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Reduction of alkyl and vinyl sulfonates using the $CuCl_2 \cdot 2H_2O$–Li–DTBB(cat.) system

Gabriel Radivoy,[a,*] Francisco Alonso,[b] Yanina Moglie,[a] Cristian Vitale[a] and Miguel Yus[b,*]

[a]*Departamento de Química, Instituto de Investigaciones en Química Orgánica (INIQO), Universidad Nacional del Sur, Avenida Alem 1253, 8000 Bahía Blanca, Argentina*

[b]*Departamento de Química Orgánica, Facultad de Ciencias, and Instituto de Síntesis Orgánica (ISO), Universidad de Alicante, Apdo. 99, 03080 Alicante, Spain*

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Dedicated to Professor Johan Mulzer on occasion of his 60th birthday

Abstract—The reduction of a series of alkyl mesylates, dimesylates and triflates to the corresponding hydrocarbons was efficiently performed using a reducing system composed of $CuCl_2 \cdot 2H_2O$, an excess of lithium sand and a catalytic amount (5 mol%) of 4,4′-di-*tert*-butylbiphenyl (DTBB), in tetrahydrofuran at room temperature. The process was also applied to enol and dienol triflates affording alkenes and dienes, respectively. The use of the deuterated copper salt $CuCl_2 \cdot 2D_2O$ allowed the simple preparation of the corresponding deuterated products.

1. Introduction

Sulfonyl esters are very useful synthetic intermediates extensively used in two important transformations in synthetic organic chemistry: (a) indirect deoxygenation of alcohols;[1] and (b) reduction of carbonyl groups, via the corresponding vinyl sulfonates, to obtain alkanes or alkenes.[2] Concerning the deoxygenation of alcohols, one of the most practical methods involves the transformation of the hydroxyl group in a better leaving group such as a tosylate, followed by reaction with sodium iodide (to give the corresponding alkyl iodide) and final palladium-catalyzed hydrogenation or other reduction methodologies.[3] More sophisticated procedures involve the transformation of alcohols into isoureas,[4] thionocarbonates,[5] dithiocarbonates[6] or thiocarbonates,[7] and further reduction with a silane, stannane or potassium in a protic solvent. More recently, lithium aminoborohydride reagents proved to be effective in the reduction of alkyl mesylates.[8] On the other hand, the paramount importance of the carbonyl group in organic synthesis makes methods for its efficient removal of considerable relevance. Among the known methods utilized for the reduction of this functionality, the conversion of carbonyl groups into their enol triflates and further reduction to the corresponding alkenes or alkanes has been widely studied. One of the simplest procedures relies on the palladium-catalyzed reduction of the corresponding triflates by using hydrogen,[9] formic acid,[10] silanes or stannanes,[11] as some conventional reducing agents. These two-step reductions of carbonyl groups have been particularly useful in synthetic transformations of steroidal skeletons. In this field, enol and dienol triflates are key synthetic intermediates in the chemical transformation of a wide variety of steroidal α,β-unsaturated ketones.[10] Another method, treatment of the tosylhydrazone of an aldehyde or a ketone with a strong base, followed by hydrolysis, leads to the formation of an alkene (the so-called Shapiro reaction[12a]). This reaction has been applied to the obtention of alkenes or 1,3-dienes from aldehydes, ketones, or α,β-unsaturated ketones, respectively, via alkyllithium mediated decomposition of the tosylhydrazones under mild reaction conditions.[12]

On the other hand, in the recent years, we have worked about the development of new reducing systems of functional groups based on the use of activated transition metals, mainly active nickel.[13] In this sense, we first studied and reported the efficiency of the $NiCl_2 \cdot 2H_2O$–Li–arene(cat.) reducing system toward a wide variety of organic functionalities, among them alkenes,[14] alkynes,[15] carbonyl

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* Corresponding authors. Fax: +54 2914595187 (G.R.); fax: +34 965903549 (M.Y.); e-mail addresses: gradivoy@criba.edu.ar; yus@ua.es

