Pergamon

Tetrahedron Letters, Vol. 35, No. 47, pp. 8801-8804, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01955-X

Potassium Tetracarbonylhydridoferrate : A Reagent for the Selective Reduction of Carbonyl Groups

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Abstract: $KHFe(CO)_4$ is an efficient reagent for the reduction of electron-deficient ketones (trifluoroacetophenone) and for the selective mono-reduction of the keto group of α-ketocarbonyl compounds such as benzil, methyl benzoylformate, N-methylisatine and methyl pyruvate. The phosphite substituted derivative $K[HFe(CO)_3\{P(OMe)_3\}]$ is also an efficient reagent for the reduction of trifluoroacetophenone.

Key words: Potassium tetracarbonylhydridoferrate; ketones; 1,2-dicarbonyl compounds; selective reduction.

Selective reduction of polycarbonyl compounds is a challenging research area in organic synthesis. Whereas hydride donors such as $LiAlH_4$, B_2H_6, or AlH_3 react with most sterically unhindered unsaturated functional groups (ketones, as well as esters, alkenes, alkynes, nitriles),[1] milder hydride donors can react selectively with electron-deficient keto groups.[2] These "activated" keto groups are found in such compounds as trifluoromethylketones, α-diketones, α-ketoesters or α-ketoamides, and have been often used as reference substrates for testing potentially enantioselective reducing agents.[3]

For the past few years, we have been investigating the reactivity of tetracarbonylhydridoferrates $M^+[HFe(CO)_4]^-$ with the goal of developing useful applications in organic synthesis.[4,5] These reagents are among the least hydridic of the anionic transition metal hydrides and have long been known to react with carbonyl groups only under particular conditions. Indeed, α,β-unsaturated carbonyl compounds are successfully reduced by $NaHFe(CO)_4$ to saturated carbonyl derivatives without being reduced further to alcohols.[6] In fact, $NaHFe(CO)_4$ does not reduce aldehydes nor ketones.[7] However, when associated with $[R_3NH]^+[HFe(CO)_4]^-$ does reduce aldehydes (as in the Reppe alcohol synthesis)[8] under conditions where acetone is not reduced.[9] The reduction of acetone by these reagents occurs only under severe conditions (100 °C, 100 bar carbon monoxide) using a catalyst generated *in situ* from $Fe(CO)_5$ and Et_3N and believed to be $[Et_3NH]^+[HFe(CO)_4]^-$.[9] More recently, aliphatic aldehydes and ketones have been reduced by $[PPN]^+[HFe(CO)_4]^-$ ($[PPN]^+$ = bis(triphenylphosphine)iminium) associated with CF_3CO_2H in THF.[10] We now wish to report that the potassium salt of $[HFe(CO)_4]^-$ reacts under neutral, mild conditions with sufficiently activated carbonyl groups to yield the corresponding alcohols.

Preliminary experiments were carried out to compare the reactivity of $KHFe(CO)_4$ towards acetophenone with its reactivity towards trifluoroacetophenone (Table1).[11] Trifluoroacetophenonone is reduced by $KHFe(CO)_4$

in either THF or methanol, the reaction being much faster and quantitative when conducted in MeOH. Analytically pure 1-phenyl-2,2,2-trifluoroethanol can be isolated from the reaction in 85% yield (run 7). In contrast, the stoichiometric reaction of acetophenone with $KHFe(CO)_4$ results in less than 5% conversion, with either THF or MeOH as solvent (runs 1-3). IR analysis of the reaction medium after 24h at 50°C indicates that $KHFe(CO)_4$ is unchanged; thus no enolisation of acetophenone is occurring. (This would generate the unstable $H_2Fe(CO)_4$, which decomposes readily.)[12] Under the same conditions, neither 2'-fluoroacetophenone nor 2',4'-difluoroacetophenone is reduced. Thus, the difference in reactivity between trifluoroacetophenone and acetophenone is not due to the enolisability of the latter, but rather to the electron-deficient character of the keto group of trifluoroacetophenone.

Table 1: Reaction of $KHFe(CO)_4$ with acetophenone and trifluoroacetophenone [a]

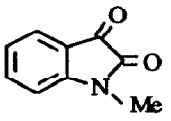
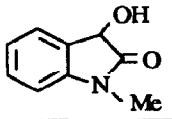
Run	Carbonyl compd	Solvent	Reaction temp. (°C)	Reaction time (h)	Conv. (%) [b]	Product	Yield (%) [c]
1	$PhC(O)CH_3$	THF	25	24	< 5	$PhCHOHCH_3$	< 5
2	$PhC(O)CH_3$	THF	50	24	< 5	$PhCHOHCH_3$	< 5
3	$PhC(O)CH_3$	MeOH	50	24	< 5	$PhCHOHCH_3$	< 5
4	$PhC(O)CF_3$	THF	25	24	36	$PhCHOHCF_3$	36
5	$PhC(O)CF_3$	THF	25	96	60	$PhCHOHCF_3$	60
6	$PhC(O)CF_3$	MeOH	25	24	80	$PhCHOHCF_3$	80
7[d]	$PhC(O)CF_3$	MeOH	50	4	100	$PhCHOHCF_3$	97 (85)

[a] reaction conditions: $KHFe(CO)_4$: 2.5 mmol; MeOH or THF: 15 mL; carbonyl compound: 2 mmol, under argon. [b] determined by GC analysis. [c] determined by GC analysis; isolated yields in parentheses. [d] reaction conditions: $KHFe(CO)_4$: 11 mmol; MeOH : 30 mL; carbonyl compound: 10 mmol, under argon.

