Efficient Reduction of 2-Haloacetophenone Derivatives to the Corresponding Halohydrins by 9,10-Dihydro-10-methylacridine in the Presence of Titanium Tetrachloride. Comparison with the Reduction in the Presence of Perchloric Acid

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(Received May 31, 1989)

Synopsis. 2-Haloacetophenone derivatives are reduced by an acid-stable NADH model compound, 9,10-dihydro-10-methylacridine, in the presence of $HClO_4$ in acetonitrile at 335 K to yield 10-methylacridinium ion and the parent acetophenone derivatives as well as halohydrins, while the reduction of 2-haloacetophenone derivatives in the presence of $TiCl_4$ in dichloromethane undergoes much more readily even at 298 K to yield the corresponding halohydrins selectively.

Acid catalysis is known to play an essential role in the efficient enzymatic reduction of carbonyl compounds by dihydronicotinamide adenine dinucleotide (NADH).[1] The catalytic center of the enzyme, zinc ion, is believed to act as a Lewis acid rather than a Brönsted acid.[1] Ohno et al.[2] reported that benzaldehyde is reduced to benzyl alcohol by an acid-stable NADH model compound, 1,2,4-trimethyl-3-(α-methylbenzylcarbamoyl)-1,4-dihydroquinoline, in the presence of a Lewis acid ($TiCl_4$ or $AlCl_3$) in tetrahydrofuran at room temperature in 12 h. The reduction of benzaldehyde derivative by acid-stable NADH model compounds is known to be catalyzed also by a Brönsted acid.[3,4]

We have recently reported that various nonactivated ketones[5] and α-halo ketones[6] can be reduced by an acid-stable NADH model compound, 9,10-dihydro-10-methylacridine ($AcrH_2$), in the presence of a Brönsted acid ($HClO_4$) in acetonitrile at 335 K to yield the corresponding halo alcohols and the parent ketones, respectively. The present work reports the comparison of the reactivities as well as the products in the reduction of 2-haloacetophenone derivatives by $AcrH_2$ in the presence of a Lewis acid ($TiCl_4$) with those in the presence of a Brönsted acid ($HClO_4$).

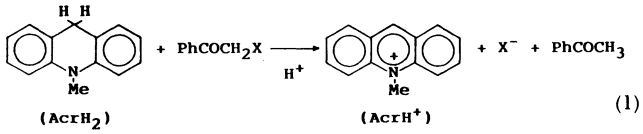
Experimental

Materials. 9,10-Dihydro-10-methylacridine ($AcrH_2$) was prepared from 10-methylacridinium iodide ($AcrH^+I^-$) by the reduction with $NaBH_4$ in methanol, and purified by recrystallization from methanol.[7] The dideuterated compound, [9,9-$^2H_2$]-9,10-dihydro-10-methylacridine ($AcrD_2$), was prepared from 10-methyl-9-acridone by the reduction with $LiAlD_4$.[8] 2-Bromoacetophenone and 2-chloroacetophenone were obtained commercially and purified by the standard methods.[9] 2-Bromo-4′-methoxyacetophenone and 2-bromo-4′-cyanoacetophenone were prepared from bromination of the corresponding acetophenone derivatives in methanol.[10] Styrene bromohydrins was prepared by the reaction of styrene with *N*-bromosuccinimide in water according to the literature.[11] Titanium tetrachloride, dichloromethane, and acetonitrile-d_3 were obtained commercially and used without further purification. Perchloric acid (70%) was obtained from Wako Pure Chemicals.