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compounds and imines,[16] alkyl and aryl halides,[17] sulfonates, aromatic and heteroaromatic compounds,[18] hydrazines, azo compounds, azoxy compounds and amine *N*-oxides,[19] and nitrones.[20] More recently and taking into account the periodic table proximity and the little work published regarding copper-mediated reducing systems, we focused on the copper-based $CuCl_2 \cdot 2H_2O$–Li–Arene (cat.) combination, which was found to be very efficient in the reduction of carbonyl compounds and imines,[21] as well as in the hydrodehalogenation of aryl and alkyl halides.[22]

As part of our research in the field above described, we want to present herein the results obtained on the reduction of alkyl and vinyl sulfonates under very mild reaction conditions, based on the use of active copper, generated from commercially available copper(II) chloride dihydrate, lithium, and a catalytic amount of an arene (DTBB) as electron carrier.[23]

2. Results and discussion

The reduction of a series of sulfonates was successfully carried out under very mild conditions, using a mixture of copper(II) chloride dihydrate (1.0 mmol), an excess of lithium sand (1:8 molar ratio, referred to the copper salt) and a catalytic amount of DTBB (0.1 mmol/mmol of copper salt, 5.0 mol%) in tetrahydrofuran at room temperature. Thus, the reaction of primary, secondary and tertiary mesylates with the above mentioned reducing system, led to the formation of the corresponding hydrocarbons resulting from a sulfonyloxy/hydrogen exchange (Table 1, entries 1–3). Dimesylates could be reduced to the corresponding hydrocarbons under the same reaction conditions using 2 equiv of the reducing system (Table 1, entry 4).

The same process was successfully applied to a variety of trifluoromethanesulfonate derivatives. As shown in Table 1, primary and secondary alkyl triflates could be reduced to the corresponding alkanes in good yields (Table 1, entries 5, 6, and 8). The reaction with cyclic triflates proved to work nicely leading to the corresponding cycloalkanes also in good yields (Table 1, entries 9 and 10). One main advantage of this methodology consists in using the deuterated salt $CuCl_2 \cdot 2D_2O$ (prepared from anhydrous $CuCl_2$ and D_2O as previously described[14]) instead of the hydrated one, thus furnishing the corresponding deuterium-labeled hydrocarbons in a simple and economic way (Table 1, entry 7).[24] It is worthy to note that the triflate functionality was more reactive than the mesylate one, as it is shown by the shorter reaction times of the former.

When the same process was applied to enol triflates, the corresponding alkenes were obtained as major products in good yields (Table 2). Thus, the enol triflates derived from nonan-5-one, 4-*tert*-butylcyclohexanone, and decalone, were easily transformed into the corresponding olefins after 6 h (Table 2, entries 1, 2, and 4). The same methodology was successfully applied to the conjugate enol triflates derived from 3,4-dihydrophenanthren-1(2*H*)-one and pulegone (Table 2, entries 5 and 6). Moreover, dienol triflates, such as those derived from isophorone and cholest-5-en-3-one, were readily reduced to the corresponding dienes by using 1 equiv of the copper salt for 8–10 h at room temperature (Table 2, entries 7 and 8). It is worthy to note that no over-reduction was observed, even using an excess of the reducing system (2 equiv) or longer reaction times (Table 2, entries 1, 2, and 6). In contrast, some time depending over-reduction was observed in the reaction with the 3,4-dihydrophenanthren-1(2*H*)-one derived enol triflate (Table 2, entry 5), in which the carbon–carbon double bond is conjugated with the aromatic system. Finally, the use of the deuterated copper salt ($CuCl_2 \cdot 2D_2O$) in the reducing system allowed the preparation of deuterium labeled alkenes (Table 2, entry 3).[24]

By comparing the active copper reducing system with the equivalent one containing nickel, it can be concluded that the latter is more versatile since the degree of reduction (to the alkene or alkane) can be easily controlled by adjusting the stoichiometry of the nickel salt.[18] However, the high selectivity and commercial availability of the former makes it the reagent of choice to stop the reduction of enol and dienol triflates at the alkene and diene stage, respectively.

