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Chemoselective reduction of ketones: trifluoromethylketones versus methylketones

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Abstract—Treatment of an equimolar mixture of trifluoromethylketones (TFMKs) and methylketones (MKs) with Et_2Zn resulted in selective reduction of the TFMKs in good yield. In contrast, treatment of an equimolar mixture of TFMKs and MKs with $NaBH_4$ in the presence of $CeCl_3$ in $EtOH/H_2O$ (10:1) at −10 °C reduced only the MKs.
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The importance of organofluorine compounds in life science is rapidly expanding, because the fluorine atom has very peculiar properties. At present, up to 20% to 30% of agrochemicals and pharmaceuticals contain one or more fluorine atoms.[1] Among organofluorine compounds, trifluoromethylated compounds constitute an important class because of their stereoelectronic properties and important bioavailability.[1a] For a long time, TFMKs have been useful for the synthesis of organofluorine compounds, and various methods for introduction of TFMKs into organic compounds as 'building blocks' have been explored.[2] The LUMO energy is lower for MKs than for TFMKs; thus, TFMKs are highly reactive and readily susceptible to nucleophilic attack.[3]

Usually, Et_2Zn is not used as a reducing agent, and MKs cannot react at room temperature. However, in our recent research we found that Et_2Zn can be used as a reducing agent of TFMKs. For example, treatment of 2,2,2-trifluoroacetophenone **1** with Et_2Zn produced reduced product **2** in good yield (Table 1). Moreover, 1 equiv of Et_2Zn reduced 2 equiv of TFMKs (entry 2). The chemoselective reduction of ketones in the presence of other reducible functional groups is an important synthetic transformation. But few methods for the chemoselective reduction of TFMKs have been reported.[4] This point led us to investigate the chemoselective reduction of TFMKs in mixture with MKs.

General reducing agents such as DIBAL-H, $LiAlH_4$ and $NaBH_4$ were used to an equimolar mixture of trifluoroacetophenone and acetophenone, but chemoselectivity was not observed (Table 2, entry 1–3). However, when an equimolar mixture of two carbonyl compounds was treated with Et_2Zn, only TFMKs were reduced (entry 4). Therefore, we examined the chemoselective reduction of TFMKs with various solvents and equivalent of Et_2Zn (Table 3). In all cases only TFMKs were reduced with a very small amount of aldol byproduct **8**. The ratio of reduced product **7** was increased by less polar solvents and an excess amount of Et_2Zn. When R was either aromatic (entries 1–13) or aliphatic (entry 14), TFMKs were reduced in good yield.

Next, we examined the chemoselective reduction of **9**–**11** that contained both TFMKs and MKs groups in the same molecule with Et_2Zn (Table 4). In all cases, TFMKs reduced with good chemoselectivity. Reduction of reactant **11** with 2 equiv Et_2Zn resulted in a low yield (entry 3). Thus, it is likely that the proton in the benzylic position reacted with Et_2Zn to produce zinc enolate, which has low reducing ability. Therefore, 5 equiv of Et_2Zn was used, and the yield increased (entry 4).

A plausible mechanism for the reduction of TFMKs with Et_2Zn is shown in Scheme 1. Previously, Mosher

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Keywords: Chemoselective reduction; Trifluoromethylketones; Methylketones; Diethylzinc.

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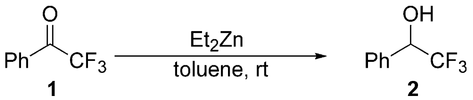
Table 1. Reduction of 2,2,2-trifluoroacetophenone with Et_2Zn



Entry	Et_2Zn (equiv)	Reaction time (h)	Yield of **2** (%)[a]
1	1.3	6	91
2	0.6	18	89

[a] Isolated yield.

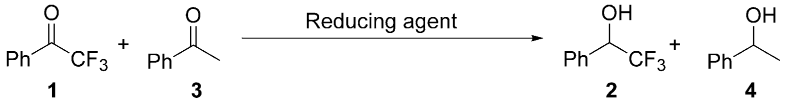
and co-workers reported a mechanism for reduction of ketones with a Grignard reagent.[5] Similarly, this reaction was regarded as a Meerwein–Ponndorf–Verley type reduction.