Reaction Procedure. Typically, $AcrH_2$ (6.0×10^{-5} mol) was added to an NMR tube that contained a deaerated acetonitrile-d_3 (CD_3CN) solution (0.60 cm^3) of 2-haloacetophenone (1.8×10^{-4} mol) and $HClO_4$ (1.8×10^{-4} mol). After the reactant solution was deaerated again by a stream of argon and sealed, the NMR tube was immersed in a water bath which was thermostatted at 335 K. In the case of the reduction of 2-haloacetophenone by $AcrH_2$ in the presence of $TiCl_4$, 2-haloacetophenone (2.0×10^{-3} mol) was firstly added to a deaerated solution of CD_2Cl_2 (0.05 cm^3) containing $AcrH_2$ (5.0×10^{-4} mol), and then $TiCl_4$ (1.3×10^{-3} mol) was added to the 2-haloacetophenone–$AcrH_2$ system under a stream of argon. The reaction was carried out also by changing the order of addition; $TiCl_4$ was firstly added to a CD_2Cl_2 solution of $AcrH_2$, and then 2-haloacetophenone was added to the $AcrH_2$–$TiCl_4$ system. The reaction was quenched by the addition of water (2.0×10^{-3} mol) after 2 min. The product yields were determined from the ^1H NMR spectra in CD_3CN (0.50 cm^3) by comparing with those of the authentic samples.[6] The NMR spectra were recorded using a Japan Electron Optics JNM-PS-100 NMR spectrometer (100 MHz).

Results and Discussion

An NADH model compound ($AcrH_2$) shows no reactivity towards 2-haloacetophenone ($PhCOCH_2X$; X=Br, Cl) in the dark at 335 K. When $HClO_4$ is added to the $AcrH_2$–$PhCOCH_2X$ system, $PhCOCH_2X$ is reduced by $AcrH_2$ at 335 K to yield 10-methylacridinium ion ($AcrH^+$) and acetophenone (Eq. 1) as well as



(1)

α-(halomethyl)benzenemethanol (Eq. 2). 2-Haloacetophenone is reduced by $AcrH_2$ much more readily even

$$ArcH_2 + PhCOCH_2X + H^+ \longrightarrow AcrH^+ + PhCH(OH)CH_2X \quad (2)$$

at 298 K in the presence of $TiCl_4$ in dichloromethane, and the corresponding halohydrin, α-(halomethyl)-benzenemethanol is obtained selectively in 70—80% yield with no dehalogenated compound in 2 min, when the reaction is quenched by water. Such selective formation of halohydrin seems interesting since the model systems that have so far been reported for the reduction of α-halo ketones undergo the reductive dehalogenation to yield parent ketones,[12] although the enzyme-mediated reduction of 2-haloacetophenone is known to yield the corresponding halo-

Table 1. Reduction of 2-Haloacetophenone Derivatives (2.0×10^{-3} mol) by $AcrH_2$ and $AcrD_2$ (5.0×10^{-4} mol) in the Presence of $TiCl_4$ (1.3×10^{-3} mol) in Dichloromethane (0.05 cm^3) at 298 K, Compared with the Reduction of the Same Substrates (1.8×10^{-4} mol) by $AcrH_2$ and $AcrD_2$ (6.0×10^{-5} mol) in the Presence of $HClO_4$ (1.8×10^{-4} mol) in Acetonitrile (0.6 cm^3) at 335 K