3. Conclusion

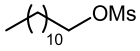
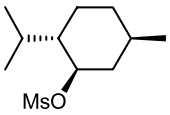
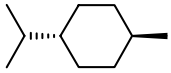
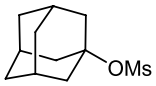
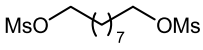
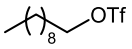
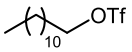
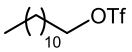
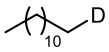
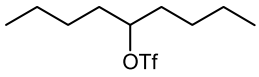
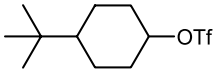
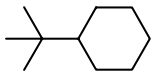
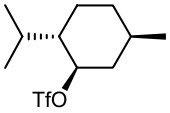
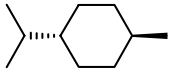
In conclusion, we have described herein a new procedure to reduce alkyl and vinyl sulfonates to the corresponding hydrocarbons under very mild reaction conditions, using the active copper-based reducing combination $CuCl_2 \cdot 2H_2O$–Li–DTBB(cat.). Some advantages of this reduction procedure should be noted, including its simple use and the clean reduction of enol and dienol triflates to alkenes and dienes, respectively. In contrast with the nickel-based analogous system,[18] no over-reduction has been detected even using an excess of the reducing combination or long reaction times. This last feature makes this copper-based reducing system an attractive alternative to the Shapiro reaction in the synthesis of olefins from carbonyl compounds. Finally, the use of the deuterated copper salt allowed the preparation of deuterium labeled alkanes or alkenes in a simple and economic way.

4. Experimental

4.1. General

All moisture sensitive reactions were carried out under nitrogen atmosphere. Anhydrous tetrahydrofuran was freshly distilled from sodium/benzophenone ketyl. Other solvents used were treated prior to use by standard methods.[25] All alcohols and carbonyl compounds for the synthesis of the corresponding sulfonates were of the best available grade (Aldrich, Fluka, Merck) and were used without further purification. Copper(II) chloride dihydrate was commercially available (Aldrich); its deuterated derivative was prepared by treating anhydrous copper(II) chloride with an excess of deuterium oxide and then by heating in vacuo (ca. 0.5 Torr) at 60 °C in Kugelrohr during 1 h. Column chromatography was performed with Merck silica gel 60 (0.040–0.063 μm, 240–400 mesh). Thin layer chromatography (TLC) was performed on precoated silica

Table 1. Reduction of alkylsulfonates

Entry	Sulfonate	Reaction conditions		Product[a]	
		$CuCl_2 \cdot 2H_2O$ (equiv)	t (h)	Structure	Yield (%)[b]
1		1	10		73
2		1	10		65
3		1	10		80
4		2	12		72[c]
5		1	4		79[c]
6		1	4		75
7		1[d]	4		70[e]
8		1	4		68[c]
9[f]		1	6		79
10		1	6		86

[a] All isolated products were >95% pure (GLC).
[b] Isolated yield after column chromatography (silica gel, hexane/EtOAc) unless otherwise stated, based on the starting sulfonate.
[c] GLC yield, high volatility compound.
[d] $CuCl_2 \cdot 2D_2O$ was used instead of $CuCl_2 \cdot 2H_2O$.
[e] ca. 70% deuterium incorporation (mass spectrometry, 300 MHz ^{1}H NMR).
[f] Starting alcohol commercially available as a *cis–trans* mixture.

gel plates (Merck 60, F254, 0.25 mm). Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker ARX-300 spectrophotometer using $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal reference. Mass spectra (EI) were obtained at 70 eV on a Hewlett Packard HP-5890 GC/MS instrument equipped with a HP-5972 selective mass detector. Infrared (FT-IR) spectra were obtained on a Nicolet-Nexus spectrophotometer. The purity of volatile compounds and the chromatographic analyses (GC) were determined with a Shimadzu GC-9A instrument equipped with a flame-ionization detector and a 2 m column (1.5% OV17 9_A SUS Chrom 103 80/1000), using nitrogen as carrier gas.

