HALIDE EXCHANGE AND REDUCTION OF PHENACYLHALIDES PROMOTED BY AQUEOUS TITANIUM (III) SALTS AT VARIOUS pHs. MECHANISTIC CONSIDERATIONS.

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Summary: While aqueous Ti₂(SO₄)₃ is an efficient reagent in acidic medium for selective debromination of phenacylbromide $\underline{1}$ to acetophenone $\underline{3}$ in the presence of phenacylchloride $\underline{2}$, aqueous TiCl₃ gives mostly halide exchange $1 \rightarrow 2$. In neutral medium, both aqueous Ti₂(SO₄)₃ and TiCl₃ bring about dehalogenation of $\underline{1}$ and $\underline{2}$ to $\underline{3}$ in less than one minute at room temperature. In basic medium, reduction of 1 and 2 goes further to methylphenylcarbinol 4.

The conversion of α -haloketones to the parent ketones is a valuable procedure in organic synthesis and several new reagents have been introduced recently 1. Among these, aqueous TiCl, has been reported 2 to promote such transformation after refluxing the substrate with the reducer for 18 h in CH₂CN.

On continuation of our studies 3a,b , partially reviewed 3c , on the reducing properties of Ti(III) salts at various pHs, we now report that at pH $\simeq 1$ aqueous Ti₂(SO₄)₃ is much more efficient than aqueous TiCl_3 in promoting debromination of phenacylbromide <u>1</u> to acetophenone <u>3</u>.

In order to clarify the mechanistic difference between $Ti_2(SO_4)_2$ and $TiCl_2$ in debromination of $\underline{1}$, we have carried out a more detailed study the results of which are summarized in Table.

Reactions in acidic medium. Reduction of 1 with aqueous $\text{Ti}_2(\text{SO}_4)_3$ proceed smothly (room temperature, 30 min) to afford $\underline{3}$ in quantitative yield (run 12). On the contrary, under the same experimental conditions, aqueous TiCl, gives debrominated $\frac{3}{2}$ only in 40% yield and quantitatively transforms unreduced 1 to the corresponding chloride 2 (run 1); if the reaction mixture is allowed to stir for additional 30 min, only an additional 5% of $\frac{2}{2}$ is reduced to $\frac{3}{2}$ (run 2).

Comparable result is obtained using CH_2COCH_2 (run 3) or CH_2CN (run 4) instead of CH_2OH as solvent; when CH₂COOH is used, the halide exchange $1 \rightarrow 2$ is somewhat slower and 3 is formed in 49 and 60% yield after 1 and 5 h, respectively (runs 5 and 6).

Runs 7-11, 13 and 14 confirm that $\frac{2}{2}$ is slowly reduced in low yield by either TiCl₂ or $\operatorname{Ti}_{2}(\operatorname{SO}_{4})_{3}$ solution; moreover the two Ti(III) salts do not differ in their redox properties for both reduce 2 yielding the same amount of 3 (cf. runs 7 and 13, 8 and 14).

On the contrary, a comparison between the redox potentials of $\frac{1}{1/2} = -0.04$ V vs. SCE at pH= 4.8⁵) and $2 (E_{1/2} = -0.58 \text{ V vs. SCE at pH= } 4.0^5)$ well indicates that the former is a better oxidant than the latter. Thus, when the counterion of Ti(III) is chloride, debromination of 1to 3 occurs in low yield because the halide exchange $1 \rightarrow 2$ is strongly competitive with the

reduction; when the counterion is sulphate, formation of the less reducible 2 is prevented and 1 is quantitatively reduced to 3 under very mild conditions.

According to these considerations, in a competitive experiment⁶ between <u>1</u> and <u>2</u> with aqueous $\operatorname{Ti}_2(\operatorname{SO}_4)_3$, <u>1</u> is quantitatively reduced to <u>3</u> while <u>2</u> is recovered unreacted.

These results are rationalized by the sequence of Scheme.