In the first phase, the metal (Zn) must coordinate with the carbonyl oxygen (**15**), which can be regarded as the most important aspect of the reaction. This aspect is different than the coordination capability of a Lewis acid between the oxygens of the TFMKs and MKs groups. In the past, Yamamoto and co-workers reported a chemoselective reaction of TFMKs and MKs.[4b] His work made clear the difference in coordination ability between TFMKs and MKs. When a powerful electron-attractive group such as CF_3 is directly linked with the carbonyl carbon, the carbonyl group is less polarized, and consequently, its coordination capability is lower. However, only TFMKs were reduced. So, the experimental result cannot be explained by the different coordination capabilities. However, a comparison of TFMKs and MKs carbonyl groups by molecular orbital calculation shows that, although the positive charge of TFMKs was lower, the LUMO energy level was lower. Consequently, the electrophilicity of the TFMKs carbonyl group is very high, resulting in reactivity even though the coordination capability of zinc was lower than that of MKs.

Polar solvents, such as THF, can affect Lewis acidity of Et_2Zn (**16**). THF coordinated with Et_2Zn forms a weak Lewis acid, weakening the coordination of the carbonyl atom of TFMKs with Et_2Zn. Consequently, the reduction rate slows and aldol-type products increase (Scheme 2).

Next, we investigated the chemoselective reduction of MKs in a mixture of TFMKs and MKs. TFMKs are so highly reactive that they are kept in ketone-hydrate equilibrium in an aqueous solution.[6] This property is

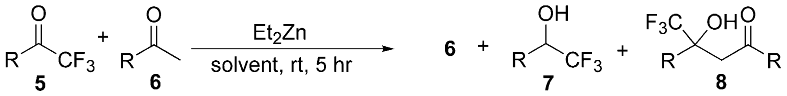
Table 2. Reduction of the mixture of **1** and **3** with a general reducing agent



Entry	Reducing agent	Yield of **2** (%)[a]	Ratio of **2**:**4**[b]
1	DIBAL-H	38	39:61
2	$LiAlH_4$	60	63:37
3	$NaBH_4$	73	55:45
4	Et_2Zn	85	100:0

[a] Isolated yield.
[b] The ratio was determined by ^1H NMR spectra.

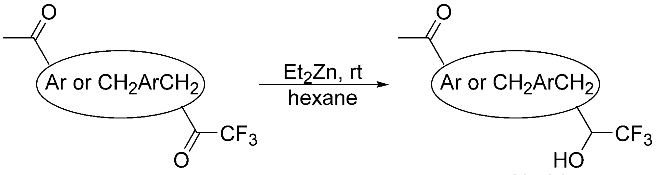
Table 3. Reduction of the mixture of **5** and **6** with Et_2Zn



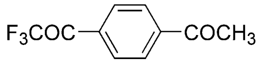
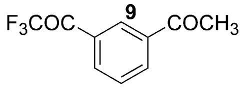
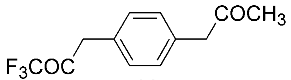
Entry	Solvent	R	Et_2Zn (equiv)	Yield of **7** (%)	Ratio of **7**:**8**[a]
1	THF	Ph	1.3	85[b]	88:12
2	Ether	Ph	1.3	89[b]	88:12
3	Toluene	Ph	1.3	85[b]	94:6
4	CH_2Cl_2	Ph	1.3	81[b]	97:3
5	Hexane	Ph	0.6	60[b]	95:5
6	Hexane	Ph	1.3	81[b]	98:2
7	Hexane	Ph	2.0	98[b]	98:2
8	Hexane	Ph	3.0	98[b]	98:2
9	Hexane	Ph	5.0	99[b]	99:1
10	Hexane	$4-MeOC_6H_4$	3.0	73[c]	99:1
11	Hexane	$4-MeC_6H_4$	3.0	79[c]	99:1
12	Hexane	$4-ClC_6H_4$	3.0	64[c]	99:1
13	Hexane	$4-CF_3C_6H_4$	3.0	72[c]	99:1
14[d]	Hexane	*c*-Hex	5.0	93[b]	99:1

[a] The ratio was determined by ^1H NMR spectra.
[b] Estimated by GC.
[c] Isolated yield.
[d] The reaction was carried out for 20 h.

