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Chemocontrolled Reduction of Aromatic α-Ketoesters by $NaBH_4$: Selective Synthesis of α-Hydroxy Esters or 1,2-Diols

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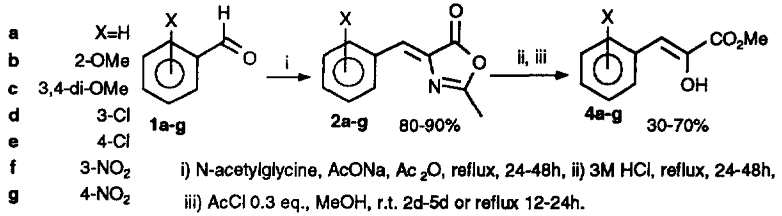
Abstract : *α-hydroxyesters 5a-g or diols 6a-g have been obtained in high yields by reduction of aromatic α-ketoesters 4 once or twice respectively by using $NaBH_4$ as the reducer under suitable conditions. The use of a solvent that does not interact with the reagent allowed the double reduction to occur with only a slight excess of borohydride in very mild conditions.*

$NaBH_4$ is a mild, unexpensive and invaluable agent used in organic synthesis for a wide range of reduction processes that principally include the transformation of ketones or aldehydes into alcohols[1], and imines[2] or iminium salts[3] into amines. Esters are more resistant towards $NaBH_4$ and a Lewis acid[4a] or a coreagent such as polyethylene glycol[4b] is generally required for the reduction to occur. Curiously, litterature reports dealing with the reduction of an ester group with $NaBH_4$ alone are quite rare[5] and mainly focused on esters α–substituted with an electron-withdrawing group[6a] and α-hydroxyesters[6b]. In addition to studies referenced in ref. 5, α- and β-oxoesters have been also doubly reduced with $NaBH_4$, thus providing 1,2-[7a] or 1,3-[7b] diols. However, due to the lack of specificity of this chemical process, diols formation appears somewhat as a competitive reaction with regard to the expected hydroxyesters formation[7]. That the mechanism of this double reduction of oxoesters was not well known was probably the principal reason for which no extensive efforts have been focused on the chemocontrol of the mono- or the double reduction. With the purpose of precisely determining the mechanism ot this kind of double reduction, we investigated the reaction of 1-hydroxy-1-methoxycarbonyl-2-aryl ethylenes **4a-g** with $NaBH_4$ with the aim of preparing an array of 3-aryl-1,2-dihydroxy-propane derivatives. We report herein our efforts in controlling the mono- and the double reduction of **4a-g** by a suitable adjustment of experimental conditions.

The requisite α-ketoesters **4a-g** were readily accessible from the commercially available aldehydes by the three step sequence depicted in scheme 1.



i) N-acetylglycine, AcONa, Ac_2O, reflux, 24-48h, ii) 3M HCl, reflux, 24-48h,
iii) AcCl 0.3 eq., MeOH, r.t. 2d-5d or reflux 12-24h.

scheme 1

Thus, the treatment of the appropriately substituted benzaldehydes by N-acetylglycine and dry sodium acetate in refluxing acetic anhydrid[8] furnished the crystalline oxazolones **2a-g** in high yields which were hydrolysed more or less efficiently (50-90%) in a refluxing 3M solution of aqueous hydrochloric acid. The esterification of the resulting cristalline α-ketoacids **3a-g** was achieved in the

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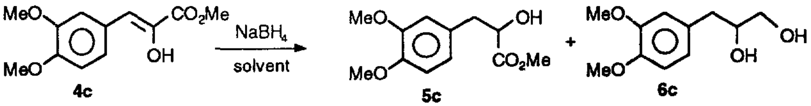
presence of acetyl chloride in methanol[9]. α-Ketoacids **3a-g** as well as their methylic esters **4a-g** appeared to exist exclusively under the enolic form as evidenced by their ^1H NMR spectra[10], regardless of the solvent used (DMSO d_6 for the acids, $CDCl_3$ and MeOD d_4 for the esters). In order to determine the optimum conditions for the achievement of the double reduction of enolic α-ketoesters **4a-g** , compound **4c** was choosen as the model (table 1).

