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SOLVENT-FREE ADDITION REACTION OF ALLYLZINC BROMIDE AND ALDIMINES

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GRAPHICAL ABSTRACT



Abstract Barbier-type allylation of aldimines with allylzinc bromide took place rapidly under solvent-free conditions. The procedure is environmentally benign and operationally simple, has good regioselectivity, and gives good to excellent yields.

Keywords Addition reaction; aldimines; allylzinc bromide; homoallylic secondary amines; solvent-free

INTRODUCTION

Allylation of imines is an important procedure to produce homoallylic amines, which are fundamental building blocks in many biologically active compounds.^[1-4] Imines have several inherent characteristics, which include their sensitivity to water, their relatively low electrophilicity, and their tendency to deprotonate when they are derived from enolizable carbonyl compounds.^[2,5] Therefore, traditional procedures for synthesis of homoallylic amines involve the exclusion of air and moisture and the use of dry solvent tetrahydrofuran (THF) or CH₃CN, alternative media such as polyethylene glycol (PEG) or poly(propylene) glycol (PPG), and highly reactive organometallic reagents.^[6–9] However, some of the methods employed earlier are associated with certain drawbacks such as long reaction times, unsatisfactory yields, and requirement for a catalyst or a nitrogen atmosphere.

Organozinc reagents have more potential application in organic synthesis because of their tolerance of a wide range of functionalities. However, their applications were limited for a long time because of their moderate reactivity. The poor reactivity of zinc organometallic reagents can be increased by adding a

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Scheme 1. The solvent-free addition reaction of allylzinc bromide and aldimines.

transition-metal catalyst such as Cu, Pd, Ni, Co, and Mn.^[11–12] In our previous article, we found that the reactivity of organozinc could be enhanced dramatically in the absence of solvent (THF). We reported the solvent-free addition reaction of allylzinc bromide and carbonyl compounds.^[13]

In this article, we report the reactions of allylzinc bromide and aldimines to give homoallylic secondary amines under solvent-free conditions. At first, allylzinc bromide was prepared in solvent (THF), then THF was evaporated, and at last allylzinc bromide was reacted with aldimines to give homoallylic secondary amines under solvent-free conditions. We found that the reactivity of organozinc could be enhanced dramatically by evaporating THF. Allylzinc bromide can react with different kinds of aldimines to give homoallylic secondary amines in a very short time (5 min) in the absence of solvent. The reaction of organozinc reagents always requires transition-metal catalyst, N_2 atmosphere, anhydrous solvent, and low temperature. However, the reaction of allylzinc bromide and aldimines proceeds well in normal atmosphere at room temperature following our route. The yields are good, and the reaction time is very short. The result is shown in Scheme 1 and Table 1.

Imines containing both electron-donating and electron-withdrawing groups in the aromatic rings were found undergo the conversion smoothly. The corresponding homoallylic secondary amines were obtained in yields ranging from 82% to 95% for imines derived from aromatic, -CH₃, Cl, F, Br substituted aromatic, and heteroaromatic aldehydes. The α , β -unsaturated (**3j**) and the –OH substituted imines (**3e**, **3f**, and **3g**) proceeded only with 1,2-additions, and the yields were good.

No.	R	R ₁	Yield (%)	Time (min)
3a	C ₆ H ₅	4-ClC ₆ H ₄	91	5
3b	C_6H_5	C_6H_5	86	5
3c	$4 - FC_6H_4$	C ₆ H ₅	95	5
3d	$4-BrC_6H_4$	C ₆ H ₅	85	5
3e	$2-OHC_6H_4$	C_6H_5	82	5
3f	$2-OHC_6H_4$	4-CH ₃ C ₆ H ₄	87	5
3g	$2-OHC_6H_4$	$2-CH_3C_6H_4$	85	5
3h		$4-CH_3C_6H_4$	86	2
3i		4-ClC ₆ H ₄	95	2
3j	Ph-CH=CH	C_6H_5	90	5

Table 1. Synthesis of homoallylic secondary amines under solvent-free conditions

Using the reaction of N-benzylidenebenzenamine with allylzinc bromide as an example, we investigated the effect of solvent (THF) on the reaction. We found that removal of THF plays a major role in the reaction. We initially studied the reaction in the presence of THF and found the reactants did not react with each other at all, even after a long reaction time(8 h). The reactivity of organozinc could be enhanced dramatically in the absence of solvent. Allylzinc bromide can react with N-benzylidenebenzenamine in 5 min without any catalysts under solventless condition, and the yield was good (86%). The reason^[14] is probably that the greater concentration of reactants in the absence of solvent leads to more favorable kinetics than in solution.

EXPERIMENTAL

Infrared (IR) spectra were measured using an Alpha Centauri Fourier transform (FT)–IR spectrophotometer. ¹H NMR spectra (400 MHz) were recorded in CDCl₃ using a Bruker AC-E 400-MHz spectrometer. Mass spectra were performed on QP-1000A. High-resolution mass spectrometry (HRMS) was performed on an Apex II FT-ICR. Gas chromatography–mass spectrometry (GC-MS) was measured by electron impact (EI) ionization at 70 eV. Purification of products was performed via flash chromatography with 200- to 400-mesh silica gel [petroleum ether (bp 60– 90 °C)–ethyl acetate, 20:1]. The chemicals were obtained from commercial sources.

