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Facile Reduction of Intermediates from Carboxylic Acids and 6-Nitro-1-(2-nitrophenylsulfonyloxy)benzotriazole with Sodium Borohydride to Alcohols

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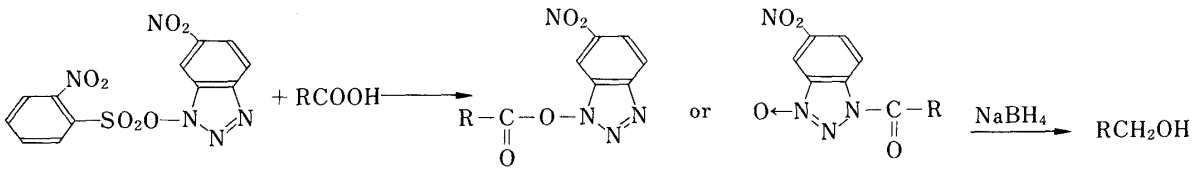
Reduction of activated intermediates derived from 6-nitro-1-(2-nitrophenylsulfonyloxy)-benzotriazole and carboxylic acids with sodium borohydride readily afforded the corresponding alcohols in 71—93% yields.

Keywords——6-nitro-1-(2-nitrophenylsulfonyloxy)benzotriazole; 1-acyloxy-6-nitrobenzotriazole; 3-acyl-6-nitrobenzotriazole 1-oxide; sodium borohydride reduction; alcohol synthesis

Activation of carbonyl groups under mild conditions is of great value in the field of organic synthesis. Recently, several heterocyclic ring moieties have proved to have much potential as leaving groups in carboxyl activating processes. In particular, the active carboxylic esters with 1-hydroxysuccinimide,[1] 1-hydroxybenzotriazole,[2] 2-hydroxypyridinium iodide,[3] and cyanuric acid[4] moieties as the leaving group are most useful intermediates in the synthesis of amides and peptides. In the preceding paper,[5] we reported that 6-nitro-1-(2-nitrophenylsulfonyloxy)benzotriazole (**1**) is an excellent carboxyl activating reagents, which permits direct preparation of versatile synthetic intermediates, 1-acyloxy-6-nitrobenzotriazoles (**3**), in which 1-hydroxy-6-nitrobenzotriazole is involved as the effective leaving group. This paper describes the application of **1** for reduction of carboxylic acids (**2**) to the corresponding alcohols (**5**).

Direct reduction of carboxylic acids to alcohols requires powerful reducing reagents such as lithium aluminum hydride, diborane, and so on. When other easily reducible functional groups are involved in the molecule, selective reduction of the carboxylic acid moiety is very difficult. Combinations of the reagents activating a carboxyl group and weaker reducing reagents have hitherto been explored for the selective reduction of carboxylic acids. Reductions of mixed anhydrides,[6,7] enol esters derived from *N*-ethyl-5-phenylisoxazolium-3′-sulfonate,[8] 1-succinimidyl esters,[9] and 3-acylthiazolidine-2-thiones[10] have been reported. These reductions, however, are troublesome regarding the work-up. Recently, Fujisawa *et al.*[11] reported an excellent preparation of alcohols by the reduction of activated carboxylates derived from *N*,*N*-dimethylchloromethyleniminium chloride. However, the procedure must be carried out at −78 °C.

The reaction of carboxylic acids (**2**) with 6-nitro-1-(2-nitrophenylsulfonyloxy)benzotriazole (**1**) in CH_2Cl_2 gave 1-acyloxy-6-nitrobenzotriazoles (**3**) or 3-acyl-6-nitrobenzotriazole 1-oxides (**4**) in excellent yields. Horiki[12] has reported that 1-acetoxybenzotriazole exists in equilibrium with 3-acetylbenzotriazole 1-oxide in dioxane and tetrahydrofuran (THF) and that two acetyl isomers can be successfully isolated. The infrared (IR) spectra showed carbonyl absorptions at 1820 and 1740 cm^{-1}, respectively. The structure were recently determined by an X-ray crystallographic analysis.[13] The melting points, yields, and the IR spec-