Scheme





In the reduction step (path <u>a</u> of Scheme), Ti(III) ion, meanwhile transfers an electron to <u>1</u>, assists in pulling off the halide. The resonance-stabilized phenacyl radical <u>A</u> equilibrates with the enolic form <u>B</u>, which, owing to its electrophilic character, is further reduced to <u>C</u>. Pre-existent coordination of the carbonyl oxygen of <u>1</u> or <u>A</u> with Ti(III) ion would make easier the second electron uptake. Protonolysis of the Ti(IV)enolate <u>C</u> affords the reduced ketone <u>3</u>. With regard to the halide exchange (path <u>b</u> of Scheme), a more detailed study is needed for the mechanistic classification of the reaction. Very probably Ti(III) or Ti(IV) ion acts as "catalyst" or "promoter" in this type of process for, in a control experiment⁸, a 15% aqueous HCl itself was found to effect slow halide exchange <u>1</u> \rightarrow <u>2</u> in poor yield.

<u>Reactions in neutral</u>⁹ and basic¹⁰ medium. In acidic medium, Ti(III) ion is a very mild reducing agent^{3,11} and is able to discriminate between substrates having little difference in their redox potentials, such as <u>1</u> and <u>2</u>. The reducing power of Ti(III) ion, however, markedly increases with increasing the $pH^{3,11}$. Thus, if the reactions are performed at $pH \simeq 7$, not only debromination of <u>1</u> is complete in less than one minute (run 15) but also dechlorination of <u>2</u> becomes thermodynamically possible, and <u>3</u> is obtained in 90% yield (run 16) in one minute at room temperature. Under these conditions, either TiCl₃ or Ti₂(SO₄)₃ solution easily performs the reductions.

At pH \simeq 10-12, the reducing power of Ti(III) ion increases to such an extent¹¹ that even the reduction of the carbonyl group of <u>3</u> (E_{1/2} = -1.60 V vs. SCE at pH = 11⁵) becomes feasible. The reduction product is methylphenylcarbinol <u>4</u>, which is formed in quantitative yield in less than one minute by reduction of either <u>1</u> (run 17) or <u>2</u> (run 18) with both aqueous TiCl₃ or aqueous Ti₂(SO₄)₃. In a control experiment, <u>3</u> itself is quantitatively reduced to <u>4</u> under comparable experimental conditions¹².

For the reductions, the overall stoichiometry between Ti(III) ion and $\underline{1}$ or $\underline{2}$ is 2:1 in acidic and neutral, 4:1 in basic medium.

Further synthetic application, which takes advantage from the different redox properties of Ti(III) ion at various pHs, is now in progress.

run	Ti(III) salt	starting substrate	solvent	unreacted substrate	pr <u>2</u>	oducts yie <u>3</u>	ld (%) ^a	reaction time	conditions ^b medium
1	TiCl	PhCOCH ₂ Br	снзон	_	60	40	_	1/2 h	acidic
2	"	"	"	-	55	45	-	1 h	**
3	19		снзсоснз	-	68	32	-	1 h	"
4		н	CH ₃ CN	-	81	19	-	5 h	"
5		"	снзсоон	43	8	49	-	1 h	"
6	"	**	"	-	40	60	-	5 h	"
7	n	PhCOCH ₂ C1	снзон	80	-	20	-	1/2 h	"
8	u –	"	"	70	-	30	-	1 h	n
9	и		CH3CN	90	-	10	-	5 h	11
10	n		снусоон	92	-	8	-	1 h	"
11	"	**	"	76	-	24	-	5 h	11
12	$Ti_2(SO_4)_3$	PhCOCH_Br	снзон	-	-	quantitat	ive -	1/2 h	"
13		PhCOCH_C1	"	80	-	20	-	1/2 h	"
14	"	"	n	70	-	30	-	1 h	"
15	с	PhCOCH_Br	CH_OH/NH	traces	-	95	traces	1 min	neutral
16		PhCOCH_C1	"	traces	-	90	traces	1 min	n
17	H	PhCOCH_Br	"	-	-	_	quantitative	e 1 min	basic
18	II	PhCOCH_C1		-	-	-	quantitative	e 1 min	"

Table. Reactions of phenacylhalides with aqueous Ti(III) salts at various pHs.

