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Sodium borohydride and vinyl triflates of α-keto esters: a new combination toward monoalkylated 1,2-diols

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Abstract—$NaBH_4$ converts a range of methyl 2-trifluoromethanesulfonyloxy 3-substituted propenoates to the corresponding monoalkylated 1,2-diols smoothly with total regiocontrol. © 2002 Elsevier Science Ltd. All rights reserved.

Vinyl triflates have emerged as very important substructures in organic synthesis during the two last decades, and their use has notably culminated in carbon–carbon bond forming processes through transition-metal-catalyzed cross coupling reactions with nucleophilic partners.[1] Curiously, organic compounds bearing a vinyl triflate adjacent to an electrophilic functional group have not been frequently exploited, despite the promising potential that such densely functionalized units could offer.[2] Notably, non-coupling tandem reactions are expected for vinyl triflates of α-keto acid derivatives due to the presumed high Michael acceptor capacity of such compounds, and the exceptional leaving group properties of the triflate group. While vinyl triflates of β-keto esters have been elegantly exploited in the synthesis of stereocontrolled enynes,[3] the chemistry of vinyl triflates of α-keto esters remains relatively dormant.[4]

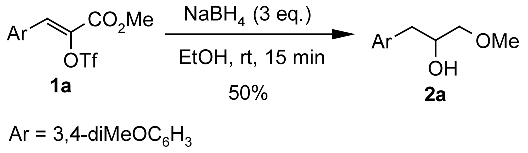
The high potential of such compounds led us to explore their tandem reactions. The work presented here was inspired by the known 1,4-addition of sodium borohydride to conjugated esters α-substituted by an electron-withdrawing group.[5] In the context of our recent studies on borohydride reductions of esters,[6–8] we felt that applying this process to vinyl triflates of α-keto esters may set the stage for tandem reactions since the resulting addition products will combine two contiguous highly electrophilic centers. Therefore, we decided to begin exploring the chemistry of vinyl triflates of α-keto esters in the field of borohydride reductions. To our satisfaction, our first experiment led us to discover an unprecedented reaction, that is the transformation of the vinyl triflate **1a** into the monomethoxy diol **2a** (Scheme 1).

The reaction proved very rapid, yielding **2a** within 5 min as a sole regioisomer in 50% yield. However, **2a** was accompanied by the side-products **3a** and **4a** (Fig. 1) from which it could be easily separated by flash chromatography (FC).

Obviously, a conjugate addition of hydride occurred initially,[5] and this was followed by multiple hydride addition with concomitant functional group recombination. The mechanism will be debated in the last part of the article.

The question then arose whether $NaBH_4$ could process a variety of such compounds to afford the corresponding monoprotected diols in mild conditions.

We report herein our preliminary results demonstrating that $NaBH_4$ combines with vinyl triflates of α-keto



Scheme 1.

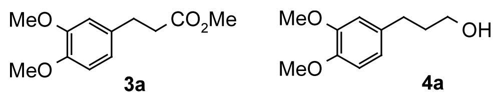


Figure 1.

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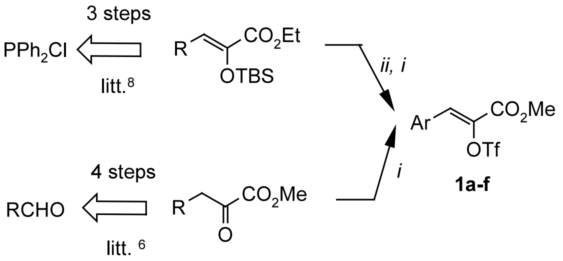
esters to provide a reliable method of formation of monoalkylated 1,2-diols. We also discuss the mechanism of the reaction.

In order to optimize the reaction, we performed a first set of experiments with **1a** on a 1 mmol scale (Table 1). It can be seen that using a large excess of reductant did not improve the production of **2a**; the optimum yield was obtained with 3 equiv. of $NaBH_4$ (run 3 versus 4). Reducing the stochiometry of $NaBH_4$ led to incomplete conversion and low yield of **2a** (runs 1 and 2 versus 3).