To illustrate further the selective character of the reducing reagent, competitive experiments were conducted with a mixture of acetophenone and trifluoroacetophenone (1 equiv. of each *vs* $KHFe(CO)_4$). As expected, trifluoroacetophenone is reduced within 5h whereas acetophenone is not reduced at all.

Non-enolisable, electron-deficient difunctional ketones such as benzil, methyl benzoylformate and N-methylisatine are selectively reduced by $KHFe(CO)_4$ (Table 2). The resulting α-hydroxycarbonyl derivatives can be isolated in good to high yield. In the case of methyl benzoylformate (run 9), a significant amount of benzaldehyde is also formed. This side-reaction is tentatively attributed to the *in situ* formation of $[PhC(O)Fe(CO)_4]^-$, which is known to give benzaldehyde on protonation.[13] Although a longer reaction time is needed to ensure complete conversion, N-methyldioxindole can be isolated in high yield from N-methylisatine using $KHFe(CO)_4$ as reducing agent (run 10). The carbonyl group of methyl pyruvate is both enolisable and electron-deficient. Methyl lactate is formed from this compound in high yield (run 11, as determined by GC), showing that even enolisable ketones may be reduced by $KHFe(CO)_4$ as long as they are sufficiently activated.

Table 2: Reaction of $KHFe(CO)_4$ with α-ketocarbonyl compounds [a]

Run	Carbonyl compd	Reaction time (h)	Conv. (%)	Product	Yield (%)
8	PhC(O)C(O)Ph	4	100[b]	PhCHOHC(O)Ph	100[b] (93)
9	PhC(O)C(O)OMe	4	100[c]	PhCHOHC(O)OMe PhCHO [d]	70[c] (65) 30
10		24	100[b]		100[b] (90)
11	MeC(O)C(O)OMe	6	100[c]	MeCHOHC(O)OMe [d,e]	90[c]

[a] reaction conditions: $KHFe(CO)_4$: 11 mmol; MeOH: 30 mL; carbonyl compound: 10 mmol, 50°C, under argon. [b] determined by ^1H NMR. [c] determined by GC analysis ; isolated yield in parentheses. [d] identified by GC-MS analysis by comparison with an authentic sample. [e] an unidentified side-product was also detected by GC.

$KHFe(CO)_4$ thus appears to be a very selective reagent for the reduction of electron-deficient carbonyl groups under mild conditions. Its chemoselectivity is all the more impressive in light of the fact that, under the conditions used, $KHFe(CO)_4$ tolerates ester, nitrile, aromatic bromide and chloride, secondary aliphatic chloride, aliphatic aldehyde and ketone functionalities.[7,14]

As part of our study of ligand exchange processes on $[HFe(CO)_4]^-$,[15,16] we have recently reported the easy synthesis of $[HFe(CO)_3\{P(OMe)_3\}]^-$ (potassium or "PPN" salt).[15] We have compared the reactivity of $K^+[HFe(CO)_3\{P(OMe)_3\}]^-$ with that of $K^+[HFe(CO)_4]^-$ towards the reduction of an electron-deficient ketone, trifluoroacetophenone (Table 3).

Table 3: Reaction of $KHFe(CO)_4$ and $KHFe(CO)_3\{P(OMe)_3\}$ with trifluoroacetophenone [a]

Run	Iron complex	Reaction temp. (°C)	Reaction time (h)	Conv. (%)[b]	Yield (%)[b]
12	$KHFe(CO)_4$	25	24	85	81
13	$KHFe(CO)_3\{P(OMe)_3\}$	25	24	100	98
14	$KHFe(CO)_4$	50	4	100	97
15	$KHFe(CO)_3\{P(OMe)_3\}$	50	4	100	98

[a] iron complex : 2.5 mmol; MeOH: 10 mL; carbonyl compound: 2 mmol, under argon. [b] determined by GC analysis

As expected, given the lower π-accepting properties of the trimethylphosphite ligand (*vs* carbon monoxide), $K^+[HFe(CO)_3\{P(OMe)_3\}]^-$ exhibits a slightly higher reactivity than $K^+[HFe(CO)_4]^-$ towards trifluoroacetophenone at 25°C (compare runs 12 and 13). Furthermore, this new reagent is thermally stable, with no decomposition occurring in reactions at 50°C (run 15).

We are currently examining the possible extension of this work to include the enantioselective reduction of electron-deficient carbonyl compounds using chiral $M^+[HFe(CO)_{4-n}L_n^*]^-$ derivatives.

Acknowledgment

The authors wish to thank Dr L. Rosenberg both for helpful discussions and for her editorial assistance.

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(*Received in France* 25 *July* 1994; *accepted* 28 *September* 1994)