Preparation of the Imines

The imines were prepared by mixing various aldehyde with aniline in the presence of a catalytic amount of toluene-4-sulfonic acid at room tempreture.^[15] The furfuraldehyde imines (3h and 3i) were produced by grinding together furfuraldehyde with aniline in a mortor in an icebath.

Preparation of Homoallylic Amine

Allylzinc bromide was prepared in an N₂ atomosphere using the Knochels procedure,^[12] which has been slightly modified. In a flame-dried, round-bottom flask fitted with a magnetic bar and dropping funnel, zinc powder (0.39 g, 6 mmol) was placed and the flask was flashed with dry nitrogen. Zinc powder was heated to 60-70°C. 1,2-Dibromoethane (0.1 ml, 1.2 mmol) and THF (1 ml) were dropped, and the temperature was kept for 10 min and then cooled to room temperature. Trimethyl-chlorosilane (0.1 ml, 0.8 mmol) and THF (0.5 ml) were added. The mixture was stirred at room temperature for 15 min. After this step, allyl bromide (0.5 g, 5 mmol) in 3 ml THF was added dropwise over 30 min and then stirred for 2 min. Solvent THF was evaporated from the solution of allylzinc bromide in a rotory evaporator, and aldimine (4 mmol) was added immediately. The resulting mixture was stirred for 5 min at room temperature. After the reaction was completed, saturated aqueous ammonium chloride was poured into the mixture and stirred for 5 min. Ethyl ether was added to the reaction mixture, and the organic layer was separated. The organic extracts were dried over anhydrous MgSO₄. The residue was purified by flash chromatography on silica gel to obtain pure product. All the isolated products were characterized by IR, ¹H NMR, ¹³C NMR, MS, and HRMS.

The spectral data for compounds 3a,^[16] 3b,^[17] 3c,^[18] 3d,^[18] 3e,^[19] 3i,^[20] and 3j,^[17] are consistent with those reported in the literature. The physical and spectra data for compounds 3f, 3g, and 3h are as follows.

2-(1-(p-Toluidino)but-3-enyl)phenol (3f)

Oil, IR (cm⁻¹): 3385, 1610, 1563, 1237. ¹H NMR: δ 9.89 (br s, 2H, OH + NH), 7.24–6.65 (m, 8H, Ar), 5.87–5.77 (m, 1H, H₃), 5.29–5.24 (m, 2H, H₄), 4.26 (t, 1H, H₁, J = 6.8 Hz), 2.64 (t, 2H, H₂, J = 7.6 Hz), 2.21 (s, 3H, CH₃). ¹³C NMR: δ 156.7, 144.1, 134.3 130.8, 129.7, 128.5, 127.7, 126.1, 119.9, 119.6, 117.1, 116.9, 60.4, 41.4, 20.5. EI-MS m/z (%): 254 (0.41) [M⁺ + 1], 253 (1.41) [M⁺], 212 (100.00), 91 (33.48), 77 (21.78). HRMS calcd for C₁₇H₁₉NO [M + H]⁺: 254.1539; found: 254.1535.

2-(1-(o-Toluidino)but-3-enyl)phenol (3g)

Oil, IR (cm⁻¹): 3343, 1610, 1562, 1439, 1274. ¹H NMR: δ 9.53 (br s, 2H, OH +NH), 7.23–6.67 (m, 8H, Ar), 5.91–5.80 (m, 1H, H₃), 5.34–5.26 (m, 2H, H₄), 4.33 (q, 1H, H₁, *J*=4.8 Hz), 2.76–2.66 (m, 2H, H₂), 2.21 (s, 3H, CH₃). ¹³C NMR: δ 156.5, 144.5, 134.7, 130.2, 128.4, 127.7, 127.1, 126.2, 125.0, 120.7, 120.0, 119.8, 117.1, 114.4, 59.5, 41.6, 17.5. EI-MS *m*/*z* (%): 253 (1.63) [M⁺], 212 (100.00), 77 (56.72). HRMS calcd. for C₁₇H₁₉NO [M + H]⁺: 254.1539; found: 254.1543.

N-(1-(Furan-2-yl)but-3-enyl)-4-methylbenzenamine (3h)

Oil, IR (cm⁻¹): 3418, 1603, 1505, 1315. ¹H NMR: δ 7.36–6.38 (m, 7H, Ar), 5.80–5.71 (m, 1H, H₃), 5.19–5.10 (m, 2H, H₄), 4.34 (q, 1H, H₁, *J*=5.2 Hz), 4.04 (br s, 1H, NH), 2.62–2.43 (m, 2H, H₂), 2.16 (s, 3H, CH₃). ¹³C NMR: δ 145.0, 143.7, 134.7, 129.5, 128.5, 126.8, 126.5, 126.3, 118.1, 113.6, 57.4, 43.2, 20.3. EI-MS *m*/*z* (%): 227 (1.73) [M⁺], 186 (100.00), 77 (37.65), 41 (39.90). HRMS calcd. for C₁₅H₁₇NO [M + H]⁺: 228.1383; found: 228.1380.

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