No significant effect was observed when $NaBH_4$ was added at −80°C and the temperature subsequently allowed to slowly rise, **2a** being isolated in this case in a comparable yield (run 5 versus runs 3 and 4). Runs 6 and 7 show that neither working at higher concentration nor on larger scale appreciably affected the outcome of the reaction, both in terms of yield and regiocontrol.[9,10] On the other hand, heating the ethanolic solution prior to adding $NaBH_4$ proved to be slightly detrimental, some new side-products[11] being formed at the expense of **2a** whose yield fell to 38% (run 8). EtOH substitution for MeOH or THF as the solvent met with poor success (runs 9, 10), particularly for the last case wherein new by-products appeared.[11] When $NaBH_4$ was exchanged for $LiBH_4$ as the reductant, the reaction profile was similar as above, but a slight improvement of the proportion of the impurities **3a** and **4a** versus **2a** was observed (run 11 versus 3). With the hope of suppressing **3a** and **4a**, the less reactive triacetoxy sodium borohydride and cyanoborohydride were tested. Unfortunately, both of them left **1a** untouched after 24 h (runs 12 and 13). In conclusion to this first set of experiments, the optimal conditions correspond to the use of 3 equiv. of $NaBH_4$, with ethanol as the solvent at room temperature. With the optimized conditions in hand, we next turned our attention toward evaluating the possibility of processing other analogous methyl esters. Five triflates **1b–f** were synthesized (Scheme 2), either by direct triflation of the parent keto esters[6] (**1b–e**) or by sequential desilylation–triflation reactions[12] (**1f**) from the corresponding enoxysilanes.[8]

The triflations were readily achieved within less than 5 min at 0°C either by using the DiPEA/Tf_2O procedure or a strong base/HMPA/$PhNTf_2$ system. In the latter case, NaH, NaHMDS and LiHMDS were equally effective as the base. The reaction did not proceed in the absence of HMPA. The six vinyl triflates used in this work were stable, they could be purified by FC and stored for months at room temperature (**1a–e**) or in the freezer (**1f**) without notable decomposition. **1b–f** were treated in our standard procedure and results are collected in Table 2.



Scheme 2. (i) Tf_2O, $\text{Pr}^i{}_2\text{NEt}$, CH_2Cl_2, 0°C, 5 min, >85% (or NaH, THF, HMPA, $PhNTf_2$, 0°C, 5 min, >85%); (ii) CsF, CH_3CN, AcOH.

Table 1. Reaction of **1a** with hydrides in various conditions[a]

Run	Reductant (equiv.)	Solvent	Yields (%)[b]			Conv. (%)
			2a	**3a**	**4a**	
1	$NaBH_4$ (1)	EtOH		17		68
2	$NaBH_4$ (2)	EtOH		29		100
3	$NaBH_4$ (3)	EtOH	50	24	10	100
4	$NaBH_4$ (10)	EtOH	49	15	19	100
5[c]	$NaBH_4$ (3)	EtOH	54	26	9	100
6[d]	$NaBH_4$ (3)	EtOH	50	Not isolated		100
7[e]	$NaBH_4$ (3)	EtOH	52	Not isolated		100
8[f]	$NaBH_4$ (3)	EtOH	38	Not isolated		100
9[g]	$NaBH_4$ (3)	MeOH	19	10	–	40
10[h]	$NaBH_4$ (3)	THF	–	12	26	100
11	$LiBH_4$ (3)	EtOH	39	18	8	100
12[i]	$NaB(OAc)_3$ (3)	EtOH	–	–	–	0
13[i]	$NaBH_3CN$ (3)	EtOH	Trace	–	–	<95

[a] Without any comments, the reactions were performed on a 1 mmol scale (370 mg) at a concentration of 0.2 M at rt for a period of 15 min.

[b] Isolated yields are given.

[c] $NaBH_4$ was added at −80°C, then the temperature was allowed to rise to rt.

[d] The reaction was performed on a 1 mmol scale at a concentration of 1 M.

[e] The reaction was performed on a 1 g scale.

[f] The mixture was heated to reflux prior to add $NaBH_4$.

[g] The reaction was pursued for an additional 45 min.

[h] The reaction was allowed to stir for 17 h.

[i] The reaction was allowed to stir for 24 h.

