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SOLVENT EFFECT IN THE REACTION OF (S)-N-ISOPROPYL-(N^{α}-BENZYLOXY CARBONYL)PROLINAMIDE WITH LITHIUM ALUMINUM HYDRIDE

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A specific solvent effect in the reduction of (S)-N-isopropyl-(N^{α}-benzyloxycarbonyl)prolinamide with lithium aluminum hydride. The reactions in diethyl ether gave mainly (S)-N-isopropyl-(N^{α}-methyl)prolinamide and (2S)-N-methyl-2-[(isopropylamino)methyl]pyrrolidine, while 3-isopropyl-2-oxo-1,3-diazabicyclo[3.3.0]oct-4-ene and (5S)-3-isopropyl-1,3-diazabicyclo[3.3.0]octane were produced in tetrahydrofuran.

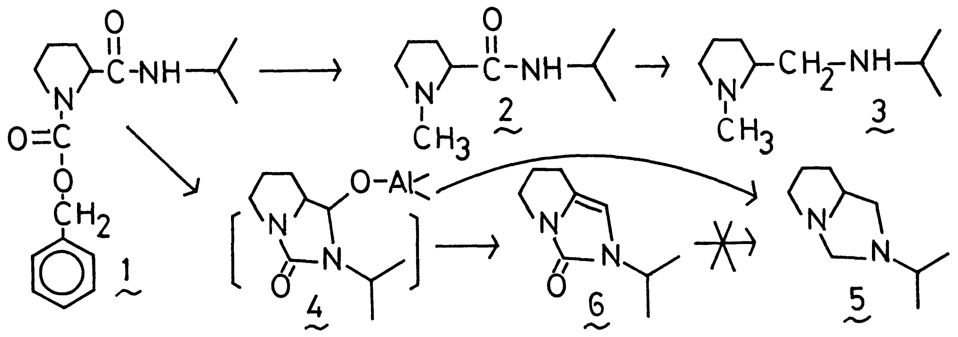
We now report a remarkable solvent effect in the lithium aluminum hydride (LAH) reduction of (S)-N-isopropyl-(N^{α}-benzyloxycarbonyl)prolinamide(1), having an N-benzyloxycarbonyl(Z) group and an amide group. The reaction of compd 1 with LAH in diethyl ether(ether) gave (S)-N-isopropyl-(N^{α}-methyl)prolinamide(2)[1] and (2S)-N-methyl-2-[(isopropylamino)methyl]pyrrolidine(3)[1] as main products, while (5S)-3-isopropyl-1,3-diazabicyclo[3.3.0]octane(5)[1] was a predominant product in tetrahydrofuran(THF). By controlling molar ratio of LAH to 1 in THF, 3-isopropyl-2-oxo-1,3-diazabicyclo[3.3.0]oct-4-ene(6)[1] was obtained, probably via an elimination of water on intermediate(4). These data are shown in Table 1. These results suggest the presence of two obviously different processes which are dependent on the character of solvent in the reaction.

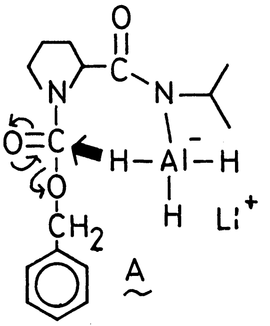
Recently, Hartshorn et al. found a solvent dependence of products in the LAH reduction of alkynols. They explained the results by an initial hydride attack on

Table 1. Product yields of reactions of 1 with lithium aluminum hydride

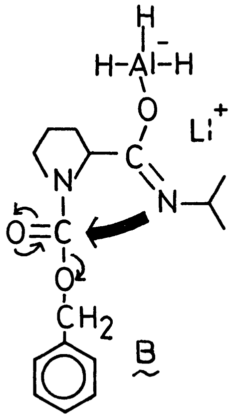
entry	molar ratio of LAH/1	solvent	reaction conditions	yield(%)[a] 2	3	5	6
1	1.53	ether	rt, 24h	51	17	trace	--
2	1.53	ether	reflux, 8h	52	23	4	--
3	3.85	ether-THF(1:1)	reflux, 4h	12	trace	78	--
4	1.53	THF	rt, 3h	--	6	81	--
5	3.85	THF	reflux, 8h	--	trace	87	--
6	0.78	THF	rt, 3h	--	--	--	62

a) Determined by GLC.





