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The first preparation of α-functionalized benzylamine

Su-Dong Cho,[a] Hyeung-Jae Kim,[a] Chuljin Ahn,[a] J. R. Falck[b,*] and Dong-Soo Shin[a,*]

[a]*Department of Chemistry, Changwon National University Changwon, 641-773 South Korea*

[b]*Departments of Biochemistry and Pharmacology, University of Texas Southwestern Medical Center, Dallas, TX 75235 USA*

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Abstract

We have investigated the α-acetoxylation of benzylamine derivatives **4** from substituted benzylphthalimide **3** using NBS/AcONa/AcOH in chlorobenzene at reflux.

α-Functionalized benzylamine (Nu=OAc, OMe, N_3) (Fig. 1) will be very useful as a starting material or synthon in organic synthesis.[1,2] The synthetic methodology of β-aminohydroxy acetate and chemical application is well known,[3] however, there is no report about α-acetoxylation of benzylamine derivatives, although some similar reports on α-functionalization of benzyl group have been known.[4–7]

Marcum et al.[4] have investigated the chlorination of benzylic sulfides by NCS, and it has been reported by Worley[5] that *N*-α-(phenylthio)alkyl phthalimide was obtained from the reaction of phthalimide and α-chloroalkyl sulfide in DMF. Recently, Wilson et al.[6] obtained benzaldehyde and amide that was obtained by reacting benzamide with NBS/AIBN. Also, α-silyl benzylcarbamates was reported from *N*-silyl-*N*-*t*-Boc-benzylamines via[1,2] silicon rearrangement.[7]

As part of a program about α-functionalization of benzylamine derivatives, we report herein the first synthetic methodology of phthalimide-benzylacetate **4** (Scheme 1).

Benzylphthalimide **3** (R=H) was synthesized from phthalimide with substituted benzyl chloride as high yield. We found that phthalimide-benzylacetate **4** was afforded in the reaction condition of NBS/NaOAc/HOAc in chlorobenzene at 137°C for 12 h in good yield.[8] The results of substituted phthalimide-benzylacetate **4** are shown in Table 1.

The yield of compound **4** differed as a result of the electron donating or electron-withdrawing ability of *para*-substrate in benzylphthalimide **3** as shown in Table 1. The reaction was not progressed in

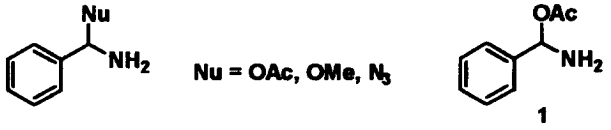

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Figure 1.

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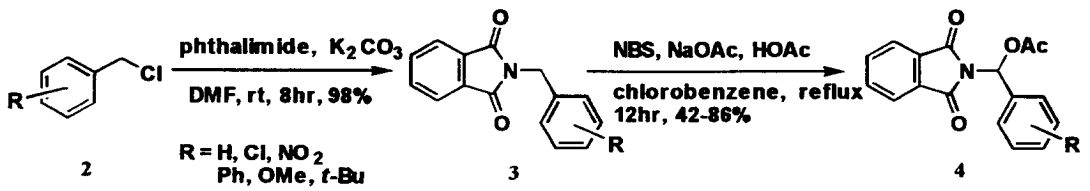

Scheme 1.

Table 1

The preparation and yield of phthalimide-benzylacetate **4** by NBS/NaOAc/AcOH

Entry	Compd. 4	Yield(%)[a]	m.p	Entry	Compd. 4	Yield(%)[a]	m.p
a	R=H	85%	111-111.5°C	e	R=OMe	86%	81°C
b	R=Cl	71%	159-160°C	f	R=*t*-Bu	79%	55°C
c	$R=NO_2$	42%	183-183.5°C	g	Octyl-phthalimide	No rxn.	
d	R=Ph	49%	177- 118°C				

[a]Isolated yield after chromatographic purification

aliphatic alkyl group (Table 1, entry 4g). Also, compound **1** was synthesized by compound **4a** with NH_2NH_2/HOAc in ethanol as 68% yield.[9]

In conclusion, we have described the first synthetic methodology of phthalimide-benzylacetate **4** from benzylphthalimide **3**. At present, we are currently exploring the synthesis of biologically active compound using amino(phenyl)methyl acetate(**1**), which will be applied to the synthesis of heterocyclic base, organic building block and drugs.

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8. (1,3-Dioxo-1,3-dihydro-2*H*-isoindoll-2-yl)(phenyl)methyl acetate **2a**: a mixture of **1a** (1 g, 1 equiv., 4.21 mmol), NBS (1.12 g, 1.5 equiv., 6.32 mmol), NaOAc (0.52 g, 1.5 equiv., 6.32 mmol) and HOAc (0.38 g, 1.5 equiv., 6.32 mmol) in chlorobenzene (25 ml) was refluxed for 12 h. After cooling, chlorobenzene was removed under reduced pressure. The crude product was extracted with ether and concentrated. The resulting mixture was applied to column chromatography (hexane:CH_2Cl_2 2:1, R_f=0.15) to give **3a** (1.06 g, 85% yield): mp=111–111.5°C; IR(KBr)cm^{-1}=1722 (C=O); ^{1}H NMR ($CDCl_3$, 500 MHz) δ=7.34–7.86 (m, 9H, aromatic), 7.69 (s, 1H, CH), 2.21 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ=169.59, 166.67, 135.49, 134.83, 132.02, 129.33, 128.87, 126.8, 124.16, 123.72, 74.63, 21.14.

9. Amino(phenyl)methyl acetate(**4**): a mixture of **3a** (1 g, 1 equiv., 3.38 mmol) and hydrazine monohydrate (0.17 g, 1 equiv., 3.38 mmol), in EtOH (10 ml) was refluxed for 20 min. After addition HOAc (0.3 g, 1.5 equiv., 5.07 mmol), the mixture was refluxed for 2 h. After cooling, EtOH was removed under reduced pressure. The crude product was extracted with CH_2Cl_2 and concentrated. The resulting mixture was applied to column chromatography (CH_2Cl_2, R_f=0.07) to give amino(phenyl)methyl acetate(**4**) (0.38 g, 68% yield): mp=139.5–140°C; IR(KBr)cm^{-1}=3193, 3075 (NH_2), 1680 (C=O); ^1H NMR ($CDCl_3$, 500 MHz) δ=10.49 (d, 2H, NH_2), 7.66–7.87 (m, 5H, aromatic), 7.68 (s, 1H, CH), 2.91 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ=174.83, 144.40, 134.36, 130.43, 129.10, 127.53, 20.74.