Table 2. Reaction of various esters **1b–f** with $NaBH_4$ in optimized conditions[a]

Run	R	1	2 (%)[b]	3 (%)	2 (%)
1	Ph	**1b**	**2b** (60)	**3b** (25)	**4b** (4)
2	4-ClC_6H_4	**1c**	**2c** (65)	**3c** (14)	**4c** (2)
3	4-$NO_2C_6H_4$	**1d**	**2d** (63)	**3d** (20)	**4d** (2)
4	3-$NO_2C_6H_4$	**1e**	**2e** (71)	**3e** (17)	**4e** (5)
5	Furyl	**1f**	**2f** (55)	**3f** (18)	**4f** (10)

[a] The reactions were performed at rt on a 1 mmol scale for a period of 15 min.

[b] Isolated yields are given.

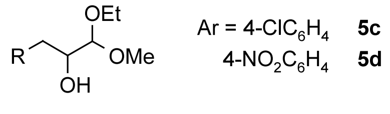
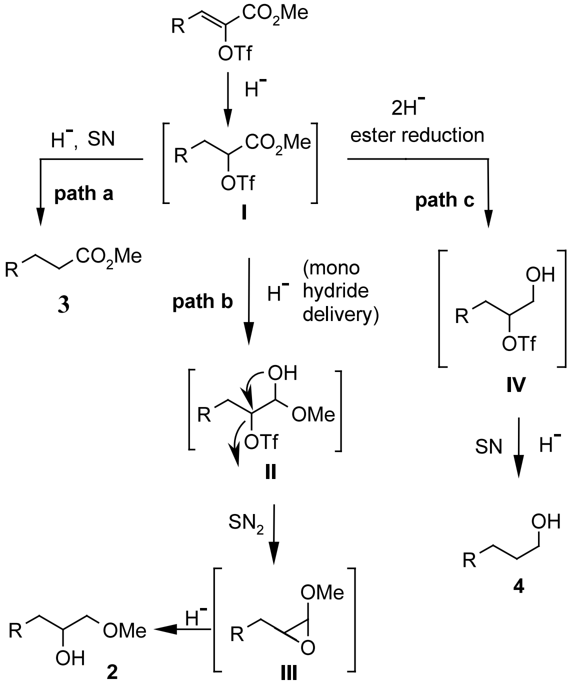


Figure 2.



Scheme 3.

The unsubstituted phenylic substrate **1b** proved slightly superior to the electron-rich model **1a**, and gave the expected product in 60% yield (run 1 versus 3 in Table 1). Electron-deficient aromatic triflates **1c–e** were exceedingly reactive since they disappeared totally within less than 1 min and furnished the desired products **2c–e** in fair yields (runs 2–4). Finally, the reaction was also compatible with heteroaromatic esters, as illustrated by the furanic substrate **1f** (run 5).

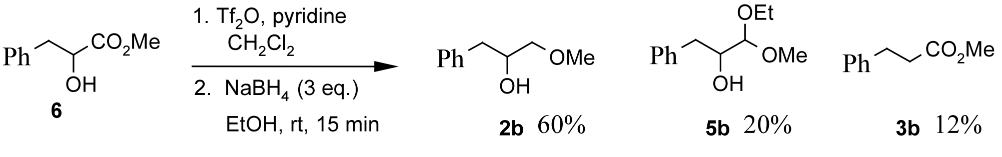
As a consequence of the increased formation of diol monoethers **2b–f** as compared with the model **1a**, common types **3** and **4** by-products were uniformly produced in lower yields than previously (runs 1–5 versus run 3 in Table 1). The two *para*-substituted substrates **1c** and **1d** led to the methyl ethyl acetals **5c–d** (Fig. 2) in non negligible amounts (10 and 11%, respectively), providing revealing information about the mechanism (see later).

The mechanism of formation of the main products **2**, **3** and **4** may be explained as follows (Scheme 3): conjugate hydride addition[5] would give the saturated triflate **I**. Once formed, this transient compound could evolve according to three routes. The first involves nucleophilic substitution (SN) of the triflate by a hydride, providing the propionyl esters **3** (path a). Another possibility is monoreduction of the ester function leading to hemiacetal **II**, followed by intramolecular SN_2 ring closing to produce a highly reactive oxiranyl acetal **III** which is opened regiospecifically by hydride delivery in a final stage (path b). The third route involves an ester reduction which provides the monotriflyloxy diol **IV**. After SN by a hydride, the latter gives the alcohols **4** (path c).

