino)ethanol (9): yellow oil; yield 85%; ^{1}H NMR δ 2.30 (s, 3H), 2.61 (t, J = 5.1 Hz, 2H), 3.12 (d, J = 6.6 Hz, 2H), 3.69 (t, J = 5.4 Hz, 2H), 5.16 (ddd, J = 17.1, 12.6, 4.8 Hz, 2H), 5.84 (ddt, J = 17.1, 10.2, 6.3 Hz, 1H); ^{13}C NMR δ 41.4, 58.0, 58.3, 60.6, 115.1, 126.6; HRMS (FAB) calcd for $C_6H_{14}NO$ (M + 1) 116.1075, found 116.1076.

General Procedure for the Synthesis of Substituted *N*-Allylbenzenesulfonamides 11. A mixture of the corresponding *N*-allylbenzotriazole **1** or **3** (3.1 mmol), an *N*-alkylbenzenesulfonamide **10** (3.5 mmol), triphenyl phosphite (0.13 g, 0.42 mmol), and $Pd(OAc)_2$ (50 mg, 0.22 mmol) in methanol (10 mL) was heated under reflux under nitrogen for 48 h. The reaction mixture obtained was allowed to cool, triturated with water and extracted with ethyl acetate. The organic fraction was washed with saturated aqueous NH_4Cl, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (Al_2O_3, hexane/ethyl acetate = 100:3).

***N*-Allyl-*N*-ethylbenzenesulfonamide (11b):** yellow oil; yield 80%; ^{1}H NMR δ 1.10 (t, J = 7.1 Hz, 3H), 3.24 (q, J = 7.1 Hz, 2H), 3.84 (d, J = 6.1 Hz, 2H), 5.15 (d, J = 10.1 Hz, 1H), 5.20 (d, J = 17.3 Hz, 1H), 5.67 (ddt, J = 16.5, 10.1, 6.3 Hz, 1H), 7.49−7.58 (m, 3H), 7.83 (d, J = 7.2 Hz, 2H); ^{13}C NMR δ 15.2, 43.5, 51.4, 120.2, 128.6, 130.6, 133.9, 134.8, 142.0. Anal. Calcd for $C_{11}H_{15}NO_2S$: C, 58.64; H, 6.71. Found: C, 58.76; H, 6.81.

Supporting Information Available: Experimental data. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0006268