4.2. Synthesis of the starting mesylates. General procedure[26]

To a solution of the corresponding alcohol (2.5 mmol) in methylene chloride (15 mL) containing triethylamine (1.1 mL, 4 mmol) at 0 to −10 °C, was added methanesulfonyl chloride (0.62 mL, 4 mmol) over a period of 5–10 min. Stirring was maintained until total conversion of the starting material (TLC, GLC). The reaction mixture was transfered to a separatory funnel with the aid of more methylene chloride (5–10 mL). The mixture was first extracted with ice water, followed by cold 10% hydrochloric acid, saturated sodium bicarbonate solution, and brine (10 mL each). Drying of the methylene chloride solution with anhydrous Na_2SO_4, followed by solvent removal gave the mesylate, which was pure enough (GLC) for its use in the reduction reactions. The following known compounds, included in Table 1, were characterised by comparison of their chromatographic and spectroscopic data (^{1}H and ^{13}C NMR, and MS) with those described in the literature: dodecyl methanesulfonate (entry 1),[27] (−)-menthyl methanesulfonate (entry 2),[28] 1-adamantyl methanesulfonate (entry 3),[26] 9-methylsulfonyloxynonyl methanesulfonate (entry 4).[29]

4.3. Synthesis of the starting alkyl triflates. General procedure[30]

To a solution of the corresponding alcohol (2.14 mmol) in pyridine (5 mL) at 0 °C was slowly added trifluoromethanesulfonyl anhydride (0.4 mL, 2.4 mmol). The solution was stirred at 0 °C for 5 min and then allowed to warm to room temperature and stirred for 25 h. The resulting mixture was poured into water and extracted with diethyl ether (2× 15 mL). The ether extract was washed sequentially with

water, cold 10% hydrochloric acid solution, water, and brine (2×10 mL each), dried over anhydrous Na_2SO_4, and concentrated to yield an oil. Chromatography (flash column, hexane/EtOAc) afforded the corresponding triflates as colorless oils. The following known compounds, included in Table 1, were characterized by comparison of their chromatographic and spectroscopic data (^1H and ^{13}C NMR, and MS) with those described in the literature: decyl trifluoromethanesulfonate (entry 5),[31] dodecyl trifluoromethanesulfonate (entries 6 and 7),[32] 4-(*tert*-butyl)cyclohexyl trifluoromethanesulfonate (entry 9),[33] (−)-menthyl trifluoromethanesulfonate (entry 10).[34] For new compound, physical and spectroscopic data follow:

4.3.1. 1-Butylpentyl trifluoromethanesulfonate. Colorless oil; t_r 14.24; IR (film): ν=2936, 2877, 1471, 1425, 1302, 1210, 1137, 1118, 968, 718 cm^{-1}; ^1H NMR: δ=0.76 (6H, t, J=6.8 Hz, 2×CH_3), 1.22 (8H, m, 2×$CH_2CH_2CH_3$), 1.96 (4H, m, 2×CH_2CH), 4.15 (1H, m, CH); ^{13}C NMR: δ_C= 12.6 (2×CH_3), 21.0 (2×CH_2CH_3), 26.7 (2×CH_2CH_2-CH_3), 34.2 (2×CH_2CH), 86.0 (CH), 119.7 (q, J=320.0 Hz, CF_3); MS: m/z=276 (M^+, 1%), 127 (10), 85 (77), 71 (93), 70 (11), 69 (43), 57 (100), 56 (18), 55 (48), 44 (62), 43 (92), 42 (15), 41 (79), 39 (25). HRMS: calcd for $C_{10}H_{19}F_3O_3S$ 276.3203, found 276.3209.