Additional proof for this mechanism is provided by the sequential two-step reaction depicted in Scheme 4. Triflation of the α-hydroxy methyl ester **6** derived of benzyl pyruvic acid gave the expected triflate **I** quantitatively. Without purification, the latter was submitted to $NaBH_4$ reduction to provide the expected monomethoxy diol **2b** along with the acetal **5b** and the ester **3b** in overall 50, 20 and 12% yield, respectively. In this experiment, the alcohol **4b** was only isolated in trace amounts.

Path b is further supported by the identification in certain cases, notably in the above reaction (Scheme 4), of type **5** methyl ethyl acetals whose formation can be explained by the opening of intermediate **III** by the ethoxide formed from the interaction between $NaBH_4$ and ethanol.

The distribution of products is the result of a subtle balance between the three pathways described above, which may be largely governed, at a first extent, by electronic factors (see Table 1, run 3 versus Table 2, runs 1–4). By comparing the combined yields of **2** and **4** with those of **3**, it appears that intermediates **I** consistently undergo the ordinary slow reduction of the ester (paths b and c),[6,7] faster than the normally favorable SN process (path a). This attests the exceptional propensity of the triflate to activate the adjacent carbonyl center to nucleophilic addition.



Scheme 4.

This unusual reaction involves four successive one-pot procedures, and offers a facile new route to monoprotected diols. Beside its synthetic interest, the work reported herein emphasizes the intuitive powerful capacity of the triflate group to boost the electrophilic character of a contiguous center. This finding complements the exceptional leaving group properties of the triflate group[13] and expands the scope of the fascinating chemistry of triflates.

In summary, we have shown that reaction of NaBH$_4$ and vinyl triflates of α-keto methyl esters provides a new, totally regiocontrolled and mild access to monomethoxy 1,2-diols. Due to easy access to α-keto esters,[14] this reaction holds promise in organic synthesis and should expand the scope of NaBH$_4$ reactions and triflate chemistry. A study aimed at developing the synthetic potential of this new reaction by addressing other esters (allyl, benzyl, silyl) and amides is currently underway in our laboratory and will be reported in due course.

Acknowledgements

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9. Typical procedure and data illustrating the 1 g scale experiment (Table 1, entry 7): NaBH$_4$ (306 mg) was added in one portion to a solution of **1a** (1 equiv.) in ethanol (15 ml). The reaction was monitored by TLC and after total consumption of the starting material (5 min), the solution was carefully hydrolyzed by using water initially (10 ml) and then a volume of an aqueous solution of hydrochloric acid 1 M (11 ml, 4 molar equiv.). Ether (25 ml) was added and the mixture was stirred for 30 min. The aqueous phase was saturated by sodium chloride and extracted three times with ether. The organic layer was washed with 10 ml of an aqueous solution of sodium hydrogenocarbonate 1 M and then with 10 ml of brine. After drying over sodium sulfate, filtration and evaporation, the crude mixture was purified by flash chromatography (gradient 7:3 to 5:5 hexane–ethyl acetate).

   3-[3,4-Dimethoxyphenyl] 2-hydroxy 1-methoxy propane **2a**: Yield 50%. Colorless oil. The ^{1}H NMR spectrum of **2a** was identical to that of the enantiopure analogue described in Ref. 10: ^{1}H NMR (200 MHz, CDCl$_3$): δ 2.3 (s, large, OH), 2.7 (d, $J=6.7$ Hz, 2H), 3.28 (dd, $J=9.5$ Hz, $J=7.1$ Hz, 1H), 3.38 (s, 3H), 3.39 (dd, $J=9.5$ Hz, $J=3.5$ Hz, 1H), 3.84 (s, 3H), 3.85 (s, 3H), 3.95 (dtd, $J=7.1$ Hz, $J=6.7$ Hz, $J=6.7$ Hz, $J=3.5$ Hz, 1H), 6.7–6.82 (m, 3H).
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