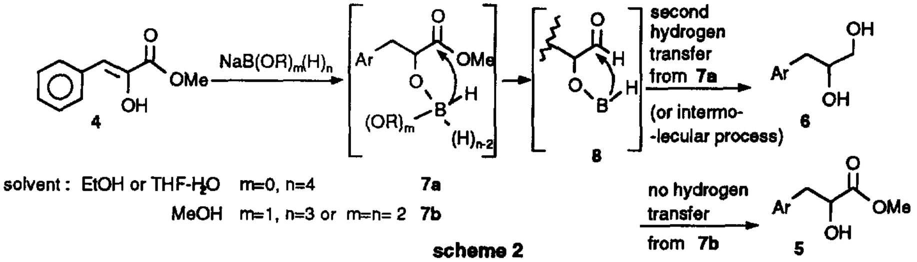


entries	eq. $NaBH_4$	solvent	temperature	reaction time	5c (yield%)[c]	6c (yield%)
1	1	MeOH	20°C	30 min	91	/
2	1	"	65°C	48h	78	/
3	1	"	65°C, Cat. HCl[11]	24h	67	/
4	3	"	20°C	24h	70	traces
5	4	"	65°C	3d	4	6
6	6	"	20°C	5d	59	31
7[a]	3.5	"	"	3d	53	24
8[a]	6	"	"	1h	31	50
9[a]	6	"	"	15h	29	49
10[a]	6	EtOH	"	1h	/	94
11[a]	6	THF-H_2O 3-1	"	1h	/	59
12[a]	3	EtOH	"	1h	/	96
13[a,b]	2	"	"	1h	/	88

a : $NABH_4$ freshly recrystallised in isopropylamine [12] was used; b : **5c** was used as substrate
c : yields have been evaluated after purification.

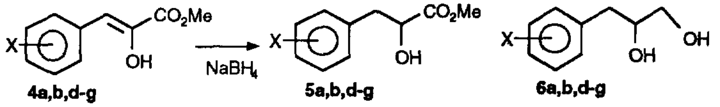
table 1

All reactions performed with one equivalent of $NaBH_4$ in MeOH readily generated the α-hydroxyester **5c** (in approximatively 30 minutes) and stopped at this stage (entries 1-3). Increasing the amount of reagent did not significantly improve the isolated yield of **6c**, (entries 4-6) and **5c** was still the major product. Note that carrying out the reaction in refluxing methanol with an excess of reducing agent led to a nearly complete decomposition (entry 5). On the other hand, using a freshly recrystallised $NaBH_4$[12] provided a substantial enhancement of the isolated diol (entries 7-9 *vs* 4-6). Moreover, this requirement for an excess of reagent together with the fact that prolonging the reaction time for a given stoechiometry of reagent did not influence the distribution of products **5c** and **6c** (entries 8 *vs* 9) supported the evidence that the reduction of the ester function can not be ensured by a species such as $NaB(H)_n(OMe)_m$ (with m+n=4), but that the "reactive species" involved is $NaBH_4$ itself. The failure for a complete reduction of **4c** probably originated from the instantaneous and vigourous reaction between $NaBH_4$ and methanol (materialized by a strong release of H_2) that acted as an impediment for the ester reduction. As a result, we turned to polar solvent systems that would be less reactive vis-à-vis $NaBH_4$ than the substrate, and we observed in these cases that the double reduction readily took place (entries 10-11)[13]. Ethanol[14] was observed to be a better solvent than the THF-H_2O system due to the modest yield of diol curiously obtained in this last case, despite the fact that the reaction was apparently clean (entry 11). Finally, diol **6c** was conveniently obtained in the presence of a slight excess of borohydride in 1 hour (entry 12). As expected, the isolated α-hydroxyester **5c** could be completely reduced in the same conditions with only 2 equivalents of reagent (entry 13). The mechanism of this double reduction may involve an alkoxy borohydride intermediate **7a**, resulting from a first reduction of the enol moiety which would then allow for the reduction of the ester in a intramolecular fashion. This would first lead to the aldehyde **8** which could be further reduced intramolecularly *via* a "global" two hydrogen transfer process or in an intermolecular manner upon the action of an other molecule of borohydride. For reactions carried out in methanol, the reduction of the enolic carbonyl may be ensured by an alkoxy borohydride species (resulting from an initial reaction between $NaBH_4$ and the solvent), leading to the intermediate **7b** with which the ester reduction by proximity effect can not be effective due to a lack of "active" hydrogen on the boron (if m=n=2, scheme 2). Thus, the reduction of the ester group requires the intermolecular action of an other molecule of borohydride which has already been partially consumed by methanol, that results in a strong decrease of the reaction rates.



scheme 2

Other esters **4a,b,d-g** were next submitted to the conditions described in table 1 (entries 1 and 12 respectively), providing in each case α-hydroxyesters **5a,b,d-g** and diols **6a,b,d-g** respectively in a very clean manner (table 2). Substrates **4a,b,d-e** showed a reactivity similar to that of **4c** (entries 1-4, table 2 compared to entries 1, 12 table 1).