Substrate	Reductant	Acid	Time	Product yield/%
$PhCOCH_2Br$	$AcrH_2$	$TiCl_4$	2 min	$PhCH(OH)CH_2Br$(80) $AcrH^+$(80)
$PhCOCH_2Br$	$AcrH_2$	$HClO_4$	11 h	$PhCOCH_3$(82) $PhCH(OH)CH_2Br$(14) $PhCH(OH)CH_3$(4) $AcrH^+$(100)
$PhCOCH_2Cl$	$AcrH_2$	$TiCl_4$	2 min	$PhCH(OH)CH_2Cl$(70) $AcrH^+$(77)
$PhCOCH_2Cl$	$AcrH_2$	$HClO_4$	110 h	$PhCOCH_3$(36) $PhCH(OH)CH_2Cl$(49) $PhCH(OH)CH_3$(14) $AcrH^+$(100)
$PhCOCH_2Br$	$AcrD_2$	$TiCl_4$	2 min	$PhCD(OH)CH_2Br$(75) $AcrD^+$(80)
$PhCOCH_2Br$	$AcrD_2$	$HClO_4$	43 h	$PhCOCH_3$(90) $PhCD(OH)CH_2Br$(7) $PhCD(OH)CH_3$(trace) $AcrD^+$(100)
$PhCOCH_2Cl$	$AcrD_2$	$TiCl_4$	2 min	$PhCD(OH)CH_2Cl$(44) $AcrD^+$(70)
	$AcrD_2$	$HClO_4$	200 h	$PhCOCH_3$(57) $PhCD(OH)CH_3$(27) $PhCD(OH)CH_3$(9) $AcrD^+$(100)
4′-$MeOC_6H_4COCH_2Br$	$AcrH_2$	$TiCl_4$	2 min	4′-$MeOC_6H_4CH(OH)CH_2Br$(52) $AcrH^+$(60)
4′-$MeOC_6H_4COCH_2Br$	$AcrH_2$	$HClO_4$	4 h	4′-$MeOC_6H_4COCH_3$(48) 4′-$MeOC_6H_4CH(OH)CH_3$(46) 4′-$MeOC_6H_4CH(OH)CH_3$(6) $AcrH^+$(100)
4′-$CNC_6H_4COCH_2Br$	$AcrH_2$	$TiCl_4$	2 min	4′-$CNC_6H_4CH(OH)CH_2Br$(50) $AcrH^+$(68)
4′-$CNC_6H_4COCH_2Br$	$AcrH_2$	$HClO_4$	7 h	4′-$CNC_6H_4COCH_3$(95) 4′-$CNC_6H_4CH(OH)CH_3$(5) $AcrH^+$(100)
$PhCOCH(C_2H_5)Br$	$AcrH_2$	$TiCl_4$	2 min	$PhCH(OH)CH(C_2H_5)Br$(6) $AcrH^+$(80)
$PhCOCH(C_2H_5)Br$	$AcrH_2$	$HClO_4$	100 h	$PhCOC_3H_7$(92) $PhCH(OH)CH(C_2H_5)Br$(6) $AcrH^+$(100)
$PhCOCH(C_8H_{17})Br$	$AcrH_2$	$TiCl_4$	2 min	$PhCH(OH)CH(C_8H_{17})Br$(10) $AcrH^+$(73)
$PhCOCH(C_8H_{17})Br$	$AcrH_2$	$HClO_4$	200 h	$PhCOC_9H_{19}$(55) $AcrH^+$(100) $PhCH(OH)CH(C_8H_{17})Br$(45)
None	$AcrH_2$	$TiCl_4$	2 min	$AcrH^+$(50)

hydrin selectively.[13]

The reaction conditions and the yields of products are compared for the reduction of various 2-haloacetophenone derivatives by $AcrH_2$ in the presence of $HClO_4$ with those in the presence of $TiCl_4$ as shown in Table 1. The much higher reaction temperature and more prolonged reaction time are required for the reactions in the presence of $HClO_4$ brought to completion than those in the presence of $TiCl_4$. In the reduction of $PhCOCH_2X$ (X=Br, Cl) by $AcrH_2$ in the presence of $TiCl_4$, the yield of the oxidized product $AcrH^+$ is about the same as that of the reduced product, $PhCH(OH)CH_2X$ (Table 1). The prolonged reaction time (e.g., 10 min) did not improve the product yields.

When $AcrH_2$ is replaced by the 9,9-dideuterated analogue ($AcrD_2$) in the reduction of 2-haloacetophenone in the presence of $HClO_4$ and also in the reduction in the presence of $TiCl_4$, the deuterium is incorporated into α-(halomethyl)benzenemethanol in both cases (Table 1). In the case of the reduction in the presence of $HClO_4$, however, no deuterium is incorporated into the dehalogenated product, acetophenone. The acetophenone is further reduced by $AcrH_2$ to yield small amount of the corresponding alcohol in which the deuterium is incorporated (Table 1). The substitution of the α-carbon of $PhCOCH_2Br$ with an alkyl group for the reduction in the presence of $TiCl_4$ results in significant decrease in the yield of halohydrin, accompanied by the recovery of the reactant, although the yield of $AcrH^+$ is rather constant (Table 1).