4.4. Synthesis of the starting enol triflates[35]

For all the starting enol triflates included in Table 2, except for enol triflate derived from cholest-5-en-3-one (Table 2, entry 8), a solution of the corresponding ketone (1.6 mmol) in THF (3 mL) was added to a solution of LDA (1.76 mmol) in THF (3 mmol) at −78 °C, and the resulting solution was allowed to be stirred for 2 h at the same temperature. A solution of *N*-phenyltrifluoromethanesulfonimide (0.63 g, 1.76 mmol) in THF (3 mL) was then added; the reaction mixture was stirred at 0 °C for 1 h and allowed to warm to room temperature. Stirring was maintained during 9 h. After solvent removal at the rotatory evaporator, the resultant yellow oil was purified by column chromatography on silica gel (hexane) to yield the enol triflate product. The following known compounds, included in Table 2, were characterized by comparison of their chromatographic and spectroscopic data (^1H and ^{13}C NMR, and MS) with those described in the literature: (*Z*)-1-butyl-1-pentenyl trifluoromethanesulfonate (entry 1),[36] 4-*tert*-butylcyclohexen-1-yl trifluoromethanesulfonate (entries 2 and 3),[35] *trans*-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl trifluoromethanesulfonate (entry 4),[9b] 3-methyl-6-(1-methylethylidene)cyclohexen-1-yl trifluoromethanesulfonate (entry 6),[37] 3,5,5-trimethyl-1,3-cyclohexadien-1-yl trifluoromethanesulfonate (entry 7).[38] For new compound, physical and spectroscopic data follow.

4.4.1. Dihydrophenanthrenyl trifluoromethanesulfonate. Pale brown oil; t_r 35.43; IR (film): ν=3067, 2970, 2890, 1650, 1596, 1491, 1394, 1207, 1133, 1067, 910, 815, 761, 695 cm^{-1}; ^1H NMR: δ=2.55 (2H, m, CH_2CH) 3.69 (2H, t, J=7.1 Hz, CH_2C), 6.01 (1H, t, J=4.8 Hz, $CHCH_2$), 7.11–7.51 (3H, m, ArH), 7.68 (1H, d, J=8.8 Hz, ArH), 7.74 (1H, d, J=7.6 Hz, ArH), 7.93 (1H, d, J=8.2 Hz, ArH); ^{13}C NMR: δ=22.6 (CH_2CH), 30.7 (CH_2C), 117.2 ($CHCH_2$), 119.1 (q, J=320.4 Hz, CF_3), 119.3, 124.1, 126.8, 127.2, 127.5, 129.4 (6×ArCH), 131.4, 133.0, 134.3, 137.3 (4×ArC), 147.2 (CO); MS: m/z=328 (M^+, 53%), 195 (32), 168 (14), 167 (100), 166 (28), 165 (75), 153 (10), 152 (43), 139 (20), 69 (27). HRMS: calcd for $C_{15}H_{11}F_3O_3S$ 328.3117, found 328.3111.

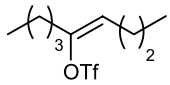
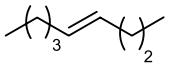
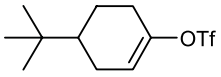
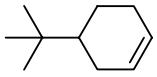
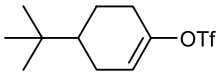
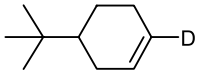
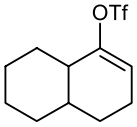
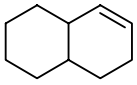
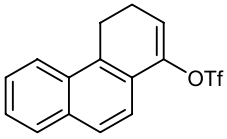
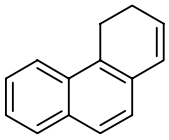
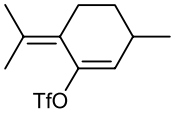
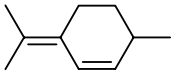
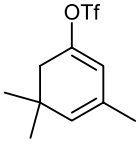
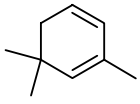
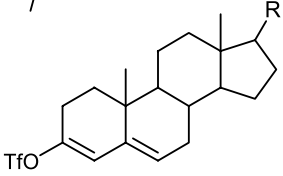
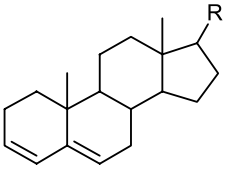
4.5. Synthesis of cholesta-3,5-dien-3-yl trifluoromethanesulfonate[39]

2,6-Di-*tert*-butylpyridine (0.226 g, 1.1 mmol) and triflic anhydride (0.186 mL, 0.111 g, 1.1 mmol) were added to a solution of cholest-5-en-3-one (0.384 g, 1 mmol) in chloroform (10 mL). The reaction mixture was stirred under reflux for 12 h. The reaction solvent was distilled and the crude reaction mixture was diluted with hexane (20 mL). The hexane solution was washed with water (20 mL) and brine (20 mL). The organic layer was filtered through basic alumina with hexane elution, and then solvents were removed by rotatory evaporation to yield the corresponding vinyl triflate pure enough to be used for the reduction reaction. The crystallized triflate (hexane) was characterized by comparison of its physical and spectroscopic data (^1H, ^{13}C NMR) with those described in the literature.[10c]

