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Efficient Reduction of Acyl Chlorides with $Zn(BH_4)_2$/*N*,*N*,*N*′,*N*′-Tetramethylethylenediamine

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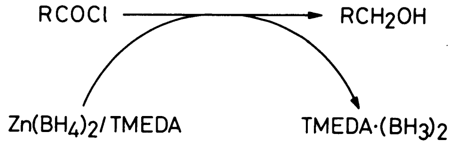
Synopsis. Aliphatic and aromatic acyl chlorides were efficiently reduced to give the corresponding alcohols when treated with $Zn(BH_4)_2$ in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine. The reactions with other bases were also examined.

The reductive synthesis of primary alcohols from carboxylic acid derivatives is a very common procedure in organic chemistry and numerous reagents have been developed.[1] In our separate work, we have required methods for the selective and mild reduction of acyl chloride function in the presence of esters.[2] The use of a well-known reagent such as $LiAlH_4$ was not satisfactory for our purpose because of its strong reducing ability. As previously reported, however, the use of $Zn(BH_4)_2$ with *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) was found to be a remarkably mild method for the reduction of acyl chlorides to the corresponding alcohols.[3] In this paper we would like to report a more detailed study of this reaction.

Contrary to the description given in the literature,[4] the reduction of benzoyl chloride with $Zn(BH_4)_2$ was very slow and showed less synthetic utility. Fortunately, we found that the reaction was highly accelerated by using one equivalent of TMEDA and gave a clean product. As listed in Table 1 for a comparison, this new reagent system is superior to the usual reagents. Under these conditions a wide variety of aliphatic and aromatic acyl chlorides could be efficiently reduced into the corresponding alcohols in high yields (Table 2). Only one exception was phthaloyl dichloride, which gave a considerable amount of phthalide along with the desired diol. Since under the same conditions phthalide was not reduced, this product must be formed by intramolecular acylation. In these reductions the functional selectivity is particularly noteworthy. Thus, chloro, nitro, ester, and conjugated double bonds were not affected by this reagent system. The limitation is a compound containing an isolated double bond, such as 3-cyclohexenecarbonyl chloride, because of the concomitant hydroboration on this function.

Coupled with this observation, we found that a TMEDA·$(BH_3)_2$ complex,[15] mp 179—180 °C (lit,[16] 179—179.5 °C), was also formed under these reactions, although the yield depended upon the runs (usually in around 40 %). As is well-known, this complex is not only exceedingly stable toward the conventional workup conditions but is insoluble in most organic solvents.[16] Therefore, the product alcohols can be simply separated from the mixture by filtration. From this evidence we concluded that during the reaction borane was generated and trapped by TMEDA. Namely, TMEDA can be regarded as an effective borane scavenger leading to clean reactions, as illustrated in Scheme 1.



Scheme 1.

With these results in hand we have examined the effect of amine on the reduction of *m*-chlorobenzoyl chloride. The result is summarized in Table 3. It will be apparent that among the several amines TMEDA is the best one. DABCO also showed a comparable yield, probably due to a similar stability of its borane complex.[16] Interestingly, the use of *N*,*N*-dimethylaniline or 2,6-lutidine gave *m*-chlorobenzyl *m*-chlorobenzoate as a major product. The formation of this ester probably accounts for the fast esterification of the starting acyl chloride with the formed alcohol catalyzed with these amines. However, attempts to develop this finding as a general procedure have been unsuccessful.

Though cyclohexene and 2,5-norbornadiene were also employable as a borane scavenger,[17] in these cases the isolation of alcohols from the mixture was not so easy.

Although there are several methods available for the reduction of acyl chlorides, we believe that the present method offers considerable advantages in terms of simpleness, functional selectivity, readily available reagents, and very mild conditions.

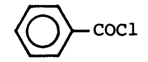
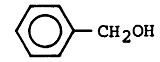
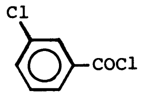
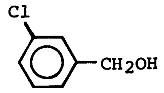
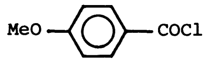
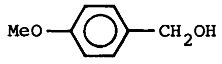
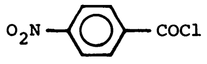
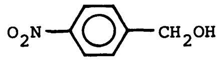
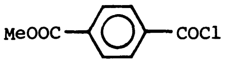
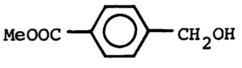
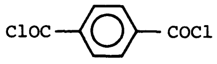
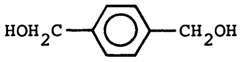
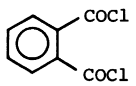
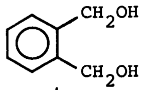
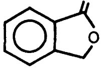
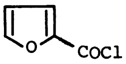
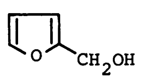
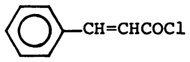
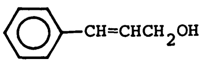
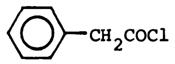
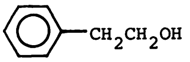
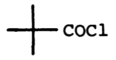
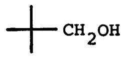
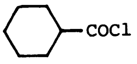
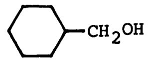
Experimental

An ethereal solution of $Zn(BH_4)_2$ was prepared from

Table 1. Reduction of Benzoyl Chloride to Benzyl Alcohol with Several Reducing Agents