 $a_{
m Yields}$ are based on the starting substrate and determined by ${}^1_{
m H}$ NMR analysis.

b All reactions were performed at room temperature.

 $c_{\text{TiCl}_3 \text{ or Ti}_2(SO_4)_3}$.

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References and Notes

- 1. A. Ono, E. Fujimoto and M. Ueno, Synthesis, 570 (1986) and references cited therein.
- 2. T.L. Ho and C.M. Wong, Synthetic Commun., 3, 237 (1973).
- a) A. Clerici and O. Porta, *Tetrahedron*, <u>38</u>, 1293 (1982); b) A. Clerici and O. Porta, J. Org. Chem., <u>50</u>, 76 (1985); c) A. Clerici and O. Porta, La Chimica e l'Industria, <u>67</u>, 187 (1985).
- 4. Typical procedure: 20 mmol of a 15% w/v TiCl_3 or a 20% w/v $\operatorname{Ti}_2(\operatorname{SO}_4)_3$ solution (from C. Erba, titrated against 0.1 N $\operatorname{Ce}(\operatorname{SO}_4)_2$ solution) were added at once under N₂ to a solution of the substrate (10 mmol) in 30 ml of solvent. The mixture was stirred at room temperature for the time indicated in Table and then extracted with ethylacetate (3x100 ml). The combined extracts were washed with H₂O, dried over Na₂SO₄ and evaporated to dryness. An aliquot of the crude residue was submitted to ¹H NMR analysis. All products have been identified by comparison with authentic samples.
- 5. L. Meites, "Polarographic techniques", 2nd Ed., John Wiley and Sons: New York, 1965, p 676.
- 6. 10 mmol of a 20% w/v Ti₂(SO₄)₃ solution were added at once to <u>1</u> (5 mmol) and <u>2</u> (5 mmol) dissolved in CH₃OH (30 ml). The mixture was stirred at room temperature under N₂ for 30 min. After workup as in note 4, an aliquot of the crude residue, added with a weighted amount of a suitable standard, was submitted to ¹H NMR analysis.
- Polarographic reduction of PhCOCH₂X shows acid catalysis to an extent dependent upon the basicity of the halide X^{*}. P.J. Elving and J.T. Leone, J. Am. Chem. Soc., <u>79</u>, 1546 (1957); *ibid.*, 82, 5076 (1960).
- 10 mmol of <u>1</u> dissolved in 30 ml of CH₃OH and 10 ml of a 15% HCl solution were allowed to stir at room temperature for 2 h. After workup as in note 4, only 30% of <u>1</u> was transformed into the corresponding <u>2</u>.
- 9. 14 mmol of a $20\% \text{ w/v Ti}_2(SO_4)_3$ solution were added at once under stirring at room temperature to a solution of the substrate (7 mmol) in 30 ml of CH₃OH and 4 ml of a 30% aqueous NH₃. The blue colour of the reducing solution was immediately discharged and Ti(IV) ion precipitated as insoluble TiO₂. Workup was as in note 4.
- 10. Procedure was as in note 9, except that 14 mmol of a 20% w/v $\text{Ti}_2(\text{SO}_4)_3$ solution, 3.5 mmol of the substrate, 50 ml of CH₃OH and 20 ml of a 30% aqueous NH₃ were used instead.
- 11. E= 0.100 0.118 pH + 0.0591 lg [Ti0²⁺]/[Ti³⁺] in acidic medium, where Ti(IV) is present as soluble Ti0²⁺; E= 0.029 0.236 pH + 0.0591 lg [Ti0₂]/[Ti³⁺] in basic medium, where Ti(IV) is present as insoluble Ti0₂. M. Pourbaix, "Atlas d'equilibres electrochimiques", Gouthier Villars: Paris, 1963, p 213.
- 12. 20 mmol of a 15% TiCl₃ solution were added at once under stirring to a solution of $\frac{3}{2}$ (10 mmol) in CH₃OH (50 ml) and 30% aqueous NH₃ (20 ml). The reduction was over in less than one minute. Workup was as in note 4.

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