4.6. Reduction of sulfonates using the $CuCl_2\cdot 2H_2O$–Li–DTBB(cat.) combination. General procedure

A solution of the corresponding sulfonate (1 mmol) in THF (5 mL) was added to a mixture of $CuCl_2\cdot 2H_2O$ (170 mg, 1 mmol) or its deuterated salt (174 mg, 1 mmol), lithium sand (56 mg, 8.0 mmol) and DTBB (27 mg, 0.1 mmol) in THF (5 mL) at room temperature under a nitrogen atmosphere. The reaction mixture, which was initially dark green, changed to black, thus indicating the formation of activated copper(0). After total conversion of the starting material (TLC or GLC), the resulting suspension was diluted with diethyl ether (20 mL) and filtered off through a pad containing silica gel and celite (ca. 3:1). The filtrate was dried over anhydrous sodium sulfate, the solvents were evaporated (15 Torr), and the resulting residue was purified by column chromatography (silica gel, hexane/EtOAc). For volatile products, the dried organic layer was analyzed by GLC using an internal standard (dodecane for alkyl triflates and cycloocta-1,5-diene for enol triflates) (see Table footnotes). The reduction products in Tables 1 and 2, were fully characterized by comparison of their chromatographic and spectral data with those of the corresponding commercially available pure samples [*n*-dodecane (Table 1, entries 1 and 6), adamantane (Table 1, entry 3), *n*-nonane (Table 1, entries 4 and 8), *n*-decane (Table 1, entry 5), *tert*-butylcyclohexane (Table 1, entry 9), (*E*)-non-4-ene (Table 2, entry 1), cholesta-3,5-diene (Table 2, entry 8)]. For the rest of compounds included in Tables 1 and 2, literature references for all known compounds follow: *p*-menthane (Table 1, entries 2 and 10),[40] 1-deuteriododecane (Table 1, entry 7),[41] 4-*tert*-butylcyclohexene (Table 2, entry 2),[11a] 4-*tert*-butyl-1-deuteriocyclohexene (Table 2, entry 3),[42] 1,2,3,4,4a,5,6,8a-octahydronaphtalene (Table 2, entry 4),[43] 3,4-dihydrophenantrene (Table 2, entry 5),[44] 3-methyl-6-(1-methylethylidene)cyclohex-1-ene (isoterpinolene) (Table 2, entry 6),[45] 3,5,5-trimethylcyclohexa-1,3-diene (Table 2, entry 7).[46]

Table 2. Reduction of enol triflates

Entry	Sulfonate	Reaction conditions		Product[a]	
		$CuCl_2 \cdot 2H_2O$ (equiv)	t (h)	Structure	Yield (%)[b]
1		2	6		72
2		2	6		65
3		1[c]	6		69[d]
4		1	6		61
5		1	6		58
6		2	8		73
7		1	8		78[e]
8[f]		1	10		66

[a] All products were >95% pure (GLC).
[b] Isolated yield after column chromatography (silica gel, hexane) unless otherwise stated, based on the starting sulfonate.
[c] $CuCl_2 \cdot 2D_2O$ was used instead of $CuCl_2 \cdot 2H_2O$.
[d] ca. 73% deuterium incorporation (mass spectrometry, 300 MHz ^{1}H NMR).
[e] GLC yield, high volatility compound.
[f] R=1,5-dimethylhexyl.

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24. Deuterium incorporation was not quantitative due probably to partial hydration of the $CuCl_2 \cdot 2D_2O$ salt during its preparation and handling. In addition, a dissolving-metal type mechanism (involving a proton abstraction from the reaction medium), that could compete with the general mechanism proposed for these reductions,[13] must not be ruled out. We thank a referee for suggesting us to clarify this aspect.
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