Reducing agent	Solvent	Reactn conditions: temp (°C)/time (h)	Yield (%)	Ref.
$LiAlH_4$	Ether	Reflux	72	5
$NaBH_4$	Dioxane	100/1—2	76	6
$NaBH(OMe)_3$	Ether	Reflux/4	66	7
Bu_4NBH_4	CH_2Cl_2	−78/0.25	98	8
$NaBH_4$/Alumina	Ether	25/2—4	90	9
$Zn(BH_4)_2$/TMEDA	Ether	40/4.5	95	

Table 2. Reduction of Acyl Chlorides with $Zn(BH_4)_2$/TMEDA

Acyl chloride	Reactn conditions:[a] temp (°C)/time (h)	Product[b]	Yield (%)[c]	Mp (°C) or bp (°C) (mmHg)[d]	
				Found	Reported[Ref]
	40/4.5		95	101—102(14)	93(10)[10]
	0/0.5[e]		98	59—60(0.9)	119(10)[11]
	0/0.5		89	99—100(0.6)	134—135(12)[10]
	0/0.25[e]		93	91—92	92—93[12]
	0/0.25[e]		95	49—49.5	49.5—50[13]
	40/24		75	115—116	115—116[10]
	40/4.5		36	62—63	65—66[10]
		+ 	39	72—74	75[10]
	40/72		80[f]	66—67(17)	68—69(20)[10]
	0/0.5[e]		86	94(1.5)	127—128(10)[10]
	0/0.5		88	96—98(5)	115—120(15)[14]
	0/0.5		98	113—114(14)	97.4(10)[10]
$CH_3(CH_2)_8COCl$	25/5	$CH_3(CH_2)_8CH_2OH$	96	92—93(1.7)	107—108(7)[10]
	25/2		(88)	113—114	114—116[10]
	0/6		93	85(15)	83(14)[10]

a) Ether as solvent, unless otherwise stated. b) Identified by GLC, IR, ^{1}H NMR, and high resolution mass spectrometry. c) Yields represent pure isolated products, value in parentheses was determined by GLC. d) Kugelrohr distillation bath temperature. All melting points and boiling points are uncorrected. e) THF/ether as solvent. f) After 92% conversion.

$NaBH_4$ and $ZnCl_2$ according to the literature method;[18] the concentration was determined by injecting aliquots of the solution into water and then measuring the evolved hydrogen.

General Procedure for the Reduction of Acyl Chlorides with $Zn(BH_4)_2$/TMEDA. To a THF or ether solution (1.8 ml) of acyl chloride (1 mmol) at 0 °C were added successively $Zn(BH_4)_2$ (0.21 M†; 6.7 ml, 1.4 mmol) and TMEDA (1 mmol). The mixture was then stirred at 0 °C or at the indicated temperature (see Table 2) until completion of the reaction, as monitored by TLC or GLC analysis. During the reaction, a white insoluble substance was gradually formed. After quenching by the addition of dilute HCl, the mixture was extracted with AcOEt. The extracts were washed with dilute HCl, satd $NaHCO_3$, and satd NaCl, dried ($MgSO_4$), and evaporated. The obtained crude product was filtered in order to remove any insoluble TMEDA·$(BH_3)_2$ complex. Then, the filtrate was purified by distillation or flash column chromatography, providing the corresponding alcohol. All of the products were known compounds and were identified by comparisons with authentic samples.

Reduction of *m*-Chlorobenzoyl Chloride with $Zn(BH_4)_2$/*N,N*-Dimethylaniline. To a THF solution (1.8 ml) of *m*-chlorobenzoyl chloride (175 mg, 1 mmol) at 0 °C were added $Zn(BH_4)_2$ (6.7 ml, 1.4 mmol) and *N,N*-dimethylaniline

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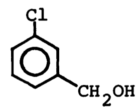
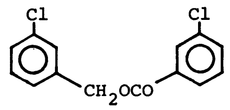
† 1 M=1 mol dm^{-3}.

Table 3. Effect of Amine on the Reduction of *m*-Chlorobenzoyl Chloride with $Zn(BH_4)_2$[a)]

Amine	Product yield (%)[b)]	
		
TMEDA[c)]	98	—
DABCO[c,d)]	93	—
Triethylamine	91	—
Pyridine	83	—
N-Methylmorpholine	86	11
N,N-Dimethylaniline[e)]	14	81
2,6-Lutidine	18	64

a) All reactions were carried out in ether–THF using 1 equiv of $Zn(BH_4)_2$ and 2 equiv of amine at 0 °C for 30 min unless otherwise stated. b) Isolated yields based on the consumed starting material. c) One equiv of amine was used. d) DABCO = 1,4-diazabicyclo[2.2.2]-octane. e) Reaction time = 40 min.

(0.3 ml, 2 mmol). After stirring for 40 min at this temperature, the excess reagent was quenched by the addition of dilute HCl and extracted with AcOEt. The extracts were washed with dilute HCl, satd $NaHCO_3$, and satd NaCl, dried ($MgSO_4$), and evaporated. The crude product was purified by preparative TLC (hexane : AcOEt= 2 : 1) to give 114 mg (81 %) of *m*-chlorobenzyl *m*-chlorobenzoate (R_f=0.67) and 20 mg (14 %) of *m*-chlorobenzyl alcohol (R_f=0.40).

***m*-Chlorobenzyl *m*-Chlorobenzoate:** bp 120—121 °C (0.32 mmHg[††]); IR (neat) 1725, 1600, 1580, 1290, 1280, 1255, 1130, and 750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=5.31 (2H, s), 7.2—7.6 (6H, m), 7.8—8.0 (2H, m); HRMS Found: *m/z* 283.9977 and 280.0032. Calcd for $C_{14}H_{10}O_2Cl_2$: M, 283.9999 and 280.0058.

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[††] 1 mmHg=133.322 Pa.