A



B

the different carbon of the triple bond.$^{2)}$ In our system, the amide proton of 1 is first abstracted by LAH and the substrate–LAH complexes are formed. Then, there are alternative routes for the following stage; that is, the reaction in ether is initiated by the attack of a hydride on the carbonyl carbon of Z group, as is shown in Fig. A, while the reaction in THF is derived to a cyclization by the attack of the imino-nitrogen on the carbonyl carbon of Z group, as is shown in Fig. B. Solvents seem to affect the substrate–LAH complexes. Studies are being continued to know how solvents participate the transition state of the reduction.

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References

1) Elemental analyses were satisfactory for all new compounds.

Compd 2: bp 121-122°C/17mmHg; $[\alpha]_D^{21}$-86.7° (c 1.91,CH_2Cl_2);IR(neat)ν=3360cm^{-1}(NH), 1655cm^{-1}(C=O);^{1}H NMR($CDCl_3$)δ=1.15 and 1.17(each 3H,d,J=6.2Hz),1.75(4H,m),2.32 (3H,s),2.80(1H,dd,J=5.4 and 9.0Hz),3.09(2H,m),4.05(1H,m),7.05(1H,br);^{13}C NMR($CDCl_3$) δ=22.8(2C,q),24.1(t),31.0(t),40.5(d),41.6(s),56.6(t),69.2(d),173.5(C=O).

Compd 3: bp 43-44°C/2mmHg; $[\alpha]_D^{21}$-53.6° (c 0.88,CH_2Cl_2);IR(neat)ν=3320cm^{-1}(NH);^{1}H NMR ($CDCl_3$)δ=1.08(6H,d,J=6.0Hz),1.10(1H,br),1.55-1.80(4H,m),1.90-2.40(3H,m),2.31(3H,s), 2.50-2.85(2H,m),3.00(1H,m);^{13}C NMR($CDCl_3$)δ=22.7(t),23.1(2C,q),29.5(t),41.1(s),50.7 (t),57.6(t),65.9(d).

Compd 5: bp 86-88°C/29mmHg; $[\alpha]_D^{24}$-1.41° (c 0.71,CH_2Cl_2);^{1}H NMR($CDCl_3$)δ=1.03 and 1.05 (each 3H,d,J=6.0Hz),1.40-2.05(4H,m),2.10-2.80(4H,m),3.05(1H,m),3.22(1H,d,J=7.2Hz), 3.52(1H,m);^{13}C NMR($CDCl_3$)δ=22.1(2C,q),26.4(t),33.0(t),53.2(d),56.1(t),57.8(t),63.3 (d),76.7(t).

Compd 6: mp 130-133°C;IR(nujol)ν=3100cm^{-1}(C=C),1665cm^{-1}(C=O),1630cm^{-1}(C=C);^{1}H NMR ($CDCl_3$)δ=1.25(6H,d,J=6.3Hz),2.20-2.80(4H,m),3.65(2H,t,J=6.6Hz),4.33(1H,m),5.86(1H, s);^{13}C NMR($CDCl_3$)δ=22.2(2C,q),22.8(t),28.1(t),42.1(t),44.3(d),97.9(s),126.4(d), 149.6(C=O).

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b) J.W.Blunt, M.P.Hartshorn, M.H.G.Munro, L.T.Soong, R.S.Thompson, and J.Vaughan, J. Chem. Soc., Chem. Commun., 1980, 820.

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