Table 4. Reduction of **9**–**11** with Et_2Zn

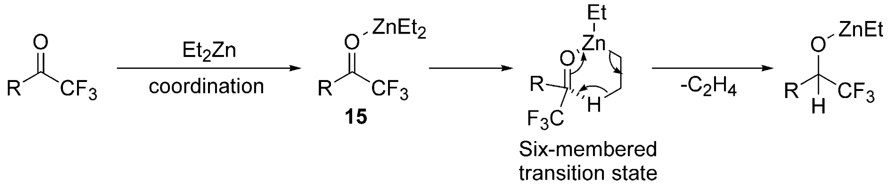


9–**11** **12**–**14**

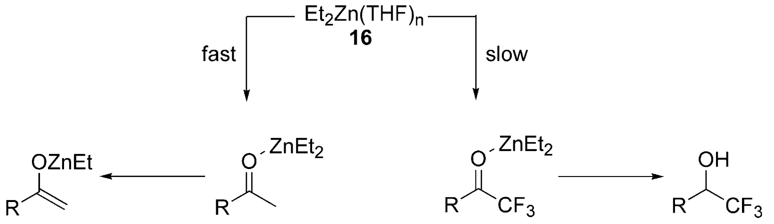
Entry	Substrates	Reaction time (h)	Et_2Zn (equiv)	Yield of **13**–**17** (%)[a]
1	 **9**	5	1.3	99 (**12**)
2	 **10**	3	1.3	>99 (**13**)
3[b]	 **11**	20	2.0	47 (**14**)
4[b]	**11**	20	5.0	93 (**14**)

[a] Isolated yield.

[b] Solvent was CH_2Cl_2.



Scheme 1. Mechanism for reduction of TFMKs with Et_2Zn.

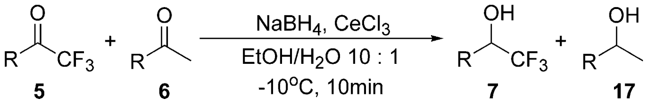


Scheme 2. Effect of the solvent on the reduction.

similar to that of ordinary aldehydes. In an earlier study, Luche and Gemal reported selective reduction of ketones with $CeCl_3$ and $NaBH_4$ in the presence of aldehydes in an aqueous solution.[7] We thought Luche's conditions could be applied to the chemoselective reduction of MKs; therefore, we used these conditions to reduce various TFMKs and MKs derivatives (Tables 4 and 5).

The result showed that chemoselective reduction of MKs occurred in all cases. $CeCl_3$ probably converted TFMKs into its corresponding hydrate, and the hydrate provided adequate protection during the $NaBH_4$ reduction steps. But the selectivity was lower when an electron-donating group such as a methoxy group was directly linked with the aromatic ring (entries 2 and 3). On the contrary, the selectivity was higher when an electron-attractive group such as a trifluoromethyl group was directly linked with the aromatic ring (entries 4 and 5). The reason for these differences was probably

Table 5. Reduction of mixture of **5** and **6** with $NaBH_4$ and $CeCl_3$

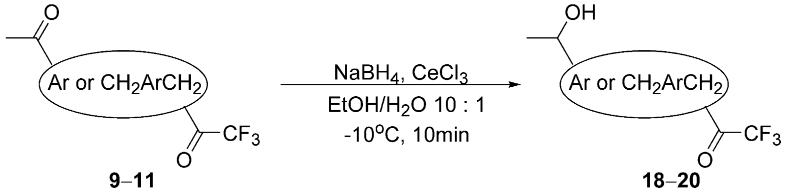


Entry	R	Yield of **17** (%)[a]	Ratio of **7**:**17**[b]
1	Ph	95	1:>99
2	4-$MeOC_6H_4$	87	28:72
3	4-MeC_6H_4	81	17:83
4	4-ClC_6H_4	93	7:93
5	4-$CF_3C_6H_4$	99	1:>99
6	*c*-Hex	81	10:90

[a] Isolated yield.

[b] The ratio was determined by ^1H NMR spectra.

Table 6. Reduction of **9**–**11** with $NaBH_4$ and $CeCl_3$



Entry	Substrate	Yield of **18**–**20**[a]
1	**9**	89 (**18**)
2	**10**	>99 (**19**)
3	**11**	66 (**20**)

[a] Isolated yield.

the change in the LUMO energy level of TFMKs. The LUMO energy level of TFMKs was lowered by the electron-attractive group, and its corresponding hydrate was stabilized (Table 6).

In conclusion, the reactions described in this study represent a solution for chemoselective reduction of TFMKs and MKs. This method for selective reduction of ketones may be useful because it does not require additional protection and deprotection steps.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.01.013.

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