1 2 3 4 5

2a : R=Ph
2b : R=α-furyl
2c : R=$PhOCH_2$
2d : R=C_6H_{11}
2e : R=*tert*-Bu
2f : R=$Br(CH_2)_3$
2g : R=PhCH=CH
2h : R=*p*-NO_2Ph
2i : R=$PhCH_2CH(NHZ)$
2j : R=$MeSCH_2CH_2CH(NHZ)$

3a : R=Ph
3d : R=*cyclo*-C_6H_{11}
3e : R=*tert*-Bu
3f : R=$Br(CH_2)_3$
3h : R=*p*-NO_2Ph
3i : R=$PhCH_2CH(NHZ)$
3j : R=$MeSCH_2CH_2CH(NHZ)$

4b : R=α-furyl
4c : R=$PhOCH_2$
4g : R=PhCH=CH

5a : R=Ph
5b : R=α-furyl
5c : R=$PhOCH_2$
5d : R=C_6H_{11}
5e : R=*tert*-Bu
5f : R=$Br(CH_2)_3$
5g : R=PhCH=CH
5h : R=*p*-NO_2Ph
5i : R=$PhCH_2CH(NHZ)$
5j : R=$MeSCH_2CH_2CH(NHZ)$

Z=benzyloxycarbonyl

Chart 1

TABLE I. 1-Acyloxy-6-nitrobenzotriazoles (**3**) and 3-Acyl-6-nitrobenzotriazole 1-Oxides (**4**)

3 or 4	R	Yield (%)	mp (°C)	IR (KBr) cm^{-1}
3a	Ph	88	166—167	1800 (C=O), 1340 (NO_2)
4b	α-Furyl	94	165—167	1675 (C=O), 1330 (NO_2)
4c	$PhOCH_2$	91	175—176	1745 (C=O), 1325 (NO_2)
3d	C_6H_{11}	87	89—90	1810 (C=O), 1335 (NO_2)
3e	*tert*-Bu	96	114—115	1800 (C=O), 1340 (NO_2)
3f	$Br(CH_2)_3$	92	77—80	1820 (C=O), 1340 (NO_2)
4g	PhCH=CH	94	220—223	1690 (C=O), 1320 (NO_2)
3h	*p*-NO_2Ph	96	221—223	1780 (C=O), 1340 (NO_2)
3i	$PhCH_2CH(NHZ)$[a]	82	92—93	3270 (NH), 1800 (C=O), 1660 (C=O), 1335 (NO_2)
3j	$MeSCH_2CH_2CH(NHZ)$[a]	77	90—91	3250 (NH), 1800 (C=O), 1650 (C=O), 1330 (NO_2)

a) Z=benzyloxycarbonyl.

TABLE II. Preparation of Alcohols (**5**) by the Reduction of **3** and **4** with Sodium Borohydride

5	R	Temperature (°C)	Time (min)	Yield (%)	bp (mmHg) or mp (°C)
a	Ph	r.t.	120	80	101—102 (23)
b	α-Furyl	r.t.	120	68	71—73 (25)
c	$PhOCH_2$	r.t.	120	75	98—100 (7)
d	C_6H_{11}	0—5	90	82	86—87 (25)
e	*tert*-Bu	0—5	90	72	112—113 (760)
f	$Br(CH_2)_3$	0—5	90	82	86 (25)
g	PhCH=CH	r.t.	90	70	121—122 (10)
h	*p*-NO_2Ph	r.t.	90	88	93—94
i	$PhCH_2CH(NHZ)$[a,b]	r.t.	120	74	93—94
j	$MeSCH_2CH_2CH(NHZ)$[c]	r.t.	120	77	64—65

a) Z=benzyloxycarbonyl. *b*) $[\alpha]_D^{17}$ −41.6° (*c*=1.98, EtOH) (lit: $[\alpha]_D^{23}$ −41.7°).[9] *c*) $[\alpha]_D^{17}$ 26.4° (*c*=1.88, EtOH).

tral data of **3** or **4** are shown in Table I.

As shown in Table I, the IR absorption of the carbonyl group adjacent to the α-furyl, phenoxymethyl, and styryl substituents appears at 1675—1745 cm^{-1}, and those of the other compounds at 1780—1810 cm^{-1}. It is presumed that the compounds having higher frequency absorption correspond to the activated esters (**3**), while the others are the activated amides (**4**).