In the absence of 2-haloacetophenone as well, $AcrH_2$ is readily oxidized by $TiCl_4$ to yield $AcrH^+$ (Table 1). In addition, no appreciable reduction of 2-haloacetophenone occurs upon the reversed addition; $AcrH_2$ is added to a dichloromethane solution of $TiCl_4$ firstly and then 2-haloacetophenone is added to the $AcrH_2$–$TiCl_4$ system. Thus, the reduction of $TiCl_4$ by $AcrH_2$ may take place firstly, and then a reduced titanium species, which would decompose in the absence of active substrates, may reduce 2-haloacetophenone derivatives to the corresponding halohydrins. The reduced titanium species may not be $TiCl_3$, since $TiCl_3$ is known to bring about reductive dehalogenation of 2-haloacetophenone to yield acetophenone exclusively.[14] In general, a Lewis acid such as $TiCl_4$ is known to activate carbonyl compounds in the reductions by various reductants.[15] Thus, a hydride transfer from $AcrH_2$ to 2-haloacetophenone may be mediated by $TiCl_4$ and facilitated by the interaction of α-halo ketones with $TiCl_4$. At present, however, the detection of a possible mediator such as a titanium hydride species by a low-temperature ^1H NMR measurement was unsuccessful. Other Lewis acids such as $SnCl_4$, $BF_3\cdot OEt_2$, and $AlCl_3$ were not effective for the reduction of α-halo ketones to halohydrins by $AcrH_2$.

References

1) H. Eklund and C.-I. Bränden, "Zinc Enzymes," ed by T. G. Spiro, Wiley-Interscience, New York (1983), Chap. 4.

2) A. Ohno, Y. Ishikawa, S. Ushida, and S. Oka, *Tetrahedron Lett.*, **23**, 3185 (1982).
3) S. Shinkai, H. Hamada, and O. Manabe, *Tetrahedron Lett.*, **1979**, 1397.
4) S. Fukuzumi, M. Ishikawa, and T. Tanaka, *J. Chem. Soc., Chem. Commun.*, **1985**, 1069; *Tetrahedron*, **42**, 1021 (1986).
5) S. Fukuzumi, M. Chiba, and T. Tanaka, *Chem. Lett.*, **1989**, 31.
6) S. Fukuzumi, S. Mochizuki, and T. Tanaka, *J. Am. Chem. Soc.*, **111**, 1497 (1989).
7) R. M. G. Roberts, D. Ostović, and M. M. Kreevoy, *Faraday Discuss. Chem. Soc.*, **74**, 257 (1982); S. Fukuzumi, S. Koumitsu, K. Hironaka, and T. Tanaka, *J. Am. Chem. Soc.*, **109**, 305 (1987).
8) P. Karrer, L. Szabo, H. J. V. Krishna, and R. Schwyzer, *Helv. Chim. Acta*, **33**, 294 (1950); D. Ostović, R. M. G. Roberts, and M. M. Kreevoy, *J. Am. Chem. Soc.*, **105**, 7629 (1983).
9) D. D. Perrin, W. L. F. Armarego, and D. R. Perrin, "Purification of Laboratory Chemicals," Pargamon Press, New York (1968).
10) R. E. Lutz, R. K. Allison, G. Ashburn, P. S. Bailey, M. T. Clark, J. F. Codington, A. J. Deinet, J. A. Freek, R. H. Jordan, N. H. Leake, T. A. Martin, K. C. Nicodemus, R. J. Rowlett, Jr., N. H. Shearer, Jr., J. D. Smith, and J. W. Wilson, III, *J. Org. Chem.*, **12**, 617 (1947).
11) C. O. Guss and R. Rosenthal, *J. Am. Chem. Soc.*, **77**, 2549 (1955).
12) H. Inoue, R. Aoki, and E. Imoto, *Chem. Lett.*, **1974**, 1157.
13) D. D. Tanner and A. R. Stein, *J. Org. Chem.*, **53**, 1642 (1988).
14) A. Clerici and O. Porta, *Tetrahedron Lett.*, **28**, 1541 (1987).
15) T. Mukaiyama, K. Banno, and K. Narasaka, *J. Am. Chem. Soc.*, **96**, 7503 (1974); A. Hosomi and H. Sakurai, *Tetrahedron Lett.*, **1976**, 1295; Y. Yamamoto and J. Yamada, *J. Am. Chem. Soc.*, **109**, 4395 (1987).