		1 eq. NaBH$_4$ in MeOH		3 eq. NaBH$_4$ in EtOH	
entries	X	product	reaction time (yield)		
1	H **4a**	**5a**	30mn (71%)	**6a**	30mn (69%)
2	2-MeO **4b**	**5b**	30mn (70%)	**6b**	30mn (67%)
3	3-Cl **4d**	**5d**	30mn (77%)	**6d**	30mn (85%)
4	4-Cl **4e**	**5e**	30mn (74%)	**6e**	30mn (77%)
5	3-NO_2 **4f**	**5f**	10mn (86%)[a]	**6f**	1h (81%)[b]
6	4-NO_2 **4g**	**5g**	10mn (89%)[a]	**6g**	10mn (86%)

a: 10% of diols **6f** and **6g** were isolated ; b: reaction was performed in MeOH with 4 eq. of NaBH$_4$.

table 2

The behaviour of the nitro compounds **4f-g** was quite different since they appeared to be strongly reactive[15]. With one equivalent of reducer, both meta- and para-nitro ketoesters were rapidly consumed, even providing nearly 10% of diols **6f-g** (entries 5-6, table 2). In the same manner, **6f** could be obtained in high yield in unusual conditions (4eq. of $NaBH_4$ in methanol, entry 5 table 2 *vs* entry 7 table 1). It is also worth of mention that the lower yields of products **5a-b** and **6a-b** (compared to **5c-g** and **6c-g**) could reflect a certain level of decomposition for the particularly sensitive parent substrates during their storage before being used[16].

In conclusion, we have shown that aromatic ketoesters of type **4** could be smoothly reduced once or twice by $NaBH_4$ under appropriate conditions. When using one equivalent of reagent in methanol, α-hydroxyesters **5** were obtained in high yield in nearly 30 mn without suffering from the competitive double reduction. Moreover, we demonstrated that the second reduction (at the ester function) occured intramolecularly and was mediated only by $NaBH_4$ itself (and not by a related species such as $NaB(H)_n(OR)_m$ (with m + n = 4)). In addition, it occured easily when reactions were performed in solvents that were inert towards the reducer such as ethanol, thus providing a convenient access to diols of type **6**. Further studies in order to delineate the scope and limitations of this double reduction of α-ketoesters are currently under investigation and will be reported in due course.

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10. For a selected example **4c** ^1H NMR (300 MHz, $CDCl_3$) δ 7.46 (1H, d, *J*=1.7 Hz), 7.24 (1H, dd, *J*=8.4 Hz, *J*=1.7 Hz), 6.85 (1H, d, *J*=8.4 Hz), 6.48 (1H, ethylenic, s), 6.35 (1H, br, s, OH), 3.88 (9H, 3s).
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14. Non anhydrous solvents (MeOH, EtOH, THF) were systematically used. With ethanol, the release of H_2 was very smooth in comparison with the case of methanol.
15. For a similar effect of a nitro substituent on the reduction's rate of hydride, see : Pelter, A.; Smith, K. *In Comprehensive Organic Chemistry*, Barton, D. and Ollis, W. D. Ed., **1979**, *3*, p767.
16. **3a-e** were subject under the AcCl-MeOH[9] procedure to an unexpected decomposition and the corresponding benzaldehydes were readily formed, probably *via* a sequencial decarboxylation-decarbonylation. Neither the $SOCl_2$-MeOH procedure nor the use of DBU and MeI in DMF[17] gave satisfactory yields of esters. Finally, carrying out the AcCl-mediated esterification upon heating was the best compromise and esters **4a-e** were obtained up to 70%. Note that these isolated methyl esters, and particularly **4a-b** were also subject to a rapid decomposition into benzaldehydes when stored at room temperature, and had to be used freshly after being prepared. On the other hand, nitro esters **4f-g** were stable several weeks at r.t.
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