Reduction of the activated compounds (**3** and **4**) to the corresponding alcohols (**5**) was easily achieved with sodium borohydride in EtOH in 71—93% yields. The structures of **5a**—**e** and **5g**—**h** were confirmed by comparison of the IR spectra with those of the authentic alcohols.[14] The structures of novel alcohols (**5f**, **5i**, and **5j**) were determined from the spectral data and the elemental analyses. The yields and reaction conditions are shown in Table II.

Carboxylic acids containing easily reducible nitro, bromo, and C=C double bond groups in the molecule could also be successfully converted to the corresponding alcohols (**5**) without any effect on these sensitive groups.

Experimental

All the melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. IR spectra were recorded with a JASCO IRA-1 grating infrared spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were determined with a JEOL 60H spectrometer. Specific rotations were measured with a JASCO DIP-360 polarimeter using 10 ml cell.

General Procedure for 1-Acyloxy-6-nitrobenzotriazoles (3) and 3-Acyl-6-nitrobenzotriazole 1-Oxides (4)——Triethylamine (1.53 ml, 11 mmol) was slowly added to a suspension of carboxylic acid (**2**) (10 mmol) and 6-nitro-1-(2-nitrophenylsulfonyloxy)benzotriazole[5] (**5**) (4.0 g, 10 mmol) in dry CH_2Cl_2 (30 ml) with stirring under cooling with ice-water. The reaction mixture was stirred for 2 h at room temperature. In the cases of **2b**,**c**,**g**—**j**, the precipitates were collected by filtration, washed with water to remove the triethylammonium salt of *o*-nitrobenzenesulfonic acid, and subjected to the following reduction without purification, because recrystallization caused decomposition. In the cases of **2a**, **d**, **e**, **f**, the CH_2Cl_2 solution was washed with water (30 ml × 3) and dried over anhydrous Na_2SO_4. After removal of CH_2Cl_2, the residue was recrystallized from $CHCl_3$–*n*-hexane.

Reduction of 3 and 4 to Alcohols (5)——A stirred suspension of **3** and **4** (5 mmol) in EtOH (20 ml) was treated with $NaBH_4$ (0.45 g, 12 mmol), which was added over 15 min under cooling with ice-water. After stirring had been continued under the reaction conditions described in Table II, the mixture was filtered. The filtrate was evaporated to dryness, and the residue was dissolved in water (20 ml) and extracted with Et_2O (30 ml × 3). The extract was washed with aqueous saturated NaCl solution, dried over anhydrous Na_2SO_4, and evaporated to dryness. The residue was purified by distillation or recrystallization from $CHCl_3$ or benzene–*n*-hexane.

5f: IR ν_{max}^{film} cm^{-1}: 3250 (OH). ^{1}H-NMR ($CDCl_3$) δ: 1.80—1.95 (5H, m, CH_2 and OH), 3.48 (2H, t, J=7 Hz, CH_2), 3.79 (2H, t, J=7 Hz, CH_2). *Anal.* Calcd for C_4H_9BrO: C, 31.40; H, 5.93. Found: C, 31.78; H, 5.83.

5i: IR ν_{max}^{KBr} cm^{-1}: 3300 (OH), 3250 (NH), 1680 (C=O) ^{1}H-NMR ($CDCl_3$) δ: 2.27 (1H, br, OH), 2.87 (2H, d, J=7 Hz, CH_2), 3.50—3.75 (2H, m, CH_2), 3.75 (1H, br, NH), 3.75—4.20 (1H, m, CH), 5.10 (2H, s, CH_2), 7.30 (5H, s, Ph), 7.40 (5H, s, Ph). *Anal.* Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.72; N, 4.91. Found: C, 71.34; H, 6.97; N, 5.01.

5j: IR ν_{max}^{KBr} cm^{-1}: 3325 (OH), 3260 (NH), 1670 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.68—1.94 (2H, m, CH_2), 1.54 (1H, br, OH), 2.05 (3H, s, Me), 2.50 (2H, t, J=7 Hz, CH_2), 3.62 (2H, m, CH_2), 3.68 (1H, s, NH), 5.07 (2H, s, CH_2), 7.30 (5H, s, Ph). *Anal.* Calcd for C_{13} $H_{19}NO_3S$: C, 57.97; H, 7.11; N, 5.20. Found: C, 58.37; H, 7.15; N, 5.20.

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